Supporting Information

Table of contents

Materials and General Synthetic Procedures. *p*-Nitrophenyl phosphate (*p*NPP) was purchased from Fluke Co. For organic synthesis, reagents were used as purchased (Aldrich, Acros, Alfa Aesar, TCI), except where noted. ^{1}H and ^{13}C NMR spectra were obtained on Brucker 500 spectrometers with TMS or residual solvent as standard. All column chromatography was performed using Dynamic Adsorbents 230-400 mesh silica gel (SiO_2) with the indicated solvent system unless otherwise noted. TLC analysis was performed using 254 nm glass-backed plates and visualized using UV light (254 nm), low-resolution mass spectra and purity data were obtained using an Agilent Technologies 6130 Quadrupole LC/MS. HPLC purification was carried out on a Waters Delta 600 equipped with a Sunfire Prep C18 OBD column (30 mm*150 mm, 5μm) with methanol-water (both containing 0.1% TFA) as mobile phase. The purity of all final tested compounds was established to be > 98% by Agilent Technologies 6130 Quadrupole LC/MS (UV, λ = 254 nm).

Methyl 4-amino-2-hydroxybenzoate (**2**). Concentrated sulfuric acid (10 mL) was added to a solution of 4-aminosalicylic acid (30.6 g, 0.2 mol) in methanol (500 mL). The reaction mixture was then heated to reflux for 24 h, after which the solvent was removed. The residue was partitioned between EtOAc (1 L) and water (1 L). The organic phase was dried over Na_2SO_4 and evaporated to provide pale solid **2** (27.7 g, 81.4%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.23 (m, 2H), 6.59 (m, 1H), 5.38 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 142.8, 142.2, 116.2, 114.3, 112.6, 51.3; HRMS (ESI): $(M+H)^+$ calcd for $C_8H_{10}NO_3$: 168.0655, found: 168.0657; LC-MS (ESI): 168.0 $(M+H)^+$; Purity: >98% (UV, λ = 254 nm).

Methyl 4-(dimethylamino)-2-hydroxybenzoate (**3**). $NaCNBH_3$ (31.4 g, 0.5 mol) in 200 mL of THF was added dropwise to a solution of **2** (16.7 g, 0.1 mol), 37% formaldehyde (81 mL, 1 mol), Acetic acid (50 mL) and THF (200 mL) under ice bath. The mixture was stirred at room temperature overnight. The mixture was poured to saturated $NaHCO_3$ (250 ml) and then the pH was adjusted by 10% NaOH solution to 7. The organic phase was washed with brine, and dried over Na_2SO_4. After evaporation, the residue was purified by silica gel column chromatography (Hexane / EtOAc = 16:1) to afford **3** (37 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.93 (s, 1H), 7.63 (d, J = 9.05 Hz, 1H), 6.19 (dd, J = 9.05, 2.5 Hz, 1H), 6.11 (d, J = 2.5

Hz, 1H), 3.86 (s, 3H), 2.99 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.67, 163.27, 155.61, 131.01, 104.13, 100.82, 97.87, 51.53, 39.93. HRMS (ESI): $(M+H)^+$ calcd for $C_{10}H_{14}NO_3$: 196.0968, found: 196.0964; LC-MS (ESI): 196.0 $(M+H)^+$; Purity: >98% (UV, λ = 254 nm).

Methyl 4-(dimethylamino)-2-hydroxy-5-iodobenzoate (**4**). A solution of iodine (2.9 g, 11.4 mmol) in ether (15 mL) was added dropwise to a mixture of compound **3** (2.5 g, 12.8 mmol), K_2CO_3 (2.6 g, 18.8 mmol) and water (15 mL) at room temperature over 2 h. The reaction mixture was then stirred at r.t. for 4h. The reaction mixture was extracted with diethyl ether. The organic fractions were washed with brine, dried over Na_2SO_4 and concentrated in vacuum. Purification by flash silica chromatography (Hexane / EtOAc = 60:1) afforded compound **4** (1.73 g, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.73 (s, 1H), 8.22 (s, 1H), 6.55 (s, 1H), 3.91 (s, 3H), 2.84 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.28, 162.82, 161.29, 141.68, 108.55, 108.11, 80.07, 52.24, 44.26. HRMS (ESI): $(M+H)^+$ calcd for $C_{10}H_{13}INO_3$: 321.9935, found: 321.9936; LC-MS (ESI): 332.0 $(M+H)^+$; Purity: >98% (UV, λ = 254 nm).

General method for the synthesis of (**5a-l**). A mixture of Methyl 4-(dimethylamino)-2-hydroxy-5-iodobenzoate **4** (6.5 g, 20.2 mmol), corresponding phenylacetylene (30.4 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.288 g, 0.41 mmol) and CuI (0.155 g, 0.81 mmol) were loaded in a flask, which was degassed and back-filled with nitrogen. Solvent DMF (10 mL) and Et_3N (40.4 mmol) were added. The resulting mixture was stirred under a nitrogen atmosphere at room temperature from 4 h to overnight. The reaction was monitored by TLC to establish completion. The solution was partitioned between EtOAc (200 mL) and brine (4*200 mL). The organic residue was purified by flash silica chromatography (Hex/EtOAc = 60:1 then 40:1; 20:1) to afford pale solid **5a-l** (80%-90%).

Methyl 4-(dimethylamino)-2-hydroxy-5-((2-(trifluoromethyl)phenyl)ethynyl)benzoate (**5a**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.0 (s, 1H), 7.98 (s, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.52 (m, 1H), 7.41 (m, 1H), 6.33 (s, 1H), 3.93 (s, 6H), 3.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 162.9, 158.9, 138.0, 133.3, 131.3, 130.5 (q, J = 30.3 Hz), 127.4, 125.8 (m), 123.7 (q, J = 271.3 Hz), 122.2, 103.9, 103.5, 102.7, 94.4, 88.4, 52.0, 42.5; HRMS (ESI): $(M+H)^+$ calcd for $C_{19}H_{17}F_3NO_3$: 364.1155, found: 364.1157; LC-MS (ESI): 364.0 $(M+H)^+$, 362.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Methyl 4-(dimethylamino)-2-hydroxy-5-((3-(trifluoromethyl)phenyl)ethynyl)benzoate (**5b**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.97 (s, 1H), 7.99 (s, 1H), 7.74 (m, 1H), 7.66 (m, 1H), 7.57 (m, 1H), 7.48 (m, 1H), 6.35 (s, 1H), 3.94 (s, 3H), 3.16 (s, 6H); ^{13}C NMR (125 MHz, DMSO): δ 170.1, 162.7, 159.7, 137.1, 134.7, 129.8 (q, J = 29.8 Hz), 129.5, 128.6, 124.9.1, 124.1 (q, J = 271.7 Hz), 119.1, 103.6, 103.5, 103.4, 92.0, 88.7, 62.4, 52.7, 43.1; HRMS (ESI): $(M+H)^+$ calcd for $C_{19}H_{17}F_3NO_3$: 364.1155, found: 364.1152; LC-MS (ESI): 364.0 $(M+H)^+$, 362.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Methyl 5-([1,1'-biphenyl]-4-ylethynyl)-4-(dimethylamino)-2-hydroxybenzoate (**5c**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.90 (s, 1H), 7.94 (s, 1H), 7.62-7.32 (m, 9H), 6.33 (s, 1H), 3.92 (s, 3H), 3.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 163.3, 160.0, 141.2, 140.6, 137.5, 133.5, 129.4, 128.9, 128.0, 127.2, 117.6, 103.9, 103.8, 102.2, 91.9, 89.5, 51.3, 42.2; HRMS (ESI): $(M+H)^+$ calcd for $C_{24}H_{22}NO_3$: 372.1594, found: 372.1599; LC-MS (ESI): 372.2 $(M+H)^+$; Purity: >98% (UV, λ = 254 nm).

Methyl 5-(cyclohexylethynyl)-4-(dimethylamino)-2-hydroxybenzoate (**5d**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.03 (s, 1H), 7.93 (s, 1H), 6.28 (s, 1H), 3.84 (s, 3H), 3.23 (s, 6H), 2.40 (m, 1H), 1.78 (m, 2H), 1.54 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 162.7, 158.3, 136.4, 104.1, 103.8, 103.0, 94.4, 75.9, 52.5, 42.2, 33.8, 24.2, 23.7, 22.8; HRMS (ESI): $(M+H)^+$ calcd for $C_{18}H_{24}NO_3$: 302.1751, found: 302.1747; LC-MS (ESI): 302.0 $(M+H)^+$, 300.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Methyl 4-(dimethylamino)-2-hydroxy-5-((4-(trifluoromethoxy)phenyl)ethynyl)benzoate (5**e**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.96 (s, 1H), 7.87 (s, 1H), 7.57 (m, 2H), 6.98 (m, 2H), 6.39 (s, 1H), 3.91 (s, 3H), 3.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 163.3, 159.5, 150.8, 136.5, 133.2, 128.8 (q, J = 255.6 Hz), 114.0, 111.8, 103.9, 103.8, 93.0, 87.9, 52.7, 42.2; HRMS (ESI): $(M+H)^+$ calcd for $C_{19}H_{17}F_3NO_4$: 380.1084, found: 380.1089; LC-MS (ESI): 380.0 $(M+H)^+$.

Methyl 4-(dimethylamino)-2-hydroxy-5-((4-(trifluoromethoxy)phenyl)ethynyl)benzoate (**5f**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.90 (s, 1H), 7.87 (s, 1H), 7.60 (m, 4H), 6.26 (s, 1H), 3.88 (s, 6H), 3.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 162.1, 158.7, 137.2, 132.6, 131.0 (q, J = 30.7 Hz), 124.3, 123.7 (q, J = 271.0 Hz), 123.2, 105.2, 102.5, 102.4, 92.6, 88.7, 52.2, 42.7; HRMS (ESI): $(M+H)^+$ calcd for $C_{19}H_{17}F_3NO_3$: 364.1155, found: 364.1150; LC-MS (ESI): 364.2 $(M+H)^+$, 362.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Methyl 4-(dimethylamino)-2-hydroxy-5-(phenylethynyl)benzoate (**5g**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.93 (s, 1H), 7.94 (s, 1H), 7.48 (m, 2H), 7.31 (m, 3H), 6.31 (s, 1H), 3.90 (s, 3H), 3.12 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.95, 162.79, 159.36, 137.37, 131.03, 128.46, 127.96, 124.02, 104.43, 104.07, 103.01, 92.64, 88.87, 51.98, 42.65; HRMS (ESI): $(M+H)^+$ calcd for $C_{18}H_{18}NO_3$: 296.1281, found: 296.1279; LC-MS (ESI): 296.0 $(M+H)^+$; Purity: >98% (UV, λ = 254 nm).

Methyl 4-(dimethylamino)-5-((3-fluorophenyl)ethynyl)-2-hydroxybenzoate (**5h**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.89 (s, 1H), 7.90 (s, 1H), 7.40 (m, 2H), 7.17 (m, 2H), 6.29 (s, 1H), 3.93 (s, 3H), 3.13 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 163.3, 161.9 (d, J = 241.8 Hz), 158.8, 136.6, 130.5, 127.2, 121.4, 119.5 (d, J = 21.9 Hz), 114.5 (d, J = 23.4 Hz), 104.9, 102.8, 102.7, 93.0, 89.2, 51.4, 41.7; HRMS (ESI): $(M+H)^+$ calcd for $C_{18}H_{17}FNO_3$: 314.1187, found: 314.1189; LC-MS (ESI): 314.0 $(M+H)^+$, 312.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Methyl 4-(dimethylamino)-5-((4-fluorophenyl)ethynyl)-2-hydroxybenzoate (**5i**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.98 (s, 1H), 7.99 (s, 1H), 7.58 (m, 2H), 7.14 (m, 2H), 6.34 (s, 1H), 3.93 (s, 3H), 3.15 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 163.0, 158.7, 158.6 (d, J = 240.9 Hz), 137.3, 134.5, 115.0 (d, J = 20.8 Hz), 114.9, 114.8, 102.9, 102.6, 93.3, 89.5, 51.3, 42.3; HRMS (ESI): $(M+H)^+$ calcd for $C_{18}H_{17}FNO_3$: 314.1187, found: 314.1193; LC-MS (ESI): 314.0 $(M+H)^+$, 312.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Methyl 4-(dimethylamino)-5-((2-fluorophenyl)ethynyl)-2-hydroxybenzoate (**5j**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.98 (s, 1H), 7.94 (s, 1H), 7.72 (m, 2H), 7.57 (m, 1H), 7.18 (m, 2H), 6.23 (s, 1H), 3.87 (s, 3H), 3.11 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 161.8, 160.4 (d, J = 241.3 Hz), 160.1, 137.5, 132.9, 125.8, 123.1, 115.7, 105.6 (d, J = 21.5 Hz), 104.4, 103.1, 102.7, 91.8, 87.9, 51.6, 43.3; HRMS (ESI): $(M+H)^+$ calcd for $C_{18}H_{17}FNO_3$: 314.1187, found: 314.1180; LC-MS (ESI): 314.0 $(M+H)^+$, 312.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Methyl 4-(dimethylamino)-2-hydroxy-5-((3-hydroxyphenyl)ethynyl)benzoate (**5k**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.97 (brs, 1H), 7.91 (s, 1H), 7.16 (m, 1H), 7.02 (m, 1H), 6.95 (s, 1H), 6.79 (m, 1H), 6.29 (s, 1H), 3.89 (s, 3H), 3.08 (s, 6H); HRMS (ESI): $(M+H)^+$ calcd for $C_{18}H_{18}NO_4$: 311.3319, found: 311.3319; LC-MS (ESI): 312.2 $(M+H)^+$, 310.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Methyl 4-(dimethylamino)-2-hydroxy-5-((3-aminophenyl)ethynyl)benzoate (**5l**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.03 (s, 1H), 8.01 (s, 1H), 6.99 (m, 2H), 6.69 (m, 1H), 6.48 (m, 1H), 6.37 (s, 1H), 3.98 (s, 3H), 3.17 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 161.8, 159.6, 146.4, 136.6, 129.8, 122.2, 121.2, 120.7, 113.7, 104.2, 103.4, 102.7, 93.3, 89.4, 52.5, 43.5; HRMS (ESI): $(M+H)^+$ calcd for $C_{18}H_{19}N_2O_3$: 310.3471, found: 310.3471; LC-MS (ESI): 311.2 $(M+H)^+$, 309.2 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

General method for the synthesis of (**6a-l**). To a solution of **5a-l** (17.6 mmol) in CH_2Cl_2 (100 mL) was added iodine (8.9 g, 35 mmol). The resulting mixture was stirred at room temperature for 4 h, then added CH_2Cl_2 (100 mL) and washed with saturated aqueous Na_2SO_3 solution (3 × 50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (Hex/EtOAc = 60:1 then 40:1; 20:1) to afford pale solid **6a-l** (80%-90%).

Methyl 6-hydroxy-3-iodo-1-methyl-2-(2-(trifluoromethyl)phenyl)-1H-indole-5-carboxylate (**6a**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.88 (brs, 1H), 8.02 (s, 1H), 7.86 (d, J = 7.4 Hz, 1H), 7.69 (m, 2H), 7.39 (d, J = 7.4 Hz, 1H), 6.82 (s, 1H), 3.97 (s, 3H), 3.38 (s, 3H); HRMS (ESI): $(M-H)^-$ calcd for $C_{18}H_{12}F_3INO_3$: 473.9819, found: 473.9828; LC-MS (ESI): 476.0 $(M+H)^+$, 474.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Methyl 6-hydroxy-3-iodo-1-methyl-2-(3-(trifluoromethyl)phenyl)-1H-indole-5-carboxylate (6b). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.93 (s, 1H), 8.05 (s, 1H), 7.76 (m, 2H), 7.68 (m, 2H), 6.87 (s, 1H), 4.04 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 171.1, 158.4, 142.5, 140.9, 143.0, 131.9, 131.1 (q, J = 32.3 Hz), 129.1, 127.6 (d, J = 3.7 Hz), 125.6 (d, J = 3.5 Hz), 124.5, 123.9, 123.9 (q, J = 270.8 Hz), 107.8, 96.2, 60.8, 52.2, 32.2; HRMS (ESI): $(M-H)^-$ calcd for $C_{18}H_{12}F_3INO_3$: 473.9819, found: 473.9830; LC-MS (ESI): 476.0 $(M+H)^+$, 474.8 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Methyl 2-([1,1'-biphenyl]-4-yl)-6-hydroxy-3-iodo-1-methyl-1H-indole-5-carboxylate (6c). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.92 (s, 1H), 8.05 (s, 1H), 7.77 (m, 2H), 7.71 (m, 2H), 7.56 (m, 2H), 7.51 (m, 2H), 7.43 (m, 1H), 6.88 (s, 1H), 4.04 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 158.3, 142.6, 142.5, 141.6, 140.2, 131.1, 129.9, 128.9, 127.7, 127.18, 127.16, 124.3, 124.2, 107.6, 96.2, 60.0, 52.2, 32.2; HRMS (ESI): $(M-H)^-$ calcd for $C_{23}H_{17}INO_3$: 482.0258, found: 482.0269; LC-MS (ESI): 484.0 $(M+H)^+$; Purity: >98% (UV, λ = 254 nm).

Methyl 2-cyclohexyl-6-hydroxy-3-iodo-1-methyl-1H-indole-5-carboxylate (6d). ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.01 (s, 1H), 7.61 (s, 1H), 6.50 (s, 1H), 4.11 (s, 3H), 3.37 (s, 3H), 2.52 (m, 1H), 1.61 (m, 2H), 1.28 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 158.3, 141.2, 137.4, 124.7, 124.6, 113.9, 108.5, 61.1, 52.7, 37.6, 33.6, 31.5, 26.3, 24.7; HRMS (ESI): $(M-H)^-$ calcd for $C_{17}H_{19}INO_3$: 412.0415, found: 412.0427; LC-MS (ESI): 414.0 $(M+H)^+$, 412.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Methyl 6-hydroxy-3-iodo-1-methyl-2-(4-(trifluoromethoxy)phenyl)-1H-indole-5-carboxylate (6e). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.92 (s, 1H), 8.04 (s, 1H), 7.52 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 6.86 (s, 1H), 4.03 (s, 3H), 3.61 (s, 3H); HRMS (ESI): $(M-H)^-$ calcd for $C_{18}H_{12}F_3INO_4$: 489.9768, found: 489.9765; LC-MS (ESI): 492.0 $(M+H)^+$, 489.8 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Methyl 6-hydroxy-3-iodo-1-methyl-2-(4-(trifluoromethyl)phenyl)-1H-indole-5-carboxylate (6f). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.91 (s, 1H), 8.02 (s, 1H), 7.78 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 8.1 Hz, 2H), 6.84 (s, 1H), 4.01 (s, 3H), 3.59 (s, 3H);); ^{13}C NMR (125 MHz, DMSO): δ 171.1, 158.4, 142.5, 141.0, 134.7, 131.1, 130.8 (q, J = 32.5 Hz), 125.5, 124.5, 123.9, 123.9 (q, J = 270.8 Hz), 107.8, 96.2, 60.7, 52.2, 32.2; HRMS (ESI): $(M-H)^-$ calcd for $C_{18}H_{12}F_3INO_3$: 473.9819, found: 473.9830; LC-MS (ESI): 476.0 $(M+H)^+$, 474.8 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Methyl 6-hydroxy-3-iodo-1-methyl-2-phenyl-1 H-indole-5-carboxylate (6g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.88 (s, 1H), 7.96 (s, 1H), 7.45 (m, 5H), 6.78 (s, 1H), 3.98 (s, 3H), 3.54 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 158.3, 142.6,

142.5, 131.2, 130.8, 129.1, 128.6, 124.3, 124.2, 107.6, 96.2, 59.5, 52.2, 32.2; HRMS (ESI): $(M-H)^-$ calcd for $C_{17}H_{13}INO_3$: 405.9946, found: 405.9952; LC-MS (ESI): 408.0 $(M+H)^+$, 405.8 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Methyl 2-(3-fluorophenyl)-6-hydroxy-3-iodo-1-methyl-1H-indole-5-carboxylate (**6h**). ^1H NMR (500 MHz, DMSO): δ 10.96 (s, 1H), 8.04 (s, 1H), 7.32 (m, 3H), 7.06 (m, 1H), 6.85 (s, 1H), 4.03 (s, 3H), 3.58 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 171.7, 161.7 (d, J = 246.8 Hz), 157.5, 142.5, 139.1, 128.3, 127.9, 125.1, 123.1, 122.9, 116.4 (d, J = 22.3 Hz), 116.2 (d, J = 21.1 Hz), 107.3, 61.0, 51.8, 32.3; HRMS (ESI): $(M-H)^-$ calcd for $C_{17}H_{12}FINO_3$: 423.9851, found: 423.9862; LC-MS (ESI): 426.0 $(M+H)^+$, 423.8 $(M-H)^-$;Purity: >98% (UV, λ = 254 nm).

Methyl 2-(4-fluorophenyl)-6-hydroxy-3-iodo-1-methyl-1H-indole-5-carboxylate (**6i**). ^1H NMR (500 MHz, DMSO): δ 10.9 (s, 1H), 7.99 (s, 1H), 7.45 (m, 2H), 7.24 (m, 2H), 6.82 (s, 1H), 4.02 (s, 3H), 3.57 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 171.1, 163.0 (d, J = 247.9 Hz), 158.2, 142.4, 141.7, 132.6 (d, J = 8.3 Hz), 127.1 (d, J = 3.4 Hz), 124.2, 123.9, 115.7 (d, J = 21.6 Hz), 107.6, 96.2, 60.1, 52.2, 32.1; HRMS (ESI): $(M-H)^-$ calcd for $C_{17}H_{12}FINO_3$: 423.9851, found: 423.9860; LC-MS (ESI): 426.0 $(M+H)^+$, 423.8 $(M-H)^-$;Purity: >98% (UV, λ = 254 nm).

Methyl 2-(2-fluorophenyl)-6-hydroxy-3-iodo-1-methyl-1H-indole-5-carboxylate (**6j**). ^1H NMR (500 MHz, DMSO): δ 10.81 (s, 1H), 8.01 (s, 1H), 7.58 (m, 2H), 7.24 (m, 1H), 7.06 (m, 1H), 6.76 (s, 1H), 4.01 (s, 3H), 3.49 (s, 3H); HRMS (ESI): $(M-H)^-$ calcd for $C_{17}H_{12}FINO_3$: 423.9851, found: 423.9847; LC-MS (ESI): 426.0 $(M+H)^+$, 423.8 $(M-H)^-$;Purity: >98% (UV, λ = 254 nm).

Methyl 6-hydroxy-2-(3-hydroxyphenyl)-3-iodo-1-methyl-1H-indole-5-carboxylate (**6k**). ^1H NMR (500 MHz, DMSO): δ 10.92 (s, 1H), 8.07 (s, 1H), 7.17 (m, 3H), 6.82 (m, 1H), 6.91 (s, 1H), 4.00 (s, 3H), 3.54 (s, 3H); HRMS (ESI): $(M-H)^-$ calcd for $C_{17}H_{13}INO_4$: 421.9895, found: 421.9899; LC-MS (ESI): 424.0 $(M+H)^+$, 422.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Methyl 6-hydroxy-2-(3-aminophenyl)-3-iodo-1-methyl-1H-indole-5-carboxylate (**6l**). ^1H NMR (500 MHz, $CDCl_3$): δ 10.90 (s, 1H), 8.02 (s, 1H), 7.31 (m, 1H), 6.84 (s, 1H), 6.80 (m, 2H), 6.76 (m, 1H), 4.03 (s, 3H), 3.83 (brs, 2H), 3.60 (s, 3H); LC-MS (ESI): 423.0 $(M+H)^+$, 421.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

General method for the synthesis of (**7a-l**). Compound **6a-l** (1 mmol) was dissolved THF (2 mL) and methanol (2 mL). Then NaOH (2 mL, 3.5M) solution was added. The mixture was stirred under room temperature for 2 days, diluted by water to 50 mL, acidified to pH 3, and extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with

brine (50 mL), dried over sodium sulfate and concentrated in vacuum. This crude product was purified by Pre-HPLC as describe to give pale solid **7a-l** (yield 50-80%).

6-hydroxy-3-iodo-1-methyl-2-(2-(trifluoromethyl)phenyl)-1H-indole-5-carboxylic acid (**7a**). ^{1}H NMR (500 MHz, DMSO): δ 11.4 (brs, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.88 (m, 1H), 7.86 (s, 1H), 7.80 (m, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.04 (s, 1H), 3.39 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 173.0, 158.3, 141.8, 140.1, 134.1, 133.3, 131.1, 130.1, 129.6 (q, J = 29.6 Hz), 126.9 (m), 124.0 (q, J = 272.3 Hz), 123.8, 123.4, 108.1, 96.9, 62.4, 32.2; HRMS (ESI): $(M-H)^-$ calcd for $C_{17}H_{10}F_3INO_3$: 459.9663, found: 459.9676; LC-MS (ESI): 462.0 $(M+H)^+$, 460.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

6-hydroxy-3-iodo-1-methyl-2-(3-(trifluoromethyl)phenyl)-1H-indole-5-carboxylic acid (**7b**). ^{1}H NMR (500 MHz, DMSO): δ 13.90 (br, 1H), 11.46 (br, 1H), 7.90-7.81 (m, 5H), 7.07 (s, 1H), 3.61 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 173.0, 158.4, 142.6, 141.2, 135.1, 132.2, 130.2, 129.9 (q, J = 31.6 Hz), 127.7, 126.0, 124.4 (q, J = 270.5 Hz), 124.2, 123.7, 108.3, 97.1, 61.8, 31.7; HRMS (ESI): $(M-H)^-$ calcd for $C_{17}H_{10}F_3INO_3$: 459.9663, found: 459.9664; LC-MS (ESI): 462.0 $(M+H)^+$, 460.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

2-([1,1'-biphenyl]-4-yl)-6-hydroxy-3-iodo-1-methyl-1H-indole-5-carboxylic acid (**7c**). ^{1}H NMR (500 MHz, DMSO): δ 7.86 (m, 3H), 7.79 (m, 2H), 7.63 (m, 2H), 7.52 (m, 2H), 7.42 (m, 1H), 7.06(s, 1H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 173.0, 158.3, 142.6, 142.5, 140.9, 139.7, 131.6, 130.1, 129.5, 128.3, 127.2, 127.1, 124.0, 123.9, 108.0, 97.0, 60.9, 32.6; HRMS (ESI): $(M-H)^-$ calcd for $C_{22}H_{15}INO_3$: 468.0102, found: 468.0117; LC-MS (ESI): 470.0 $(M+H)^+$, 468.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

2-cyclohexyl-6-hydroxy-3-iodo-1-methyl-1H-indole-5-carboxylic acid (**7d**). ^{1}H NMR (500 MHz, DMSO): δ 13.8 (br, 1H), 11.25 (brs, 1H), 7.73 (s, 1H), 6.96 (s, 1H), 3.72 (s, 3H), 2.98 (m, 1H), 2.02 (m, 2H), 1.85-1.72 (m, 4H), 1.44-1.23 (m, 4H); HRMS (ESI): $(M-H)^-$ calcd for $C_{16}H_{17}INO_3$: 398.0258, found: 398.0255; LC-MS (ESI): 400.0 $(M+H)^+$, 398.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

6-hydroxy-3-iodo-1-methyl-2-(4-(trifluoromethoxy)phenyl)-1H-indole-5-carboxylic acid (**7e**). ^{1}H NMR (500 MHz, DMSO): δ 13.76 (br, 1H), 11.43 (br, 1H), 7.86 (s, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.05 (s, 1H), 3.59 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 173.0, 158.4, 149.0, 142.5, 141.5, 133.2, 130.4, 124.1, 123.7, 121.4, 120.5 (q, J = 255.2 Hz), 108.2, 97.1, 61.3, 32.6; HRMS (ESI): $(M-H)^-$ calcd for $C_{17}H_{10}F_3INO_4$: 475.9612, found: 475.9608; LC-MS (ESI): 478.0 $(M+H)^+$, 475.8 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

6-hydroxy-3-iodo-1-methyl-2-(4-(trifluoromethyl)phenyl)-1H-indole-5-carboxylic acid (**7f**). ^{1}H NMR (500 MHz, DMSO): δ 13.90 (br, 1H), 11.46 (br, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.87 (s, 1H), 7.78 (d, J = 8.1 Hz, 2H), 7.06 (s, 1H), 3.61 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 173.0, 158.5, 142.7, 141.3, 135.3, 131.9, 129.5 (q, J = 31.6 Hz), 125.9, 124.6 (q, J = 270.8 Hz), 124.3, 123.8, 108.3, 97.1, 61.7, 32.6; HRMS (ESI): $(M-H)^-$ calcd for $C_{17}H_{10}F_3INO_3$: 459.9663, found: 459.9679; LC-MS (ESI): 462.0 $(M+H)^+$, 460.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

6-hydroxy-3-iodo-1-methyl-2-phenyl-1H-indole-5-carboxylic acid (**7g**). ^{1}H NMR (500 MHz, DMSO): δ 13.78 (br, 1H), 11.36 (br, 1H), 7.85 (s, 1H), 7.58-7.49 (m, 5H), 7.04 (s, 1H), 3.54 (s, 3H); HRMS (ESI): $(M-H)^-$ calcd for $C_{16}H_{12}INO_3$: 391.9789, found: 391.9795; LC-MS (ESI): 392.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

2-(3-fluorophenyl)-6-hydroxy-3-iodo-1-methyl-1H-indole-5-carboxylic acid (**7h**). ^{1}H NMR (500 MHz, DMSO): δ 13.78 (br, 1H), 11.37 (br, 1H), 7.86 (s, 1H), 7.63-7.59 (m, 1H), 7.41-7.36 (m, 3H), 7.05 (s, 1H), 3.60 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 173.0, 162.3 (d, J = 242.9 Hz), 158.4, 142.5, 141.5, 133.4 (d, J = 8.3 Hz), 131.1 (d, J = 8.6 Hz), 127.4, 124.1, 123.7, 117.9 (d, J = 22.2 Hz), 116.3 (d, J = 20.6 Hz), 108.2, 97.0, 61.3, 32.5; HRMS (ESI): $(M-H)^-$ calcd for $C_{16}H_{10}FINO_3$: 409.9695, found: 409.9716; LC-MS (ESI): 412.0 $(M+H)^+$, 410.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

2-(4-fluorophenyl)-6-hydroxy-3-iodo-1-methyl-1H-indole-5-carboxylic acid (**7i**). ^{1}H NMR (500 MHz, DMSO): δ 13.74 (br, 1H), 11.46 (br, 1H), 7.84 (s, 1H), 7.58 (m, 2H), 7.41 (m, 2H), 7.04 (s, 1H), 3.58 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 173.0, 162.8 (d, J = 245.0 Hz), 158.3, 142.4, 140.0, 133.4 (d, J = 8.6 Hz), 127.6, 123.9, 123.7, 116.1 (d, J = 21.6 Hz), 108.0, 97.0, 61.0, 32.5; HRMS (ESI): $(M+H)^+$ calcd for $C_{16}H_{12}FINO_3$: 411.9841, found: 411.9828; HRMS (ESI): $(M-H)^-$ calcd for $C_{16}H_{10}FINO_3$: 409.9695, found: 409.9711; LC-MS (ESI): 412.0 $(M+H)^+$, 410.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

2-(2-fluorophenyl)-6-hydroxy-3-iodo-1-methyl-1H-indole-5-carboxylic acid (**7j**). ^{1}H NMR (500 MHz, DMSO): δ 13.6 (br, 1H), 11.5 (br, 1H), 7.88 (s, 1H), 7.62-7.38 (m, 4H), 7.04 (s, 1H), 3.54 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 173.0, 160.6 (d, J = 245.3 Hz), 158.4, 142.2, 137.5, 133.7, 132.4 (d, J = 8.3 Hz), 125.2, 124.0, 123.7, 119.1 (d, J = 15.2 Hz), 116.5 (d, J = 21.3 Hz), 108.2, 96.9, 62.5, 32.1; HRMS (ESI): $(M+H)^+$ calcd for $C_{16}H_{12}FINO_3$: 411.9841, found: 411.9828; LC-MS (ESI): 412.0 $(M+H)^+$, 410.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

6-hydroxy-2-(3-hydroxyphenyl)-3-iodo-1-methyl-1H-indole-5-carboxylic acid (**7k**). ^{1}H NMR (500 MHz, DMSO): δ 13.75 (br, 1H), 11.35 (brs, 1H), 9.75 (brs, 1H), 7.84 (s, 1H), 7.35 (m, 1H), 7.02 (s, 1H), 6.89 (m, 3H), 3.66 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 173.0, 158.2, 157.7, 143.0, 142.4, 132.2, 130.1, 123.9, 123.8, 121.5, 117.8, 116.4, 107.9, 97.0,

60.3, 23.5; HRMS (ESI): $(M-H)^-$ calcd for $C_{16}H_{11}INO_4$: 407.9738, found: 407.9748; LC-MS (ESI): 410.0 $(M+H)^+$, 407.8 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

6-hydroxy-2-(3-aminophenyl)-3-iodo-1-methyl-1H-indole-5-carboxylic acid (**7l**). ^{1}H NMR (500 MHz, DMSO): δ 7.85 (s, 1H), 7.47 (m, 1H), 7.14 (m, 3H), 7.04 (s, 1H), 3.58 (s, 3H); LC-MS (ESI): 409.0 $(M+H)^+$, 407.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Methyl 3-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-6-hydroxy-1-methyl-2-(2-(trifluoromethyl) phenyl)-1H-indole-5-carboxylate (**8**). A mixture of **6a** (180 mg, 0.38 mmol), tert-butyl prop-2-yn-1-ylcarbamate (117 mg, 0.76 mmol) and bis(triphenylphosphine)palladium(II) chloride (27 mg, 0.04 mmol) and CuI (15.2 mg, 0.08 mmol) were loaded in a flask, which was degassed and back-filled with nitrogen. Solvent DMF (5 mL) and Et_3N (0.76 mmol) were added. The resulting mixture was stirred under a nitrogen atmosphere at room temperature overnight. The reaction was monitored by TLC to establish completion. The solution was partitioned between EtOAc (200 mL) and water (3*200 mL). The organic residue was purified by flash silica chromatography (Hex/EtOAc = 8:1, then 4:1) to afford viscous oil **8** (130 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.88 (s, 1H), 8.24 (s, 1H), 7.85 (m, 1H), 7.66 (m, 2H), 7.43 (m, 1H), 7.19 (m, 1H), 6.82 (s, 1H), 4.04 (m, 2H), 3.99 (s, 3H), 3.33 (s, 3H), 1.44 (s, 9H); HRMS (ESI): $(M+H)^+$ calcd for $C_{26}H_{26}F_3N_2O_5$: 503.1789, found: 503.1797; LC-MS (ESI): 525.0 $(M+Na)^+$, 501.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

3-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-6-hydroxy-1-methyl-2-(2-(trifluoromethyl)phenyl)-1H-indole-5-carboxylic acid (**9**). Compound **8** (130 mg, 0.26 mmol) was dissolved in THF (3 mL) and methanol (1 mL). Then 20% NaOH (2 mL) solution was added. The mixture was stirred under room temperature for 2 days, then diluted by water to 50 mL, acidified to pH 3, and extracted with EtOAc (3*100 mL). The organic layers were combined, washed with brine, dried over sodium sulfate and concentrated in vacuum. This crude product was purified by Pre-HPLC as describe to give pale solid **9** (110 mg, 87%). ^{1}H NMR (500 MHz, DMSO): δ 10.67 (s, 1H), 8.10 (s, 1H), 7.95 (m, 1H), 7.81 (m, 2H), 7.59 (m, 1H), 7.23 (m, 1H), 7.10 (s, 1H), 3.95 (s, 3H), 3.82 (m, 2H), 1.38 (s, 9H); HRMS (ESI): $(M+H)^+$ calcd for $C_{25}H_{24}F_3N_2O_5$: 489.1632, found: 489.1645; LC-MS (ESI): 511 $(M+Na)^+$, 487.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

3-(3-aminopropanoyl)-6-hydroxy-1-methyl-2-(2-(trifluoromethyl)phenyl)-1H-indole-5-carboxylic acid (**10**). Compound **9** (110 mg, 0.226 mmol) was dissolved in CH_2Cl_2 (5 mL) and then TFA (1 mL) was added to the solution under room temperature overnight. The solution was concentrated in vacuum. This crude product was purified by Pre-HPLC as describe to give pale solid **10** as TFA salt (102 mg, 91.5%).^{1}H NMR (500 MHz, DMSO): δ 8.74 (s, 1H), 8.02 (m, 1H), 7.87 (m, 2H), 7.68 (m, 2H), 6.94 (s, 1H), 3.31 (s, 3H), 2.94 (m, 2H), 2.61 (m, 2H); ^{13}C NMR (125 MHz, DMSO): δ 192.2, 173.2, 158.9

(q, J = 34.9 Hz, CF_3COOH), 158.5, 143.9, 141.5, 133.7, 132.8, 131.5, 129.5, 128.5 (q, J = 29.5 Hz), 127.4 (m), 125.3, 123.9 (q, J = 272.2 Hz), 119.0, 116.6 (q, J = 292.0 Hz, CF_3COOH), 115.6, 109.9, 97.3, 38.0, 34.5, 31.3; HRMS (ESI): $(M+H)^+$ calcd for $C_{20}H_{18}F_3N_2O_4$: 407.1213, found: 407.1218; LC-MS (ESI): 407.2 $(M+H)^+$, 405.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Procedure for the assembling of Library 11: Compound **10** (10 mM) in DMF (4 μL) reacted with 102 acids (0.1 M) (Figure 3a, 3b) in DMF (4 μL) respectively in the presence of HOBT (10 mM, 4 μL), HBTU (10 mM, 4 μL) and TEA (20 mM, 4 μL) in DMF overnight to assemble the combinatorial amide library **11** in 96 well plates. 10 of the reactions were picked up randomly and monitored by LC-MS, which showed an average of 70% yield desired products.

General method for the synthesis of (11a-e). Compound **10** (33.2 mg, 0.066 mmol) dissolved in DMF (0.5 mL) was added to a solution of corresponding carboxylic acids (0.33 mmol), HOBT (12 mg, 0.079 mmol), HBTU (30 mg, 0.079 mmol), and TEA (18.36 μL, 0.132 mmol) in DMF (1 mL). The mixture was stirred under room temperature for 2 h, then diluted by water to 50 mL, acidified to pH 3, and extracted with EtOAc (2*50 mL). The organic layers were combined, washed with brine, dried over sodium sulfate and concentrated in vacuum. This crude product was purified by Pre-HPLC as described to give pale solid **11a-e** (50% - 70%).

3-(3-(3,5-dibromobenzamido)propanoyl)-6-hydroxy-1-methyl-2-(2-(trifluoromethyl)phenyl)-1H-indole-5-carboxylic acid (11a). ^{1}H NMR (500 MHz, DMSO): δ 13.82 (br, 1H), 11.44 (brs, 1H), 8.85 (s, 1H), 8.59 (m, 1H), 8.02 (m, 2H), 7.90-7.82 (m, 4H), 7.71 (m, 1H), 7.11 (s, 1H), 3.38 (m, 2H), 3.35 (s, 3H), 2.37 (m, 2H); ^{13}C NMR (125 MHz, DMSO): δ 193.5, 173.2, 163.6, 158.4, 143.3, 141.5, 138.4, 136.1, 133.6, 132.9, 131.3, 129.8, 129.5, 128.5 (q, J = 29.4 Hz), 127.3 (m), 125.4, 124.0 (q, J = 272.5 Hz), 122.9, 119.2, 116.3, 109.6, 97.2, 35.2, 31.3, 29.5; HRMS (ESI): $(M+H)^+$ calcd for $C_{27}H_{20}Br_2F_3N_2O_5$: 666.9686, found: 666.9682; LC-MS (ESI): 668.8 $(M+H)^+$, 666.8 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

6-hydroxy-3-(3-(3-iodobenzamido)propanoyl)-1-methyl-2-(2-(trifluoromethyl)phenyl)-1H-indole-5-carboxylic acid (11b). ^{1}H NMR (500 MHz, DMSO): δ 11.46 (br, 1H), 8.85 (s, 1H), 8.45 (m, 1H), 8.02 (m, 2H), 7.90-7.70 (m, 5H), 7.25 (m, 1H), 7.11 (s, 1H), 3.33 (s, 3H), 3.29 (m, 2H), 2.38 (m, 2H); HRMS (ESI): $(M+H)^+$ calcd for $C_{27}H_{21}F_3IN_2O_5$: 637.0442, found: 637.0448; LC-MS (ESI): 637.0 $(M+H)^+$, 634.8 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

6-hydroxy-3-(3-(2-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)acetamido)propanoyl)-1-methyl-2-(2-(trifluoromethyl)phenyl)-1H-indole-5-carboxylic acid (11c). ^{1}H NMR (500 MHz, DMSO): δ 11.44 (brs, 1H), 8.87 (s, 1H), 8.01 (m, 1H), 7.93-7.85 (m, 2H), 7.71 (m, 1H), 7.20 (m, 1H), 6.98 (s, 1H), 3.50 (s, 2H), 3.38 (m, 2H), 3.37 (s, 3H), 2.17 (m,

2H), 2.10 (m, 3H), 1.54 (m, 2H), 1.28 (m, 4H), 0.86 (m, 10H); HRMS (ESI): $(M+H)^+$ calcd for $C_{34}H_{38}BF_3N_2O_6$: 603.2677, found: 603.2685; LC-MS (ESI): 603.2 $(M+H)^+$, 601.2 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

3-(3-(2-(2-bromophenyl)-1H-benzo[d]imidazole-6-carboxamido)propanoyl)-6-hydroxy-1-methyl-2-(2-(trifluoromethyl)phenyl)-1H-indole-5-carboxylic acid (**11d**). ^{1}H NMR (500 MHz, DMSO): δ 11.46 (brs, 1H), 8.85 (s, 1H), 8.35 (m, 1H), 8.05 (s, 1H), 8.02 (m, 1H), 8.00-7.75 (m, 4H), 7.70-7.45 (m, 4H), 7.52 (m, 1H), 7.12 (s, 1H), 3.34 (s, 3H), 3.29 (m, 2H), 2.41 (m, 2H); HRMS (ESI): $(M+H)^+$ calcd for $C_{34}H_{25}BrF_3N_4O_5$: 705.0955, found: 705.0968; LC-MS (ESI): 705.0 $(M+H)^+$, 703.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

3-(3-acetamidopropanoyl)-6-hydroxy-1-methyl-2-(2-(trifluoromethyl)phenyl)-1H-indole-5-carboxylic acid (**11e**). ^{1}H NMR (500 MHz, DMSO): δ 11.44 (brs, 1H), 8.86 (s, 1H), 8.03 (m, 1H), 7.90 (m, 2H), 7.70 (m, 2H), 7.11 (s, 1H), 3.33 (s, 3H), 3.13 (m, 2H), 2.20 (m, 2H), 1.67 (s, 3H); HRMS (ESI): $(M+H)^+$ calcd for $C_{22}H_{20}F_3N_2O_5$: 448.1319, found: 448.1325; LC-MS (ESI): 449.0 $(M+H)^+$, 447.0 $(M-H)^-$; Purity: >98% (UV, λ = 254 nm).

Protein Expression and Purification: Briefly, pET28b-mPTPB (a generous gift from Dr. Christoph Grunder, University of California, Berkeley) was used to transform into E.coli BL21/DE3 and grown in LB medium containing 50 μg/ml kanamycin at 37°C to an OD600 of 0.5. Following the addition of IPTG to a final concentration of 20 μM, the culture was incubated at 20°C with shaking for additional 16 hr. The cells were harvested by centrifugation at 5000 rpm for 5 min at 4°C. The bacterial cell pellets were resuspended in 20 mM Tris, pH 7.9, 500 mM NaCl, 5 mM imidazole, and were lysed by passage through a French press cell at 1,200 p.s.i. twice. Cellular debris was removed by centrifugation at 16,000 rpm for 30 min at 4°C. The protein was purified form the supernatant using standard procedures of Ni-nitrilotriacetic acid-agarose (Qiagen) affinity purification. The protein eluted from Ni-NTA column was concentrated with an Amicon Ultra centrifugal filter device (Millipore) and the buffer was changed to 20 mM Tris, pH 7.5, 150 mM NaCl, 1 mM EDTA and 1 mM DTT. Protein concentration was determined using the Bradford dye binding assay (Bio-Rad) diluted according to the manufacturer's recommendations with bovine serum albumin as standard. The purified mPTPB were made to 20% glycerol and stored at -20°C.

Inhibition Study: The inhibition assays were performed at 25°C in 50 mM 3,3-dimethylglutarate buffer, pH 7.0, containing 1 mM EDTA with an ionic strength of 0.15M adjusted by NaCl. The salicylic acid based library was screened in a 96-well format at 1 μM compound concentration. The reaction was started by the addition of 5 μl of the enzyme to 195 μl of reaction mixture containing 2.5 mM (the Km value) of *p*NPP and various concentrations of the inhibitor. The reaction was

quenched after 5 min by the addition of 50 µl of 5M NaOH, and then 200 µl of reaction mixture was transferred to a 96-well plate. The absorbance at 405 nm was detected by a Spectra MAX340 microplate spectrophotometer (Molecular Devices). IC_{50} values were calculated by fitting the absorbance at 405 nm versus inhibitor concentration to the following equation:

$$A_I/A_0=IC_{50}/(IC_{50}+[I])$$

Where A_I is the absorbance at 405 nm of the sample in the presence of inhibitor; A_0 is the absorbance at 405 nm in the absence of inhibitor; and [I] is the concentration of the inhibitor.

The inhibition constants (K_i) for the inhibitor for mPTPB were determined at pH 7.0 and 25°C. The mode of inhibition and K_i value were determined in the following manner. At various fixed concentrations of inhibitor (0-1.5 K_i), the initial rate at a series of pNPP concentrations was measured by following the production of p-nitrophenol as describe above, ranging from 0.2- to 5-fold the apparent Km values. The data were fitted to appropriate equations using SigmaPlot-Enzyme Kinetics to obtain the inhibition constant and to assess the mode of inhibition. For selectivity studies, the PTPs, including the bacterial mPTPA and YopH, the mammalian cytosolic PTPs, SHP1, SHP2, PTP1B, TC-PTP, Lyp, HePTP and FAP1, the receptor-like PTPs, CD45, PTPε, PTPγ, PTPµ, and PTPσ, and the dual specificity phosphatases Laforin, VHR, VHX, VHZ, MKP3, and Cdc14A, were expressed and purified from E. coli. The inhibition assay for these PTPs were performed under the same conditions as mPTPB except using a different *p*NPP concentration corresponding to the K_m of the PTP studied.

Cellular activity evaluation: Raw264.7 mouse macrophages were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% FBS (Invitrogen), penicillin (50 units/mL), and streptomycin (50 µg/mL) under a humidified atmosphere containing 5% CO_2 at 37°C. Transfected Raw264.7 cells (Vector, WT-mPTPB) were seeded in a 12-well plate at a density of 4 x 10^4 cells/well. The following day cells were treated with mPTPB inhibitor **11a** for 1hr, then stimulated with IFN-γ (200 U/ml) for 1 h. Subsequently, the cells were washed with ice-cold phosphate buffered saline, and lysed with lysis buffer on ice for 30 min. Cell lysate was then cleared by centrifuging at 13,000 rpm for 15 min. The phosphorylation of ERK1/2 and AKT was detected by Western blotting.

Figure S1

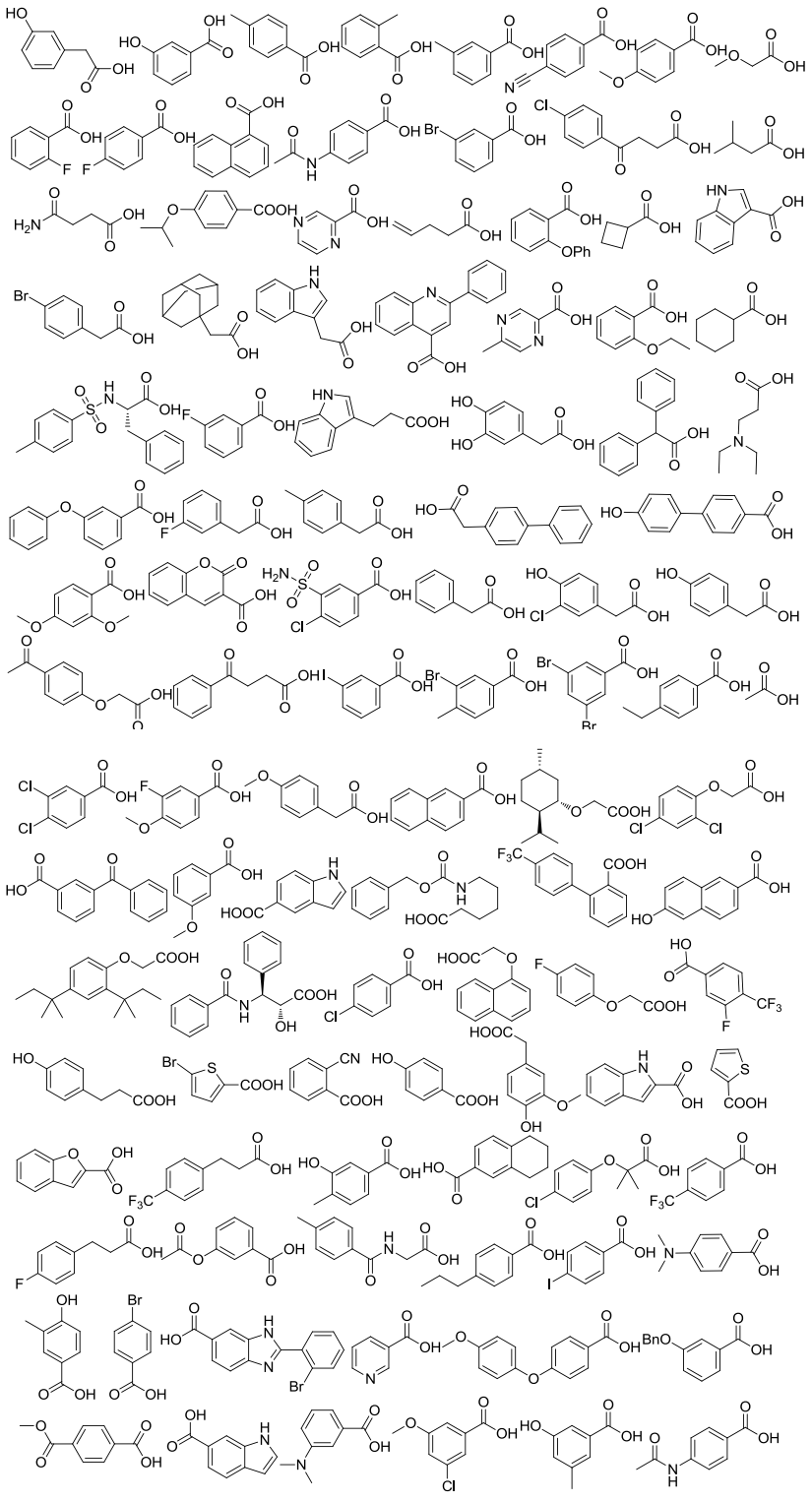
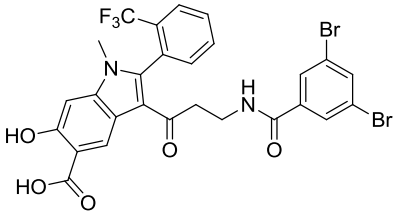
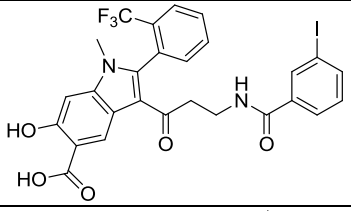
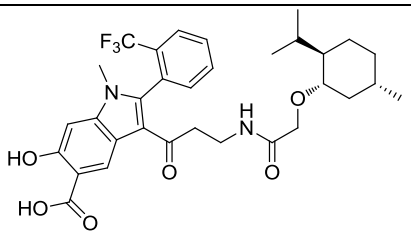
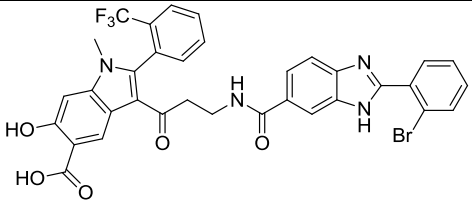
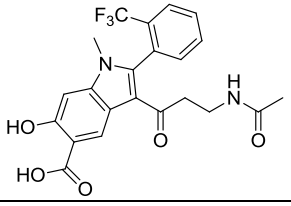


Figure S1. Chemical structures of the 102 acids used in combinatorial library **11**

Table S1. Percent inhibition at 1 μM and IC_{50} of selected compounds from library **11** against mPTPB

ID	Structure	Inhibition% at 1 μM	IC_{50} (μM)
11a		81	0.079 ± 0.01
11b		52	0.68 ± 0.04
11c		5	3.3 ± 0.1
11d		10	5.2 ± 0.2
11e		0	>20