Supporting Information

Fischer *et al.* 10.1073/pnas.0806129105

SI Text

Determination of the Folding Free Enthalpy. The folding equilibrium of the torsion balances was determined by integration of the line-fitted (100% Lorentz functions) ^{1}H NMR (500 MHz) resonance signals of the CH_3 group on C3′. Equation **S1** gives the folding free enthalpy from the relative population of both atropisomeric states.

$$\Delta G = -RT\ln K = -RT\ln\frac{c_{folded}}{c_{unfolded}} \quad [S1]$$

Error Analysis. Standard deviation of the equilibrium constant (K) determined by multiple measurements and integration of the line-fitted (100% Lorentz functions) ^{1}H NMR (500 MHz) spectra: $\delta(K) \leq 5\%$.

Only the error resulting from the experimental standard deviation is considered, because the error that results from the integration method is smaller and of systematic nature, it therefore applies equally to all compared experiments.

$$\delta(\ln K) = \frac{\delta K}{K} = 0.05 \quad [S2]$$

$$\delta(\Delta G) = RT[\delta(\ln K)] = 0.12\ \text{kJ mol}^{-1} \quad [S3]$$

$$\delta(\Delta\Delta G_{c=o\cdots c=o}) = \sqrt{\delta(\Delta G_{(\pm)-1})^2 + \delta(\Delta G_{(\pm)-2})^2 + \delta(\Delta G_{(\pm)-3})^2 + \delta(\Delta G_{(\pm)-4})^2} = 0.25\ kJ\ mol^{-1} \quad [S4]$$

General Methods and Materials. TLC was conducted on aluminum sheets coated with SiO_2 F_{254} obtained from Macherey-Nagel. Visualization was performed with an UV lamp (254 or 366 nm) or by reaction with basic aqueous $KMnO_4$ solution. Column chromatography was carried out on Ultra Pure Silica Gel (230–400 mesh) purchased from Silicycle or on Silica Gel 60 (230–400 mesh) purchased from Fluka by using redistilled technical solvents and an overpressure of 0.2–0.6 bar. Melting points (m.p.) were determined in an open capillary using a Büchi Melting Point B540 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini 300, Varian Mercury 300, Varian Mercury-VX 300, and a Bruker ARX 300 operating at 299.9 MHz for the ^{1}H nucleus. ^{1}H decoupled ^{13}C NMR spectra were recorded on a Varian Gemini 300, Varian Mercury 300, Varian Mercury-VX 300, and a Bruker ARX 300 operating at 75.4 MHz for the ^{13}C nucleus and decoupling at 299.9 MHz. Chemical shifts are reported in δ units (ppm) relative to the residual deuterated solvent signal of $CDCl_3$ (^{1}H NMR: δ 7.26 ppm; ^{13}C NMR: δ 77.0 ppm); CD_2Cl_2 (^{1}H NMR: δ 5.30 ppm; ^{13}C NMR: δ 53.5 ppm); $C_2D_2Cl_4$ (^{1}H NMR: δ 5.91 ppm; ^{13}C NMR: δ 74.2 ppm); CD_3OD (^{1}H NMR: δ 3.31 ppm; ^{13}C NMR: δ 49.0 ppm); C_6D_6 (^{1}H NMR: δ 7.16 ppm; ^{13}C NMR: δ 128.0 ppm) or relative to an external standard. The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad signal). The coupling constant J is given in Hz. One-dimensional ^{1}H NMR spectra were recorded using the acquisition parameters: 26.4° pulse, 3.138 s acquisition time, 5099.4 Hz spectral width, 32 K data size, number of transients 16, at 298 K. ^{13}C NMR spectra were recorded using the acquisition parameters: 45.0° pulse, 1.300 s acquisition time, 20,000.0 Hz spectral width, 64 K data size, number of transients >512, at 298 K. ^{1}H NMR spectra for thermodynamic analysis were recorded on a Bruker AMX-500 spectrometer operating at 500.1 MHz for the ^{1}H nucleus using the acquisition parameters: 30.0° pulse, 5.000 s acquisition time, 8012.8 Hz spectral width, 8.000 s D1 delay, 64 K data size, number of transients 64. The exact temperature was monitored by an external thermoelement. All data were processed using Bruker TopSpin 2.1.0. Binding titration data were processed using a software package provided by Hunter and coworkers (1). Deuterated solvents in the highest possible purity were used as purchased from ARMAR Chemicals. IR spectra were recorded as neat samples on a Perkin–Elmer Spectrum BX II spectrometer. The absorption bands are referenced in wavenumbers (cm^{-1}). Mass spectrometry was performed by the MS-Service of the Laboratory of Organic Chemistry ETH Zurich on a Waters Autospec NT (EI) spectrometer. High-resolution (HR) EI-MS spectra were measured on a Waters Autospec NT spectrometer. The most important signals are reported in m/z units with M^+ as the molecular ion. Reagents and solvents were purchased at reagent grade from Acros, Aldrich, Fluka, Merck, ABCR, TCI, Strem, and Apollo Scientific and used as received. Solvents were purified and dried by standard procedures and freshly distilled under an atmosphere of N_2. Unless otherwise stated, all reactions were performed in flame-dried glassware under an inert atmosphere of N_2 or Ar. The IUPAC name of each new compound was determined using the ACD/Name software from ACD/Labs. 6-Hydroxyisoquinolin-1(2*H*)-one (2), and torsion balances (±)-**5**, and (±)-**6** were synthesized according to literature procedures (3). The synthesis of torsion balances (±)-**1** to (±)-**4** is depicted in supporting information (SI) Fig. S1 and Fig. S2.

Synthetic Procedures

(±)-2-(1-Acetyl-6*H*,12*H*-5,11-methanoindolo[*6,5-c*][1,5]benzodiazocin-8-yl)-3-methylbenzoic acid ((±)-9). A flame-dried *Schenk* tube was charged under Ar with (±)-**5** (280.0 mg, 0.71 mmol), and DMAP (865.0 mg, 7.10 mmol) in dry CH_2Cl_2 (10 mL). Ac_2O (1.5 mL, 15.84 mmol) was added via syringe and the mixture stirred for 72 h at 24 °C. The solvent was evaporated on a rotary evaporator. Column chromatography (CH_2Cl_2/MeOH, 100/2 to 100/6) yielded (±)-**9** (180.0 mg, 60%) as an orange solid. m.p. 160–164 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1 H), 7.62 (s, 1 H), 7.59 (dd, J = 3.5, 5.5, 1 H), 7.26–7.34 (m, 3 H), 7.23 (d, J = 8.2, 1 H), 7.16 (d, J = 7.9, 1 H), 6.82 (s, 1 H), 6.58 (d, J = 3.7, 1 H), 4.84 (d, J = 17.0, 1 H, -CH_aH_bN-), 4.34–4.49 (m, 2 H, -NCH_2N-), 4.19 (d, J = 17.0, 1 H, -CH_aH_bN-), 4.15 (d, J = 13.1, 1 H, -CH_aH_bN-), 3.64 (d, J = 13.2, 1 H, -CH_aH_bN-), 2.56 (s, 3 H, COCH_3), 2.03 (s, 3 H, ArCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 145.0, 131.5, 139.4, 137.4, 136.4, 134.3, 133.2, 132.0, 129.9, 128.9, 127.0, 126.7, 126.0, 125.9, 125.8, 126.6, 124.2, 116.4, 114.4, 108.9, 65.5 (-NCH_2N-), 58.6 (-CH_2N-), 58.2 (-CH_2N-), 23.7 (COCH_3), 20.8 (ArCH_3). IR (neat) $\tilde{\nu}$ 2951, 2845, 1721, 1592, 1557, 1519, 1465, 1435, 1349, 1324, 1293, 1209, 1173, 1137, 1091, 1068, 1034, 1008, 958, 922, 892, 839, 811, 789, 768, 713, 671, 652, 628. MS (EI) m/z 437.2 (100, M^+). HRMS (EI) m/z 437.1731 (M^+, $C_{27}H_{23}N_3O_3^+$, calc. 437.1734).

(±)-1-Oxo-1,2-dihydroisoquinolin-6-yl 2-(1-acetyl-6*H*,12*H*-5,11-methanoindolo[*6,5-c*][1,5]benzodiazocin-8-yl)-3-methylbenzoate ((±)-1). A flame-dried *Schlenk* tube was charged under Ar with (±)-**9** (120.0 mg, 0.27 mmol), 6-hydroxyisoquinolin-1(2*H*)-one (133.1

mg, 0.83 mmol), and BOP (244.0 mg, 0.55 mmol) in dry CH_2Cl_2 (12 mL). NEt_3 (222.0 mg, 2.19 mmol) was added dropwise via a syringe and the mixture stirred for 51 h at 24 °C. The solvents were evaporated, and the residue was taken up in AcOEt (50 mL). The organic phase was washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and concentrated on a rotary evaporator. Column chromatography (CH_2Cl_2/MeOH, 100/1 to 100/3) yielded (±)-**1** (78.2 mg, 50%) as a colorless foam. m.p. 195–197 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33/9.95 (s, 1 H), 8.35 (d, *J* = 8.7, 0.5 H), 8.05/8.08 (s, 1 H), 7.71/7.77 (d, *J* = 7.3, 1 H), 7.40–7.46 (m, 2 H), 7.32–7.37 (m, 2 H), 7.22–7.24 (m, 1 H), 7.09–7.14 (m, 2 H), 6.87–6.96 (m, 2 H), 6.78/6.82 (d, *J* = 1.6, 1 H), 6.52/6.57 (d, *J* = 3.7, 1 H), 6.44 (d, *J* = 7.4, 0.5 H), 6.19 (d, *J* = 7.2, 0.5 H), 5.59 (dd, *J* = 2.2, 8.7, 0.5 H), 4.68–4.92 (m, 2 H, -C*H*$_a$H$_b$N-),4.18–4.47 (m, 4 H, -NC*H*$_2$N-, -CH$_a$*H*$_b$N-), 2.58/2.69 (s, 3 H, COC*H*$_3$), 2.05/2.16 (s, 3 H, ArC*H*$_3$). ^{1}H NMR (500 MHz, C_6D_6) δ 8.24/8.47 (b, 1 H, H13), 7.83/7.89 (d, *J* = 7.7, 1 H, H10), 7.31 (s, 1 H, H1″), 7.30/8.63 (d, *J* = 8.8, 1 H, H4″), 7.16–7.21 (m, 1 H, H8″), 7.09–7.14 (m, 1 H, H4′), 7.04–7.08 (m, 2 H, H9, H6′), 7.00–7.02 (m, 1 H, H5′), 6.84 (d, *J* = 2.2, 1 H, H4), 6.63/6.66 (d, *J* = 1.7, 1 H, H7), 6.50/7.23 (b, 1 H, NH), 6.14/6.32 (d, *J* = 3.7, 1 H, H7″), 5.93/6.25 (b, 1 H, H2), 5.55/5.89 (d, *J* = 7.0, 1 H, H3), 5.47/6.86 (dd, *J* = 2.2, 8.7, 1 H, H3″), 4.44–4.57 (m, 2 H, H6$_{endo}$, H12$_{endo}$), 4.01–4.18 (m, 4 H, H6$_{exo}$, H12$_{exo}$, H14), 1.73/2.54 (s, 3 H, COCH$_3$), 1.71/2.04 (s, 3 H, CH$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4/169.2, 166.8/167.3, 162.2/162.9, 153.4/154.0, 147.2/147.4, 143.9/144.5, 141.1/141.2, 139.8/139.3, 137.6/137.7, 135.6/135.8, 132.8/133.7, 131.1/131.3, 129.9/130.0, 129.1/129.3, 128.1/128.2, 128.0, 127.6/127.7, 127.5, 127.2, 127.0/127.3, 126.7/126.8, 125.5/125.6, 124.8, 124.6/124.9, 123.6/123.9, 119.6/120.8, 117.7, 116.3/116.6, 114.3/114.5, 108.2/109.0, 105.9/106.2, 67.1 (-NCH$_2$N-), 59.4 (-CH$_2$N-), 59.3 (-CH$_2$N-), 23.7/23.9 (COCH$_3$), 20.7/20.8 (ArCH$_3$). IR (neat) $\tilde{\nu}$ 3062, 2931, 2899, 1739, 1699, 1657, 1637, 1611, 1575, 1497, 1447, 1380, 1332, 1296, 1271, 1229, 1208, 1172, 1147, 1108, 1081, 1064, 1003, 961, 928, 873, 840, 781, 761, 714, 681, 625, 606. MS (EI) *m*/*z* 580.2 (11, M^+). HRMS (EI) *m*/*z* 580.2102 (M^+, $C_{36}H_{28}N_4O_4^+$, calc. 580.2105).

(±)-Naphthalen-2-yl 2-(1,12-dihydro-6*H*-5,11-methanoindolo[*6,5-c*][1,5]benzodiazocin-8-yl)-3-methylbenzoate ((±)-10). A flame-dried *Schlenk* tube was charged under Ar with (±)-**5** (150.0 mg, 0.38 mmol), naphthalene-2-ol (163.9 mg, 1.14 mmol), and BOP (335.5 mg, 0.76 mmol) in dry CH_2Cl_2 (12 mL). NEt_3 (306.8 mg, 3.03 mmol) was added dropwise via syringe and the mixture stirred for 72 h at 24 °C. The solvent was evaporated, and the residue was taken up in CH_2Cl_2 (50 mL). The organic phase was washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and concentrated on a rotary evaporator. Column chromatography (CH_2Cl_2/MeOH, 100/1) yielded (±)-**10** (142.0 mg, 72%) as a colorless foam. m.p. 271–272 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93–8.08 (m, 1 H), 7.66–7.82 (m, 2 H), 7.31–7.53 (m, 6 H), 7.10–7.26 (m, 4 H), 6.70–6.95 (m, 2 H), 6.45–6.52 (m, 1 H), 6.24 (d, *J* = 8.1, 1 H), 5.66 (dd, *J* = 2.5, 9.6, 1 H), 4.69–4.94 (m, 2 H, -C*H*$_a$H$_b$N-), 4.20–4.46 (m, 4 H, -NC*H*$_2$N-, -CH$_a$*H*$_b$N-), 2.08/2.19 (s, 3 H, ArC*H*$_3$). ^{1}H NMR (500 MHz, C_6D_6) δ 7.85/7.88 (d, *J* = 7.5, 1 H, H10), 7.24 (s, 1 H, H1″), 7.26/7.59 (d, *J* = 7.6, 1 H, H5″), 7.18–7.32 (m, 4 H, H4, H6″,H7″, H8″), 7.21/7.60 (d, *J* = 8.0, 1 H, H5″), 7.11–7.15 (m, 2 H, H4′, H6′), 7.01–7.09 (m, 2 H, H9, H5′), 6.73 (d, *J* = 1.8, 1 H, H7), 6.60/6.81 (b, 1 H, NH), 6.51/6.69 (b, 1 H, H2), 6.36/6.43 (b, 1 H, H3), 6.30/6.34 (s, 1 H, H13), 6.06/7.50 (d, *J* = 8.9, 1 H, H4″), 5.75/7.08 (dd, *J* = 2.3, 8.9, 1 H, H3″), 4.66/4.74 (d, *J* = 16.4, 1 H, H12$_{endo}$), 4.52/4.53 (d, *J* = 16.9, 1 H, H6$_{endo}$), 4.04–4.34 (m, 4 H, H6$_{exo}$, H12$_{exo}$, H14), 1.72/2.07 (s, 3 H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6/168.2, 147.8/148.2, 147.4, 141.0/141.2, 140.6/140.9, 137.4, 135.4/135.6, 133.6, 133.5, 122.3/133.4, 133.2, 131.9/132.0, 131.0/131.3, 129.1, 128.0/128.1, 127.9, 127.5/127.6, 127.4/127.7, 127.0/127.1, 126.9, 126.4/126.8, 125.6/126.0, 125.0, 124.8/124.9, 124.7, 122.1/122.5, 119.7/120.8, 118.0/118.2, 116.1, 108.2, 102.0/102.4, 67.1/67.2 (-NCH$_2$N-), 59.7 (-CH$_2$N-), 59.2/59.3 (-CH$_2$N-), 20.9/21.0 (ArCH$_3$). IR (neat) $\tilde{\nu}$ 3401, 3051, 2946, 2895, 2849, 2653, 2050, 1983, 1729, 1630, 1599, 1568, 1499, 1460, 1406, 1343, 1280, 1239, 1211, 1153, 1125, 1082, 1004, 961, 934, 873, 842, 805, 762, 732, 627. MS (EI) *m*/*z* 521.2 (35, M^+). HRMS (EI) *m*/*z* 521.2100 (M^+, $C_{35}H_{27}N_3O_2^+$, calc. 521.2098).

(±)-Naphthalen-2-yl 2-(1-acetyl-6*H*,12*H*-5,11-methanoindolo[*6,5-c*][1,5]benzodiazocin-8-yl)-3-methylbenzoate ((±)-3). A flame-dried *Schenk* was charged under Ar with (±)-**10** (80.0 mg, 0.15 mmol), DMAP (2.0 mg, 0.02 mmol), and Et_3N (1.0 mL, 7.17 mmol) in dry CH_2Cl_2 (1 mL). Ac_2O (0.2 mL, 2.12 mmol) was added via syringe and the mixture stirred for 72 h at 24 °C. The solvent was evaporated on a rotary evaporator. Column chromatography (CH_2Cl_2/MeOH, 100/1) yielded (±)-**3** (59.0 mg, 68%) as a colorless foam. m.p. 160–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08–8.15 (m, 1 H), 7.68–7.83 (m, 2.5 H), 7.48–7.55 (m, 7.5 H), 7.11–7.24 (m, 2.5 H), 6.89–6.93 (m, 0.5 H), 6.80–6.88 (m, 1 H), 6.72–6.77 (m, 0.5 H), 6.53–6.57 (m, 1 H), 5.59–5.64 (m, 0.5 H), 4.69–4.97 (m, 2 H, -C*H*$_a$H$_b$N-), 4.18–4.50 (m, 4 H, -NC*H*$_2$N-, -CH$_a$*H*$_b$N-), 2.57/2.63 (s, 3 H, COC*H*$_3$), 2.07/2.18 (s, 3 H, ArC*H*$_3$). ^{1}H NMR (500 MHz, C_6D_6) δ 8.21/8.29 (b, 1 H, H13), 7.85/7.88 (d, *J* = 7.3, 1 H, H10), 7.44/7.53 (d, *J* = 7.8, 1 H, H6″), 7.27–7.29 (m, 2 H, H4, H1″), 7.26/7.59 (d, *J* = 7.6, 1 H, H5″), 7.17–7.23 (m, 2 H, H7″, H8″), 7.13 (d, *J* = 6.7, 1 H, H4′), 7.05–7.12 (m, 2 H, H9, H6′), 6.98–7.03 (m, 1 H, H5′), 6.68/6.73 (s, 1 H, H7), 6.68/7.48 (d, *J* = 8.8, 1 H, H4″), 6.50/6.85 (b, 1 H, H2), 6.13/6.18 (d, *J* = 3.6, 1 H, H3), 5.78/7.05 (dd, *J* = 2.2, 8.8, 1 H, H3″), 4.51/4.55 (d, *J* = 17.1, 1 H, H12$_{endo}$), 4.47/4.49 (d, *J* = 16.5, 1 H, H6$_{endo}$), 4.01–4.20 (m, 4 H, H6$_{exo}$, H12$_{exo}$, H14), 1.73/1.95 (s, 3 H, COC*H*$_3$), 1.73/2.06 (s, 3 H, ArC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2/168.4, 167.7/168.0, 147.7/148.3, 147.3, 144.4/144.5, 140.6/141.0, 137.4/137.5, 135.6/135.8, 133.3/133.6, 133.2, 132.7, 131.9, 131.0/131.3, 129.9/130.1, 129.0/129.1, 128.2/128.4, 127.6/127.7, 127.4/127.5, 127.2, 127.0/127.1, 127.0 (2 C), 126.9, 126.1/126.4, 125.6, 125.1/125.2, 124.9, 119.6/120.8, 118.2, 116.6/116.7, 114.5, 109.0/109.2, 66.9/67.0 (-NCH$_2$N-), 59.3 (-CH$_2$N-, 2 C), 23.7/23.8 (COCH$_3$), 20.8 (ArCH$_3$). IR (neat) $\tilde{\nu}$ 3368, 3155, 3058, 2948, 2901, 2849, 1733, 1699, 1630, 1600, 1573, 1536, 1499, 1445, 1380, 1332, 1276, 1239, 1207, 1154, 1126, 1082, 1003, 961, 928, 84, 841, 806 733, 629. MS (EI) *m*/*z* 563.2 (5, M^+), 420.2 (2, [M^+-$C_{10}H_7O$]). HRMS (EI) *m*/*z* 563.2206 (M^+, $C_{35}H_{29}N_3O_3^+$, calc. 563.2204).

(±)-Methyl 2-(1-acetyl-6*H*,12*H*-5,11-methanoindolo[*6,5-c*][1,5]benzodiazocin-8-yl)-3-methylbenzoate ((±)-11). A flame-dried *Schlenk* tube was charged under Ar with (±)-**6** (427.1 mg, 1.04 mmol), DMAP (20.0 mg, 0.16 mmol), and Et_3N (2.2 mL, 15.82 mmol) in dry CH_2Cl_2 (10 mL). Ac_2O (1.0 mL, 10.56 mmol) was added via syringe and the mixture stirred for 16 h at 24 °C. The solvent was evaporated on a rotary evaporator. The residue was taken up in CH_2Cl_2, washed with H_2O, saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl solution, dried ($MgSO_4$), and concentrated on a rotary evaporator. Column chromatography (CH_2Cl_2/MeOH, 100/2) yielded (±)-**11** (404.8 mg, 86%) as a colorless foam. m.p. 119–121 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02–8.10 (m, 1 H), 7.48–7.61 (m, 1 H), 7.28–7.37 (m, 3 H), 7.21–7.27 (m, 1 H), 7.15–7.20 (m, 1 H), 6.95–7.01 (m, 1 H) 6.64–6.68 (m, 1 H), 6.53–6.58 (m, 1 H), 4.74–4.92 (m, 2 H, -C*H*$_a$H$_b$N-), 4.14–4.48 (m, 4 H, -NC*H*$_2$N-, -CH$_a$*H*$_b$N-), 2.72/3.58 (s, 3 H, OC*H*$_3$), 2.58 (s, 3 H, COC*H*$_3$), 1.96/2.09 (s, 3 H, ArC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9/169.3, 168.1/168.2, 146.3/146.4, 143.7/144.0, 140.5/140.8, 136.7/137.2, 135.7/135.8, 132.8, 132.5/132.7, 131.9/132.3, 129.8, 127.8/128.0, 127.1, 126.9, 126.8, 126.6, 125.5, 125.2/125.4, 124.1/124.4, 116.2/116.4, 114.3/114.4, 108.8, 66.9/67.4 (-NCH$_2$N-), 59.3/59.8 (2 C, -CH$_2$N-), 51.0/51.9 (OCH$_3$), 23.8 (COCH$_3$), 20.8/20.9 (ArCH$_3$). IR (neat) $\tilde{\nu}$ 2946,

2901, 2847, 1702, 1614, 1573, 1536, 1499, 1446, 1379, 1331, 1290, 1266, 1238, 1205, 1155, 1137, 1096, 1078, 1033, 1014, 963, 928, 871, 841, 789, 762, 714, 683, 627, 606. MS (EI) *m/z* 415.2 (100, M^+). HRMS (EI) *m/z* 451.1889 (M^+, $C_{28}H_{25}N_3O_3^+$, calc. 451.1890).

(±)-Methyl 2-(1-thioacetyl-6*H*,12*H*-5,11-methanoindolo[*6,5-c*][1,5]benzodiazocin-8-yl)-3-methylbenzoate ((±)-12). A flame-dried *Schlenk* tube was charged under Ar with (±)-**11** (200.0 mg, 0.44 mmol), and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (107.5 mg, 0.27 mmol) in dry toluene (5 mL), and the mixture stirred for 20 h at 100 °C. The solvent was evaporated on a rotary evaporator. Column chromatography (CH_2Cl_2/MeOH, 100/1) yielded (±)-**12** (130.2 mg, 63%) as a yellow foam. m.p. 131–133 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1 H), 7.64 (s, 1 H), 7.50–7.61 (m, 1 H), 7.29–7.37 (m, 2 H), 7.22–7.28 (m, 1 H), 7.15–7.21 (m, 1 H), 6.95–7.02 (m, 1 H), 6.65–6.70 (m, 1 H), 6.59–6.63 (m, 1 H), 4.74–4.92 (m, 2 H, -C*H*$_a$H$_b$N-), 4.17–4.48 (m, 4 H, -NC*H*$_2$N-, -CH$_a$*H*$_b$N-), 3.09 (s, 3 H, CSC*H*$_3$), 2.78/3.58 (s, 3 H, OC*H*$_3$), 1.98/2.15 (s, 3 H, ArC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 168.8/169.1, 146.3/146.4, 144.9/145.2, 140.4/140.7, 136.7/137.0, 134.0/134.1, 132.7, 131.8/132.2, 131.4, 127.7/128.0, 127.2, 126.9, 126.8 (2 C), 126.7, 126.5, 125.7/125.9, 124.1/124.4, 116.7/116.9, 115.8, 110.2/110.3, 66.8/67.3 (-NCH$_2$N-), 59.5/59.9 (-*C*H$_2$N-), 59.1/59.4 (-*C*H$_2$N-), 50.9/51.8 (OCH$_3$), 37.4 (CS*C*H$_3$), 20.8/20.9 (Ar*C*H$_3$). IR (neat) $\tilde{\nu}$ 2946, 2900, 2846, 1721, 1615, 1578, 1543, 1498, 1458, 1432, 1385, 1352, 1325, 1290, 1272, 1222, 1203, 1171, 1128, 1097, 1077, 1011, 997, 960, 931, 859, 839, 827, 785, 761, 713, 682, 646, 625. MS (EI) *m/z* 467.2 (100, M^+). HRMS (EI) *m/z* 467.1663 (M^+, $C_{28}H_{25}N_3O_2S^+$, calc. 467.1662).

(±)-Methyl 2-(1-ethyl-6*H*,12*H*-5,11-methanoindolo[*6,5-c*][1,5]benzodiazocin-8-yl)-3-methylbenzoate ((±)-7). A *Schlenk* tube was charged under Ar with H_2O, MeOH, and dry THF-washed RaNi (≈1.0 g) in dry THF (5 mL). Compound (±)-**12** (122.0 mg, 0.26 mmol) in dry THF (2 mL) was added via syringe and the mixture stirred for 25 min at 24 °C. The solution was filtered over Celite, and the RaNi was washed with AcOEt (100 mL). The combined organic phases were concentrated on a rotary evaporator to give (±)-**7** (113 mg, 98%) as a colorless foam. m.p. 96–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.61 (m, 1 H), 7.40–7.45 (m, 1 H), 7.28–7.37 (m, 1 H), 7.21–7.27 (m, 1 H), 7.16–7.20 (m, 1 H), 7.00–7.07 (m, 1 H), 6.95–6.99 (m, 1 H), 6.83–6.93 (m, 1 H), 6.63–6.70 (m, 1 H), 6.35–6.43 (m, 1 H), 4.75–5.00 (m, 2 H, -C*H*$_a$H$_b$N-), 4.18–4.52 (m, 4 H, -NC*H*$_2$N-, -CH$_a$*H*$_b$N-), 3.99–4.13 (m, 2 H, C*H*$_2$CH$_3$), 2.65/3.58 (s, 3 H, OC*H*$_3$), 2.00/2.17 (s, 3 H, Ar*C*H$_3$), 1.36/1.42 (t, *J* = 7.2, 3 H, CH$_2$*C*H$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9/169.2, 146.6/146.8, 140.6, 140.0/140.7, 136.7/137.1, 135.4/135.5, 133.3/133.5, 132.6, 132.0/132.3, 127.9/128.1, 127.7, 127.5, 127.0, 126.8, 126.7, 126.5, 123.9/124.2, 121.7/121.8, 116.0/116.3, 106.0/106.3, 100.3, 67.0/67.7 (-NCH$_2$N-), 60.1/60.2 (-*C*H$_2$N-), 59.4/59.5 (-*C*H$_2$N-), 50.8/51.8 (OCH$_3$), 40.9 (*C*H$_2$CH$_3$), 20.8/20.9 (Ar*C*H$_3$), 15.4 (CH$_2$*C*H$_3$). IR (neat) $\tilde{\nu}$ 2943, 2891, 2846, 1712, 1499, 1461, 1432, 1339, 1289, 1215, 1194, 1172, 1137, 1097, 1075, 1054, 1012, 963, 933, 871, 838, 788, 763, 712, 683, 623. MS (EI) *m/z* 437.2 (100, M^+). HRMS (EI) *m/z* 437.2099 (M^+, $C_{28}H_{27}N_3O_2^+$, calc. 437.2098).

(±)-2-(1-Ethyl-6*H*,12*H*-5,11-methanoindolo[*6,5-c*][1,5]benzodiazocin-8-yl)-3-methylbenzoic acid ((±)-8). A round-bottom flask was charged with LiOH·H_2O (733.6 mg, 17.48 mmol) in CH_3OH/H_2O (10 mL, 4:1). A solution of (±)-**7** (450.0 mg, 1.03 mmol) in CH_3OH (5 mL) was added dropwise over 30 min. The flask was sealed with a septum and stirred for 17 h at 50 °C. The mixture was concentrated on a rotary evaporator, and the residue was taken up in H_2O (50 mL). The pH was adjusted to 4.5 with 2N HCl, and the white precipitate was extracted with AcOEt. The combined organic phases were dried ($MgSO_4$), and concentrated on a rotary evaporator to yield (±)-**8** (406.5 mg, 93%) as a colorless solid. m.p. 240 °C (decomp.). ^{1}H NMR (300 MHz, CD_3OD) δ 7.51–7.64 (m, 2 H), 7.24–7.42 (m, 4 H), 7.15 (s, 1 H), 7.05–7.09 (m, 1 H), 6.82–6.86 (m, 1 H), 6.42–6.44 (m, 1 H), 4.38–5.04 (m, 6 H, -NC*H*$_2$N-, -C*H*$_a$*H*$_b$N-), 4.15 (q, *J* = 7.2, 2 H, C*H*$_2$CH$_3$), 1.87/2.07 (s, 3 H, ArC*H*$_3$), 1.38 (t, *J* = 7.2, 3 H, CH$_2$C*H*$_3$). ^{13}C NMR (75 MHz, CD_3OD) δ 172.0, 145.2, 141.5/141.6, 138.6, 138.2, 136.4, 134.7/134.8, 133.8, 133.7, 130.2, 130.1, 129.6, 128.3 (2 C), 128.2, 127.7, 127.5, 125.5, 121.3, 116.6, 108.3, 68.3 (-NC*H*$_2$N-), 60.0/60.1 (-*C*H$_2$N-), 59.3/59.4 (-*C*H$_2$N-), 42.0 (*C*H$_2$CH$_3$), 20.8/20.9 (Ar*C*H$_3$), 15.9 (CH$_2$*C*H$_3$). IR (neat) $\tilde{\nu}$ 2921, 2855, 2453, 1693, 1501, 1466, 1444, 1403, 1343, 1293, 1259, 1216, 1175, 1148, 1097, 1080, 1048, 1015, 965, 920, 910, 869, 838, 808, 762, 718, 668, 622. MS (EI) *m/z* 423.2 (100, M^+). HRMS (EI) *m/z* 423.1939 (M^+, $C_{27}H_{25}N_3O_2^+$, calc. 423.1941).

(±)-1-Oxo-1,2-dihydroisoquinolin-6-yl 2-(1-ethyl-6*H*,12*H*-5,11-methanoindolo[*6,5-c*][1,5]benzodiazocin-8-yl)-3-methylbenzoate ((±)-2). A flame-dried *Schlenk* tube was charged under Ar with (±)-**8** (170.0 mg, 0.40 mmol), 6-hydroxyisoquinolin-1(2*H*)-one (194.0 mg, 1.20 mmol), and BOP (355.0 mg, 0.80 mmol) in dry CH_2Cl_2 (12 mL). NEt_3 (324.0 mg, 3.20 mmol) was added dropwise via syringe and the mixture stirred for 61 h at 24 °C. The solvents were evaporated, and the residue was taken up in CH_2Cl_2 (50 mL). The organic phase was washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and concentrated on a rotary evaporator. Column chromatography (CH_2Cl_2/MeOH, 200/1 to 100/2) yielded (±)-**2** (65.4 mg, 29%) as a colorless solid. m.p. 201–203 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63/10.03 (s, 1 H), 8.36 (d, *J* = 8.6, 0.5 H), 7.74/7.76 (d, *J* = 8.8, 1 H), 7.51 (d, *J* = 8.7, 0.5 H), 7.42–7.47 (m, 2 H), 7.33–7.37 (m, 1 H), 7.21–7.25 (m, 1 H), 7.09–7.10 (m, 0.5 H), 7.08/7.09 (d, *J* = 2.0, 1 H), 7.05/7.16 (d, *J* = 3.2, 1 H), 6.86–6.93 (m, 3 H), 6.79/6.83 (d, *J* = 1.1, 1 H), 6.44 (d, *J* = 7.2, 0.5 H), 6.39/6.41 (d, *J* = 3.1, 1 H), 6.05 (d, *J* = 7.1, 0.5 H), 5.91 (dd, *J* = 1.6, 8.7, 0.5 H), 4.70–4.99 (m, 2 H, -C*H*$_a$H$_b$N-), 4.21–4.48 (m, 4 H, -NC*H*$_2$N-, -CH$_a$*H*$_b$N-), 4.05–4.16 (m, 2 H, C*H*$_2$CH$_3$), 2.08/2.17 (s, 3 H, Ar*C*H$_3$), 1.38 (t, *J* = 7.3, 3 H, CH$_2$C*H*$_3$). ^{1}H NMR (500 MHz, C_6D_6) δ 7.83/7.88 (d, *J* = 7.6, 1 H, H10), 7.58/8.64 (d, *J* = 8.8, 1 H, H4″), 7.57 (s, 1 H, H1″), 7.11–7.32 (m, 2 H, H4′, H8″), 6.99–7.08 (m, 3 H, H9, H5′, H6′), 6.81/6.88 (d, *J* = 1.8, 1 H, H4), 6.61/6.69 (d, *J* = 1.8, 1 H, H7), 6.45/6.72 (s, 1 H, H13), 6.41/6.49 (d, *J* = 2.9, 1 H, H7″), 5.96/6.20 (b, 1 H, H2), 5.72/6.89 (dd, *J* = 2.3, 8.6, 1 H, H3″), 5.46/5.91 (d, *J* = 7.2, 1 H, H3), 4.51–4.80 (m, 2 H, H6$_{endo}$, H12$_{endo}$), 4.10–4.38 (m, 4 H, H6$_{exo}$, H12$_{exo}$, H14), 3.29–3.35/3.93–4.05 (m, 2 H, C*H*$_2$CH$_3$), 1.69/2.05 (s, 3 H, C*H*$_3$), 0.81/1.19 (t, *J* = 7.3, 3 H, CH$_2$C*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0/167.1, 152.6/163.0, 153.6/154.0, 147.6/147.7, 140.9/141.2, 140.5/140.6, 138.9/139.3, 137.6/137.8, 135.4/135.5, 133.6/133.7, 131.0/131.5, 129.2/129.3, 128.1/128.2/128.3 (3 C), 127.9/128.0, 127.6, 127.5/127.7, 127.2 (2 C), 126.9/127.1, 124.8, 123.6/123.9, 121.2/122.0, 120.2/120.8, 117.7/117.9, 116.4/116.5, 106.3/106.4, 106.1/106.2, 100.2/100.3, 67.2/67.3 (-NCH$_2$N-), 59.6 (-*C*H$_2$N-), 59.4/59.5 (-*C*H$_2$N-), 41.0 (*C*H$_2$CH$_3$), 20.8 (Ar*C*H$_3$), 15.3/15.4 (CH$_2$*C*H$_3$). IR (neat) $\tilde{\nu}$ 3180, 3076, 2933, 2890, 1734, 1664, 1606, 1457, 1342, 1457, 1342, 1271, 1220, 1145, 1109, 1072, 1003, 932, 878, 837, 760, 726, 675. MS (EI) *m/z* 566.2 (8, M^+), 161.0 (100, $C_9H_7NO_2^+$). HRMS (EI) *m/z* 566.2316 (M^+, $C_{36}H_{30}N_4O_3^+$, calc. 566.2313).

(±)-Naphthalen-2-yl 2-(1-ethyl-6*H*,12*H*-5,11-methanoindolo[*6,5-c*][1,5]benzodiazocin-8-yl)-3-methylbenzoate ((±)-4). A flame-dried *Schlenk* tube was charged under Ar with (±)-**8** (150.0 mg, 0.35 mmol), naphthalene-2-ol (153.0 mg, 1.06 mmol), and BOP (313.0 mg, 0.71 mmol) in dry CH_2Cl_2 (12 mL). NEt_3 (287.0 mg, 2.84 mmol) was added dropwise via syringe and the reaction mixture stirred for 40 h at 24 °C. The solvents were evaporated, and the residue was taken up in CH_2Cl_2 (50 mL). The organic phase was washed with saturated aqueous NaCl solution, dried ($MgSO_4$),

and concentrated on a rotary evaporator. Column chromatography (CH_2Cl_2/MeOH, 500/1 to 200/1) yielded (±)-**4** (92.3 mg, 48%) as a colorless foam. m.p. 119–121 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73–7.82 (m, 2 H), 7.68 (d, J = 7.5, 0.5 H), 7.39–7.51 (m, 4 H), 7.33–7.37 (m, 1 H), 7.29–7.33 (m, 1.5 H), 7.11–7.24 (m, 3 H), 7.05 (d, J = 3.1, 0.5 H), 6.81–6.93 (m, 2.5 H), 6.41/6.50 (d, J = 3.1, 1 H), 6.10 (d, J = 8.8, 0.5 H), 5.60 (dd, J = 2.1, 8.9, 0.5 H), 4.78–4.98 (m, 2 H, -CH_aH$_b$N-), 4.21–4.48 (m, 4 H, -NCH_2N-, -CH$_a$$H_b$N-), 4.02–4.11 (m, 2 H, CH_2CH$_3$), 2.09/2.18 (s, 3 H, ArCH_3), 1.38/1.43 (t, J = 7.2, 3 H, CH$_2$CH_3). ^{1}H NMR (500 MHz, C_6D_6) δ 7.85/7.89 (d, J = 7.4, 1 H, H10), 7.32/7.53 (d, J = 7.9, 1 H, H6″), 7.26/7.62 (d, J = 7.7, 1 H, H5″), 7.25 (d, J = 2.3, H1″), 7.13–7.26 (m, 3 H, H4, H7″, H8″), 7.08 (d, J = 7.6, 1 H, H9), 6.99–7.13 (m, 3 H, H4′, H5′, H6′), 6.75 (d, J = 1.7, 1 H, H7), 6.60/6.81 (d, J = 3.1, 1 H, H2), 6.44/6.46 (s, 1 H, H13), 6.41/6.52 (d, J = 3.0, 1 H, H3), 6.02/7.48 (d, J = 8.9, 1 H, H4″), 5.75/7.07 (dd, J = 2.2, 8.8, 1 H, H3″), 4.74/4.79 (d, J = 16.5, 1 H, H12$_{endo}$), 4.54/4.55 (d, J = 17.0, 1 H, H6$_{endo}$), 4.07–4.39 (m, 4 H, H6$_{exo}$, H12$_{exo}$, H14), 3.32/3.48 (q, J = 7.2, 2 H, CH_2CH$_3$), 1.72/2.08 (s, 3 H, CH_3), 0.81/0.93 (t, J = 7.2, 3 H, CH$_2$CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 67.8/168.3, 147.9, 147.7/148.3, 147.6, 140.6/141.0, 137.5/137.6, 135.5/135.6, 133.6/133.7, 133.2/133.9, 133.1/133.3, 132.0/132.1, 131.0/131.4, 129.1/129.2, 128.3/128.5, 128.0/128.1, 127.7, 127.6, 127.4, 127.2/127.3, 127.0/127.1, 126.8/126.9, 126.0/126.5, 125.6, 125.0, 124.8, 121.7/122.0, 119.8/120.8, 118.2/118.3, 116.5/116.6, 106.4/106.5, 100.4/101.0, 67.1/67.2 (-NCH$_2$N-), 59.6/59.7 (-CH$_2$N-), 59.3/59.4 (-CH$_2$N-), 40.9/41.0 (CH$_2$CH$_3$), 20.7/20.8 (ArCH$_3$), 15.4 (CH$_2$CH$_3$). IR (neat) $\tilde{\nu}$ 3055, 3020, 2973, 2936, 2890, 2846, 1730, 1630, 1600, 1561, 1500, 1477, 1462, 1359, 1341, 1277, 1239, 1214, 1172, 1153, 1125, 1100, 1081, 1055, 1003, 961, 934, 872, 839, 807, 761, 749, 727, 713, 683. MS (EI) m/z 549.2 (45, M^+). HRMS (EI) m/z 549.2411 (M^+, $C_{37}H_{31}N_3O_2^+$, calc. 549.2411).

1. Bisson AP, Hunter CA, Morales JC, Young K (1998) Cooperative interaction in a ternary mixture. *Chem Eur J* 4:845–851.
2. Fisher MJ, *et al.* (1999) Fused Bicyclic Gly-Asp β-turn mimics with specific affinity for GPIIb-IIIa. *J Med Chem* 42:4875–4889.
3. Fischer FR, Schweizer WB, Diederich F (2007) Molecular torsion balances: evidence for favorable orthogonal dipolar interactions between organic fluorine and amide groups. *Angew Chem Int Ed* 46:8270–8273.

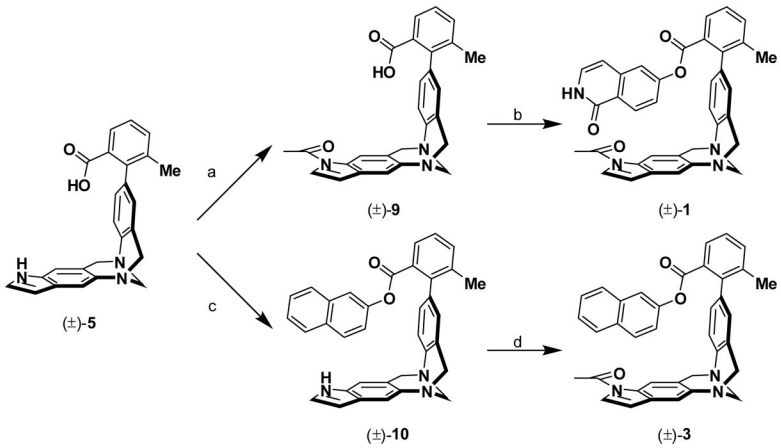

Fig. S1. Synthesis of the molecular torsion balances (±)-1 and (±)-3 starting from the common carboxylic acid precursor (±)-5. (*a*) Ac_2O, DMAP, NEt_3, CH_2Cl_2, 24 °C, 72 h, 60%. (*b*) 6-Hydroxyisoquinolin-1(2*H*)-one, BOP, NEt_3, CH_2Cl_2, 24 °C, 45 h, 50%. (*c*) Naphthalen-2-ol, BOP, NEt_3, CH_2Cl_2, 24 °C, 72 h, 72%. (*d*) Ac_2O, DMAP, NEt_3, CH_2Cl_2, 24 °C, 72 h, 68%. DMAP, 4-*N*,*N*-(dimethylamino)pyridine; BOP, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate.

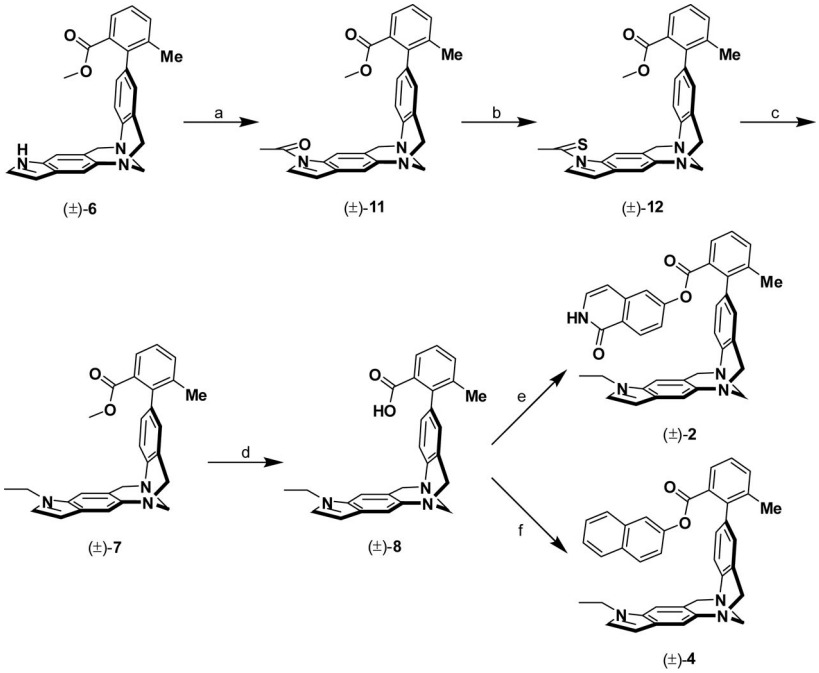

Fig. S2. Synthesis of the molecular torsion balances (±)-2 and (±)-4 starting from the common methyl benzoate precursor (±)-6. (*a*) Ac_2O, DMAP, NEt_3, CH_2Cl_2, 24 °C, 16 h, 86%. (*b*) Lawesson's reagent, PhMe, 100 °C, 20h, 63%. (*c*) RaNi, THF, 24 °C, 25 min, 98%. (*d*) LiOH, MeOH, H_2O, 50 °C, 17 h, 93%. (*e*) 6-Hydroxyisoquinolin-1(2*H*)-one, BOP, NEt_3, CH_2Cl_2, 24 °C, 45 h, 29%. (*f*) Naphthalen-2-ol, BOP, NEt_3, CH_2Cl_2, 24 °C, 72 h, 48%. RaNi, Raney nickel.

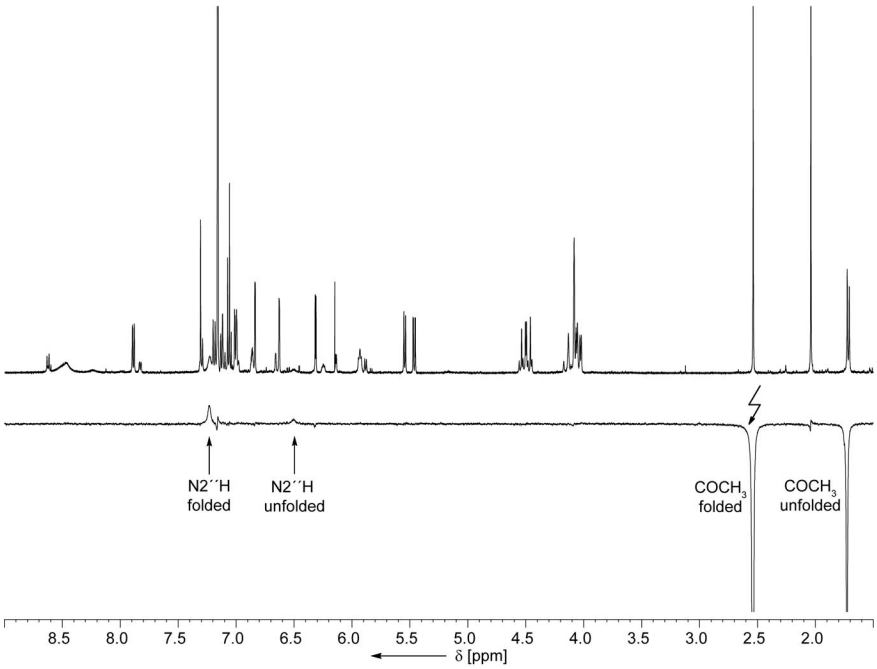

Fig. S3. ^{1}H NOE difference spectrum of (±)-1 in C_6D_6 proving the proximity between the $COCH_3$ group and the isoquinolin-1(2*H*)-one N2′′H in the folded conformation.

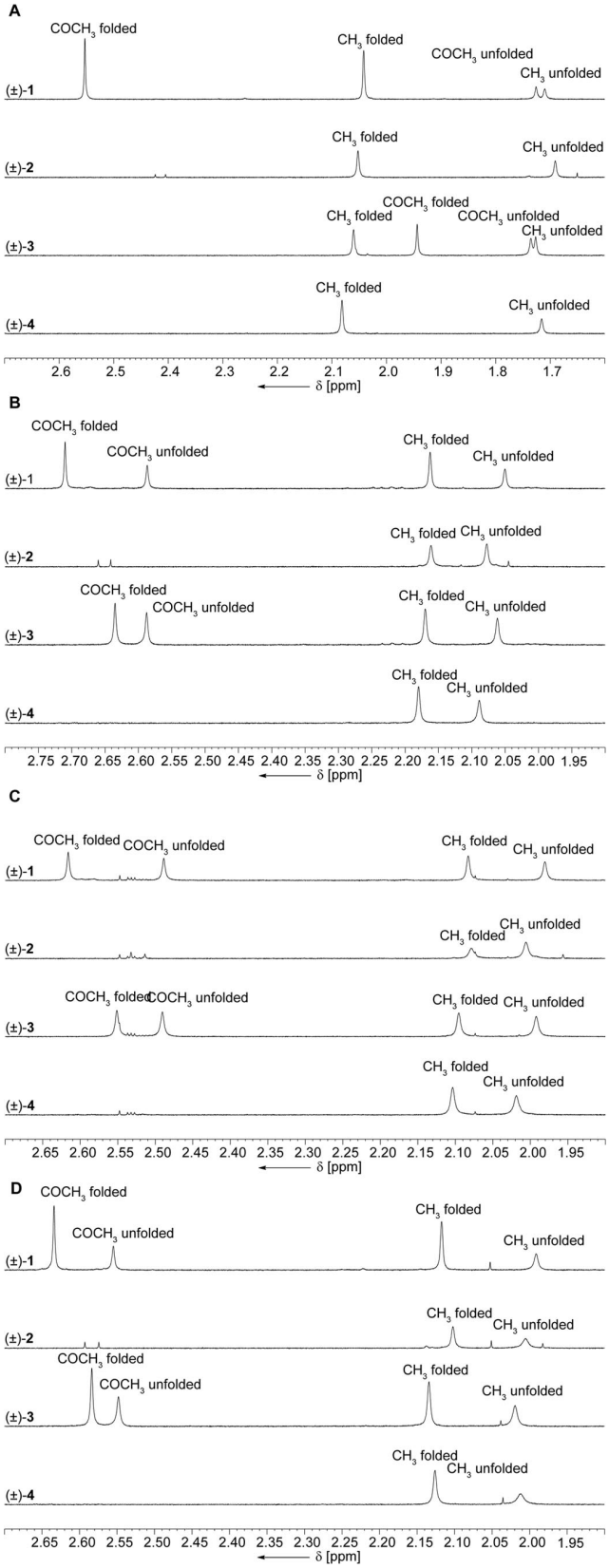

Fig. S4. ^{1}H NMR spectra of (±)-1, (±)-2, (±)-3, and (±)-4 as 2 mM solutions in C_6D_6 (*A*), $CDCl_3$ (*B*), $C_2D_2Cl_4$ (*C*), and CD_2Cl_2 (*D*) acquired at 298 K.

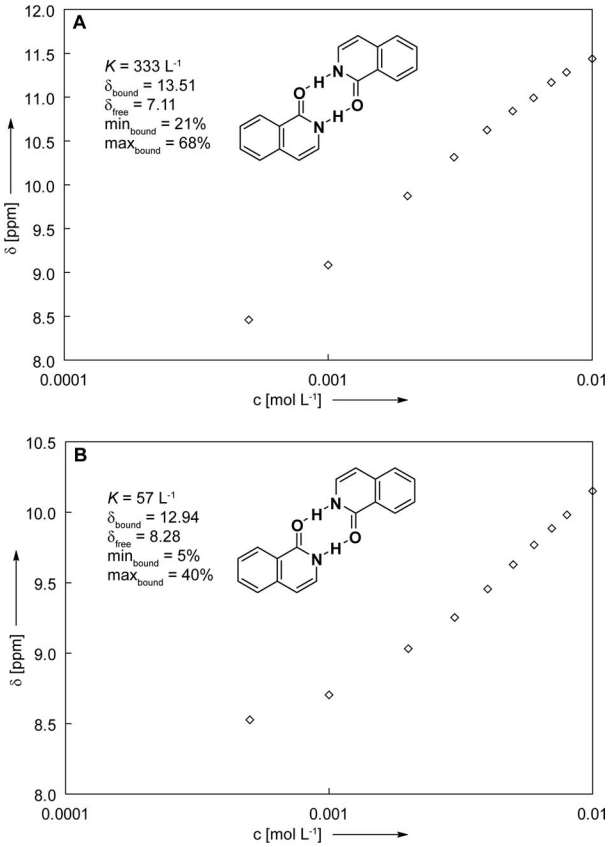

Fig. S5. Dilution study of isoquinolin-1(2*H*)-one in C_6D_6 (*A*) and $CDCl_3$ (*B*). The shift of the NH resonance signal was monitored by ^1H NMR spectroscopy.

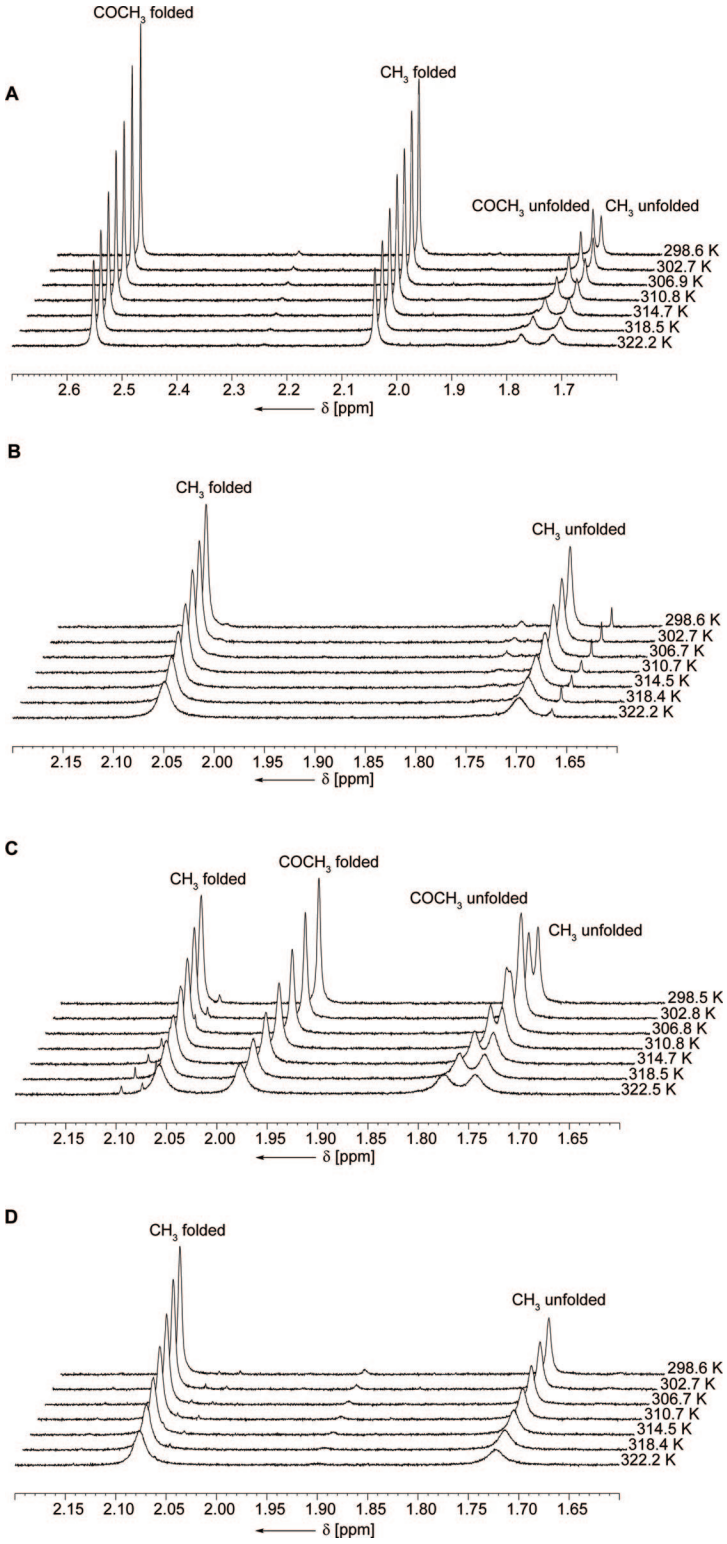

Fig. S6. ^{1}H NMR spectra of (±)-1 (*A*), (±)-2 (*B*), (±)-3 (*C*), and (±)-4 (*D*) as 2 mM solution in C_6D_6 at variable temperatures.

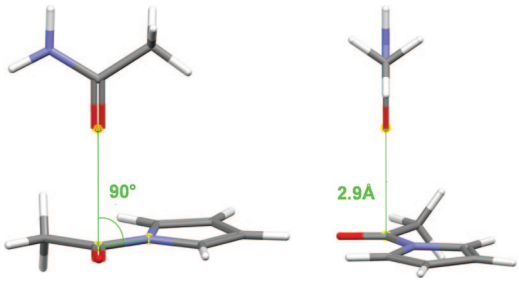

Fig. S7. Views of the acetamide/*N*-acetylpyrrole dimer geometry used for IMPT intermolecular interaction calculations. Color code: red, oxygen; blue, nitrogen; gray, carbon; white, hydrogen.

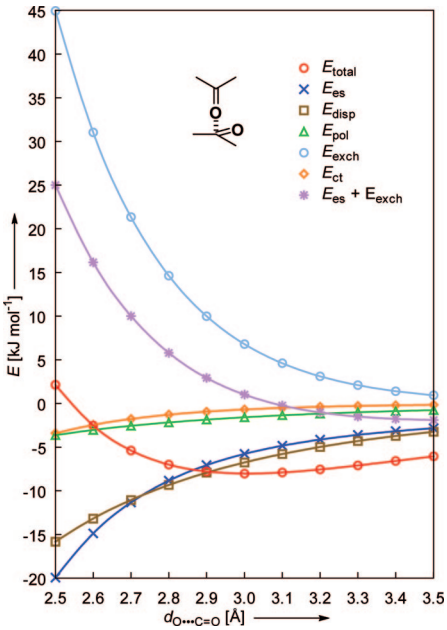

Fig. S8. Ab initio-based molecular orbital calculations (6–31G**) using intermolecular perturbation theory (IMPT) applied to an orthogonal propan-2-one dimer.