Supporting Information

Identification and Optimization of Anthranilic Acid based Inhibitors of RPA

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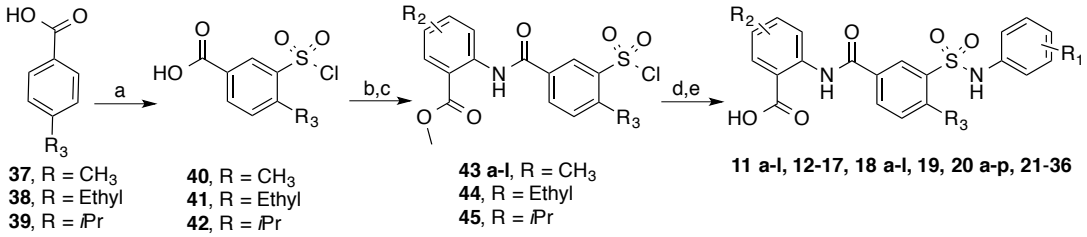
General Methods: All chemicals, reagents, and solvents were used as purchased from commercial sources, without further purification. All NMR spectra were recorded at room temperature on a 400 MHz Bruker spectrometer with a DRX-400 console, a 500 MHz Bruker spectrometer with a DRX-500 console, or a 600 MHz Bruker spectrometer with an AV-II console. ^{1}H chemical shifts are reported in δ values in ppm downfield with the deuterated solvent as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet, ovlp = overlap), coupling constant (Hz), and integration. Low-resolution mass spectra were obtained on an Agilent 1200 series 6140 mass spectrometer with electrospray ionization. All samples were of ≥90% purity as analyzed by LC–UV/vis–MS. Analytical HPLC was performed on an Agilent 1200 series with UV detection at 214 and 254 nm along with ELSD detection. LC–MS parameters were as follows: Phenomenex-C18 Kinetex column, 50 mm × 2.1 mm, 2 min gradient, 5% to 100% (H_2O/MeCN with 0.1% TFA). Preparative purification was performed on a Gilson HPLC (Phenomenex-C18, 100 mm × 30 mm, 10 min gradient, (H_2O/MeCN with 0.1% TFA) or by automated flash column chromatography (Teledyne Isco, Inc. Combiflash Rf).

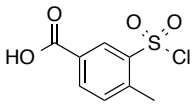
General Procedure for anthranilic acid-based inhibitors

The anthanilic-based inhibitors **11a-l**, **12-17**, **18a-l**, **19**, **20a-p**, and **21-36** were prepared by the similar procedures. This procedure is exemplified for compound **11**.[1]

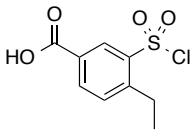


Reagents and conditions:a) Chlorosulfonic acid, reflux, 16 hrs; b) thionyl chloride, 75°C, 4 hrs; c) methyl 2-aminobenzoate-R_2, THF, 12 hrs d) aniline-R_1, toluene, 70°C, 12hrs; e) 2M LiOH, 55°C, 2 hrs.

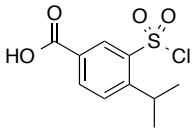
Scheme 1: Synthesis of anthanilic-based inhibitors



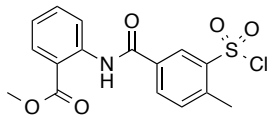
3-(chlorosulfonyl)-4-methylbenzoic acid 40: 4-methylbenzoic acid **37** (1.0 g, 7.35 mmol, 1 eq) was dissolved in chlorosulfonic acid (10 mL). The reaction was heated t reflux and stirred overnight. The next day, the reaction was cooled to room temperature and then poured onto ice. The solid was filtered, dissolved in DCM, and washed with 1M HCl. The DCM layer was then driesd (Na_2SO_4) and evaporated in vacuo to give the desired product **37** (1.22 g, 71%). ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 8.32 (d, *J* = 1.9 Hz, 1 H), 7.77 (dd, *J* = 2.0 Hz, 7.7 Hz, 1 H), 7.26 (d, *J* = 7.9 Hz, 1 H), 2.58 (s, 3H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ =167.2, 146.4, 141.2, 131.2, 129.6, 127.7, 127.5, 20.3. MS (ESI) $[M+H]^+$ m/z = 234.9.



3-(chlorosulfonyl)-4-ethylbenzoic acid 41: Synthesized according to procedure for **40** in 57%. ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 8.33 (d, *J* = 2.0 Hz, 1 H), 7.81 (dd, *J* = 2.0 Hz, 7.7 Hz, 1 H), 7.31 (d, *J* = 7.8 Hz, 1 H), 3.07 (q, *J* = 7.4 Hz, 2 H), 1.17 (t, *J* = 7.7 Hz, 3 H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 167.2, 147.0, 146.1, 129.8, 129.5, 128.1, 127.3, 25.6, 15.2. MS (ESI) [M+ H]$^+$ *m/z* = 249.0.

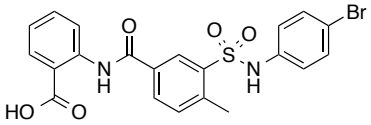


3-(chlorosulfonyl)-4-isopropylbenzoic acid 42: Synthesized according to procedure for **40** in 55%. ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 8.35 (d, *J* = 1.9 Hz, 1 H), 7.81 (dd, *J* = 1.9 Hz, 8.0 Hz, 1 H), 7.45 (d, *J* = 8.2 Hz, 1 H), 4.17 (sept, *J* = 6.7 Hz, 1 H), 1.16 (d, *J* = 7.1 Hz, 6 H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 167.2, 152.0, 145.6, 129.9, 128.0, 127.2, 126.6, 28.3, 23.7. MS (ESI) [M+ H]$^+$ *m/z* = 263.0.

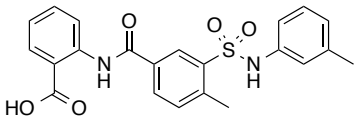


methyl 2-(3-(chlorosulfonyl)-4-methylbenzamido)benzoate 43a: The intermediate **40** (235 mg, 1 mmol, 1 eq) was dissolved in thionyl chloride (4 mL). The reaction was heated to 75°C and stirred for 4 hours. Solvents were removed *in vacuo*. The resulting syrup was dissolved in toluene (3 x 5 mL) and evaporated. The product was taken forward without further purification.

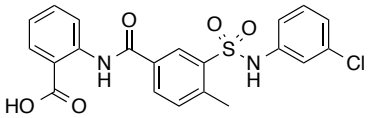
The appropriate methyl-2-aminobenzoate (151 mg, 1 mmol, 1 eq) was dissolved in THF (4 mL) and NaH (40 mg, 1 mmol, 1 eq) was added and stirred for 20 min. The acyl chloride (1 mmol, 1 eq) was added and the reaction was stirred at rt for 2 hours. The reaction was diluted with DCM and washed with water. The DCM layer was dried (Na_2SO_4) and then evaporated *in vacuo*. The residue was taken forward without further purification (367 mg, quantitative). ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 8.57 (dd, *J* = 0.8 Hz, 8.5 Hz, 1 H), 8.39 (d, *J* = 2.1 Hz, 1 H), 8.00 (dt, *J* = 1.9 Hz, 8.0 Hz, 1 H), 7.80 (dd, *J* = 2.1 Hz, 7.8 Hz, 1 H), 7.67 (m, 1 H), 7.37 (d, *J* = 7.9 Hz, 1 H), 7.22 (m, 1 H), 3.90 (s, 3 H), 2.62 (s, 3 H). ^{13}C-NMR (150 MHz, DMSO-d_6): δ = 168.0, 164.7, 146.9, 140.5, 140.3, 134.3, 131.4, 131.1, 130.8, 127.0, 125.7, 123.3, 120.9, 117.1, 52.7, 20.2. MS (ESI) [M+ H]$^+$ *m/z* = 368.0.



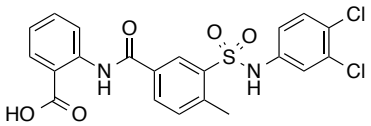
2-(3-(*N*-(4-bromophenyl)sulfamoyl)-4-methylbenzamido)benzoic acid 11: The sulfonyl chloride **43a** (62 mg, 0.17 mmol, 1 eq) was dissolved in toluene (2 mL). The 4-bromoaniline (86 mg, 0.5 mmol, 3 eq) is added and the rxn is stirred at 70°C overnight. The solvents were removed *in vacuo*. The resulting residue was dissolved in DCM and washed with water. The DCM layer was evaporated *in vacuo* and the residue was dissolved in THF (2 mL) and 2M LiOH (0.5 mL) was added. The reaction was stirred at 55°C for 2 hours. The reaction was neutralized with 2 M HCl (0.5 mL) and the solvents were removed *in vacuo*. The residue was purified via preparative HPLC to give the desired product (23 mg, 28%). ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 10.78 (s, 1 H), 8.67 (dd, *J* = 0.8 Hz, 8.4 Hz 1 H), 8.52 (d, *J* = 1.9 Hz, 1 H), 8.08-8.05 (m, 2 H), 7.68 (m, 1 H), 7.62 (d, *J* = 8.1 Hz, 1 H), 7.43-7.41 (m, 2 H), 7.24 (m, 1 H), 7.09-7.06 (m, 2 H), 3.39 (broad s, 1 H), 2.66 (s, 3 H). ^{13}C-NMR (150 MHz, DMSO-d_6): δ = 170.6, 163.5, 141.6, 141.3, 138.3, 137.1, 134.9, 134.1, 133.0, 132.7, 131.9, 131.8, 128.7, 123.8, 121.5, 120.5, 117.2, 116.2, 20.2. MS (ESI) $[M+H]^+$ *m*/*z* = 489.1.



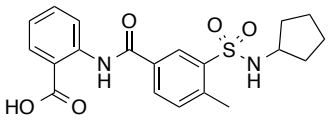
2-(4-methyl-3-(*N*-(*m*-tolyl)sulfamoyl)benzamido)benzoic acid 13 : Synthesized according to procedure for **11** in 44%. ^{1}H-NMR (400 MHz, d_6-DMSO): δ = 10.51 (s, 1 H), 8.48 (s, 1 H), 8.39 (d, *J* = 8.3 Hz, 1 H), 8.01 (m, 2 H), 7.69 (t, *J* = 7.4 Hz, 1 H), 7.60 (d, *J* = 7.9 Hz, 1 H), 7.28 (t, *J* = 7.7 Hz, 1 H), 7.09 (t, *J* = 7.9 Hz, 2 H), 6.91 (m, 2 H), 6.80 (d, *J* = 7.4 Hz, 1 H), 2.67 (s, 3 H), 2.17 (s, 3 H). MS (ESI) $[M+H]^+$ *m*/*z* = 425.2.



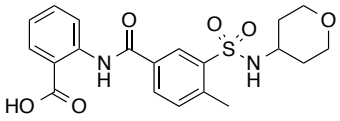
2-(3-(*N*-(3-chlorophenyl)sulfamoyl)-4-methylbenzamido)benzoic acid 18: Synthesized according to procedure for **11** in 42%. ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 10.88 (s, 1 H), 8.67 (dd, *J* = 0.9 Hz, 8.4 Hz 1 H), 8.55 (d, *J* = 1.9 Hz, 1 H), 8.09-8.06 (m, 2 H), 7.68 (m, 1 H), 7.63 (d, *J* = 8.1 Hz, 1 H), 7.27-7.23 (m, 2 H), 7.12-7.09 (m, 2H), 7.04 (m, 1H), 3.40 (broad s, 1 H), 2.67 (s, 3 H). ^{13}C-NMR (150 MHz, DMSO-d_6): δ = 170.1, 162.9, 141.2, 140.7, 138.8, 137.8, 134.4, 133.6, 133.5, 132.5, 132.4, 131.4, 131.3, 131.1, 128.2, 123.4, 123.3, 120.0, 118.1, 116.9, 19.7. MS (ESI) $[M+H]^+$ *m*/*z* = 445.2.



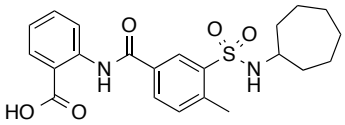
2-(3-(*N*-(3,4-dichlorophenyl)sulfamoyl)-4-methylbenzamido)benzoic acid 20: Synthesized according to procedure for **11** in 41%. ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 11.03 (s, 1 H), 8.67 (dd, *J* = 0.7 Hz, 8.4 Hz, 1 H), 8.55 (d, *J* = 1.9 Hz, 1 H), 8.08 (dd, *J* = 1.9 Hz, 8.2 Hz, 2 H), 7.68 (m, 1 H), 7.64 (d, *J* = 8.2 Hz, 1 H), 7.50 (d, *J* = 8.9 Hz, 1 H), 7.28 (d, *J* = 2.6 Hz, 1 H), 7.24 (m, 1 H), 7.12 (dd, *J* = 2.5 Hz, 8.9 Hz, 1 H), 3.38 (broad s, 1 H), 2.67 (s, 3 H). ^{13}C-NMR (150 MHz, DMSO-d_6): δ = 170.6, 163.4, 141.7, 141.2, 138.0, 137.9, 134.9, 134.2, 133.0, 132.1, 132.0, 131.9, 131.8, 128.7, 126.1, 123.8, 120.5, 120.3, 118.8, 117.3, 20.2. MS (ESI) $[M+H]^+$ m/z = 479.1.



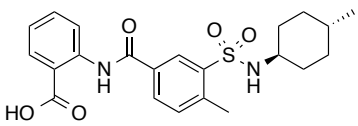
2-(3-(*N*-cyclopentylsulfamoyl)-4-methylbenzamido)benzoic acid 27: Synthesized according to procedure for **11** in 37%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.95 (d, *J* = 8.3 Hz, 1 H), 8.62 (d, *J* = 1.7 Hz, 1H), 8.18 (dd, *J* = 1.0 Hz, 8.3 Hz, 1H), 8.15 (dd, *J* = 1.8 Hz, 7.9 Hz, 1H), 7.69 (m, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 4.54 (d, *J* = 7.6 Hz, 1 H), 3.69 (m, 1 H), 2.75 (s, 3 H), 1.69-1.63 (m, 3H), 1.57-1.51 (m, 4H), 1.45-1.38 (m, 3H). MS (ESI) $[M+H]^+$ m/z = 430.2.



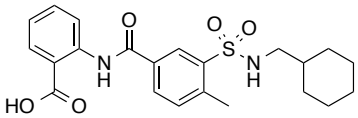
2-(4-methyl-3-(*N*-(tetrahydro-2*H*-pyran-4-yl)sulfamoyl)benzamido)benzoic acid 29: Synthesized according to procedure for **11** in 26%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.93 (d, *J* = 8.4 Hz, 1 H), 8.68 (d, *J* = 1.7 Hz, 1H), 8.19-8.16 (m, 2 H), 7.69 (m, 1 H), 7.51 (d, *J* = 7.9 Hz, 1 H), 7.21 (t, *J* = 7.7 Hz, 1 H), 4.69 (d, *J* = 7.5 Hz, 1 H), 3.93-3.90 (m, 2 H), 3.49 (m, 1 H), 3.40 (dt, *J* = 1.7 Hz, 11.8 Hz, 2 H) 2.75 (s, 3 H), 1.84-1.81 (m, 2 H), 1.65-1.55 (dq, *J* = 4.4 Hz, 11.1 Hz, 2 H). MS (ESI) $[M+H]^+$ m/z = 419.2.



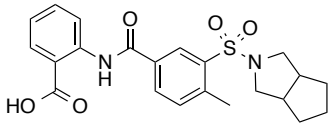
2-(3-(*N*-cycloheptylsulfamoyl)-4-methylbenzamido)benzoic acid 30: Synthesized according to procedure for **11** in 18%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.95 (d, *J* = 8.5 Hz, 1 H), 8.68 (d, *J* = 1.9 Hz, 1 H), 8.20 (dd, *J* = 1.2 Hz, 7.8 Hz, 1 H), 8.15 (dd, *J* = 1.9 Hz, 7.8 Hz, 1 H), 7.69 (m, 1 H), 7.49 (d, *J* = 7.9 Hz, 1 H), 7.21 (t, *J* = 7.1 Hz, 1 H), 4.58 (d, *J* = 7.9 Hz, 1 H), 3.48-3.43 (m, 1 H), 2.74 (s, 3 H), 1.86-1.80 (m, 2 H), 1.55-1.33 (m, 10 H). MS (ESI) $[M+H]^+$ m/z = 431.2.



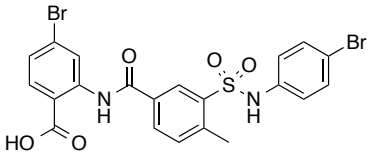
2-(4-methyl-3-(*N*-((1*r*,4*r*)-4-methylcyclohexyl)sulfamoyl)benzamido)benzoic acid 31: Synthesized according to procedure for **11** in 30%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.94 (d, *J* = 8.4 Hz, 1 H), 8.68 (d, *J* = 1.8 Hz, 1 H), 8.21 (dd, *J* = 1.3 Hz, 8.0 Hz, 1 H), 8.15 (dd, *J* = 1.8 Hz, 7.9 Hz, 1 H), 7.70 (m, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.21 (t, *J* = 7.5 Hz, 1 H), 4.57 (broad s, 1 H), 3.14 (m, 1 H), 2.74 (s, 3 H), 1.87-1.84 (m, 2H), 1.64-1.61 (m, 2H), 1.28-1.13 (m, 3H), 0.97-0.96 (m, 2H), 0.83 (d, *J* = 6.5 Hz, 3 H). MS (ESI) $[M+H]^+$ m/z = 431.2.



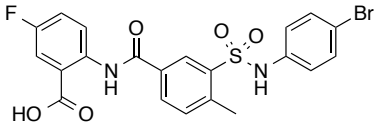
2-(3-(*N*-(cyclohexylmethyl)sulfamoyl)-4-methylbenzamido)benzoic acid 32: Synthesized according to procedure for **11** in 22%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.95 (d, *J* = 8.3 Hz, 1 H), 8.62 (d, *J* = 1.6 Hz, 1H), 8.20-8.15 (m, 2 H), 7.69 (m, 1 H), 7.49 (d, *J* = 8.1 Hz, 1 H), 7.20 (t, *J* = 7.3 Hz, 1 H), 4.56 (m, 1 H), 2.86-2.82 (m, 2 H), 2.72 (s, 3 H), 1.46-1.40 (m, 2H), 1.20-1.12 (m, 5H), 0.93-0.80 (m, 4H). MS (ESI) $[M+H]^+$ m/z = 431.2.



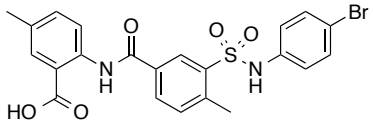
2-(3-((hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)sulfonyl)-4-methylbenzamido) benzoic acid 35: Synthesized according to procedure for **11** in 23%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.86 (d, *J* = 8.8 Hz, 1 H), 8.49 (m, 1 H), 8.15-8.08 (m, 2 H), 7.62 (m, 1 H), 7.44 (d, *J* = 8.1 Hz, 1 H), 7.14 (t, *J* = 7.4 Hz, 1 H), 3.32-3.28 (m, 2 H), 2.99-2.96 (m, 2 H), 2.68 (s, 3 H), 2.63-2.60 (m, 2 H), 1.76-1.69 (m, 2 H), 1.65-1.58 (m, 1 H), 1.49-1.40 (m, 1 H), 1.38-1.33 (m, 2H). MS (ESI) $[M+H]^+$ m/z = 429.3.



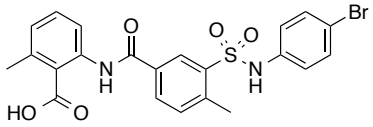
4-bromo-2-(3-(*N*-(4-bromophenyl)sulfamoyl)-4-methylbenzamido)benzoic acid 11c: Synthesized according to procedure for **11** in 40%. ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 10.80 (s, 1 H), 8.92 (d, *J* = 2.2 Hz, 1 H), 8.51 (d, *J* = 1.9 Hz, 1 H), 8.04 (dd, *J* = 1.9 Hz, 7.9 Hz, 1 H), 7.98 (d, *J* = 8.5 Hz, 1 H), 7.62 (d, *J* = 8.1 Hz, 1 H), 7.44 (dd, *J* = 2.0 Hz, 8.5 Hz, 1 H), 7.42-7.40 (m, 2 H), 7.08-7.06 (m, 2 H), 3.40 (broad s, 1 H), 2.66 (s, 3 H). ^{13}C-NMR (150 MHz, DMSO-d_6): δ = 169.6, 163.3, 141.8, 141.4, 137.9, 136.6, 133.6, 133.0, 132.2, 132.1, 132.0, 131.5, 131.4, 128.3, 127.7, 126.1, 122.4, 122.2, 120.7, 115.8, 19.7. MS (ESI) $[M+H]^+$ m/z = 568.9.



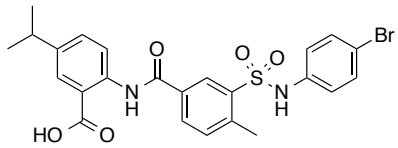
2-(3-(*N*-(4-bromophenyl)sulfamoyl)-4-methylbenzamido)-5-fluorobenzoic acid 11f: Synthesized according to procedure for **11** in 33%. ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 10.78 (s, 1 H), 8.62 (dd, *J* = 5.4 Hz, 9.3 Hz, 1 H), 8.51 (d, *J* = 1.9 Hz, 1 H), 8.05 (dd, *J* = 1.9 Hz, 8.0 Hz, 1 H), 7.77 (dd, *J* = 3.1 Hz, 9.2 Hz, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.55 (dt, *J* = 3.1 Hz, 9.2 Hz, 1 H), 7.43-7.40 (m, 2 H), 7.08-7.05 (m, 2 H), 2.65 (s, 3H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 168.8, 163.0, 158.1, 156.2, 141.1, 137.8, 137.1, 136.7, 133.6, 132.4, 132.2, 131.4, 128.3, 122.5, 122.5, 121.0, 120.7, 119.6, 117.1, 115.8, 19.8. MS (ESI) [M+ H^+] m/z = 507.1.



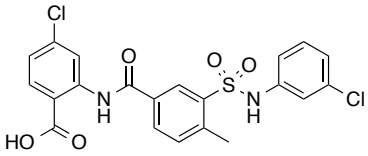
2-(3-(*N*-(4-bromophenyl)sulfamoyl)-4-methylbenzamido)-5-methylbenzoic acid 11g: Synthesized according to procedure for **11** in 21%. ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 10.79 (s, 1 H), 8.55 (m, 1 H), 8.51 (d, *J* = 1.9 Hz, 1 H), 8.04 (dd, *J* = 1.9 Hz, 7.9 Hz, 1 H), 7.96 (d, *J* = 8.1 Hz, 1 H), 7.61 (d, *J* = 8.1 Hz, 1 H), 7.42-7.41 (m, 2 H), 7.08-7.07 (m, 2 H), 7.05 (m, 1 H), 2.66 (s, 3 H), 2.39 (s, 3 H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 170.2, 163.0, 144.9, 141.1, 140.9, 137.8, 136.7, 133.6, 132.5, 132.2, 132.1, 131.4, 131.3, 128.2, 124.0, 120.7, 120.6, 120.1, 115.7, 113.9, 21.7, 19.8. MS (ESI) [M+ H]$^+$ m/z = 503.0.



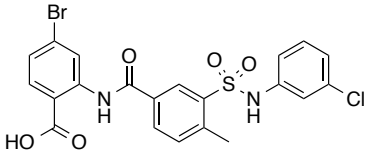
2-(3-(*N*-(4-bromophenyl)sulfamoyl)-4-methylbenzamido)-6-methylbenzoic acid 11h: Synthesized according to procedure for **11** in 4%. ^{1}H-NMR (400 MHz, CD_3OD): δ = 8.53 (s, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 8.01 (d, *J* = 7.5 Hz, 1 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.35 (d, *J* = 8.8 Hz, 2 H), 7.28 (t, *J* = 7.9 Hz, 1 H), 7.07-7.05 (m, 3H), 2.67 (s, 3 H), 2.52 (s, 3 H). MS (ESI) [M+ H]$^+$ m/z = 503.1.



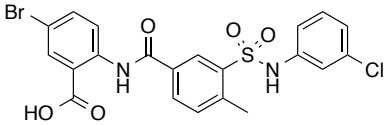
2-(3-(*N*-(4-bromophenyl)sulfamoyl)-4-methylbenzamido)-5-isopropylbenzoic acid 11k: Synthesized according to procedure for **11** in 33%. ^{1}H-NMR (400 MHz, CD_3OD): δ = 8.68 (d, *J* = 8.6 Hz, 1 H), 8.60 (s, 1H), 8.05 (d, *J* = 7.9 Hz, 1 H), 8.03 (s, 1 H), 7.52 (d, *J* = 8.7 Hz, 2 H), 7.34 (d, *J* = 8.8 Hz, 2 H), 7.06 (d, *J* = 8.8 Hz, 2 H), 2.95 (m, 1 H), 2.70 (s, 3 H), 1.28 (d, *J* = 6.9 Hz, 6 H). MS (ESI) [M+ H]$^+$ m/z = 531.1.



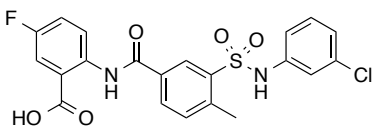
4-chloro-2-(3-(*N*-(3-chlorophenyl)sulfamoyl)-4-methylbenzamido)benzoic acid 18a: Synthesized according to procedure for **11** in 44%. ^{1}H-NMR (400 MHz, CD_3OD): δ = 8.91 (s, 1 H), 8.66 (s, 1 H), 8.14 (d, *J* = 8.4 Hz, 1 H), 8.08 (d, *J* = 7.7 Hz, 1 H), 7.54 (d, *J* = 7.9 Hz, 1 H), 7.20 (m, 2 H), 7.14 (s, 2 H), 7.00 (d, *J* = 7.6 Hz, 1 H), 2.73 (s, 3 H). MS (ESI) $[M+H]^+$ m/z = 479.1.



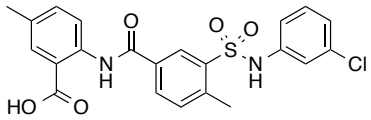
4-bromo-2-(3-(*N*-(3-chlorophenyl)sulfamoyl)-4-methylbenzamido)benzoic acid 18c: Synthesized according to procedure for **11** in 34%. ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 10.91 (s, 1 H), 8.93 (d, *J* = 2.0 Hz 1 H), 8.55 (d, *J* = 2.0 Hz, 1 H), 8.06 (dd, *J* = 1.8 Hz, 7.4 Hz, 1 H), 7.99 (d, *J* = 8.4 Hz 1 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 7.44 (dd, *J* = 2.0 Hz, 8.6 Hz, 1 H), 7.27 (t, *J* = 8.1 Hz 1 H), 7.13-7.10 (m, 2 H), 7.05 (m, 1 H), 3.42 (broad s, 1 H), 2.68 (s, 3 H). ^{13}C-NMR (150 MHz, DMSO-d_6): δ = 168.0, 161.5, 140.1, 139.8, 137.1, 136.2, 132.1, 131.9, 131.3, 130.3, 129.8, 129.5, 126.6, 126.1, 124.5, 121.8, 120.6, 116.5, 115.2, 114.2, 18.1. MS (ESI) $[M+H]^+$ m/z = 568.9.



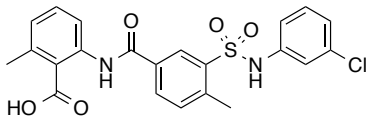
5-bromo-2-(3-(*N*-(3-chlorophenyl)sulfamoyl)-4-methylbenzamido)benzoic acid 18d: Synthesized according to procedure for **11** in 36%. ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 10.89 (broad s, 1 H), 8.60 (d, *J* = 8.9 Hz, 1 H), 8.54 (d, *J* = 1.9 Hz, 1 H), 8.12 (d, *J* = 2.7 Hz, 1 H), 8.06 (dd, *J* = 1.9 Hz, 8.0 Hz, 1 H), 7.86 (dd, *J* = 2.7 Hz, 8.9 Hz, 1 H), 7.62 (d, *J* = 8.1 Hz, 1 H), 7.26 (t, *J* = 8.1 Hz, 1 H), 7.11 (t, *J* = 2.1 Hz, 1 H), 7.09 (m, 1 H) 7.04 (m, 1H), 2.66 (s, 3 H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 168.9, 163.1, 141.4, 140.0, 138.9, 137.9, 136.9, 133.8, 133.6, 133.4, 132.2, 131.5, 131.2, 128.4, 123.6, 122.3, 119.3, 118.2, 117.0, 114.8, 19.8. MS (ESI) $[M+H]^+$ m/z = 568.9.



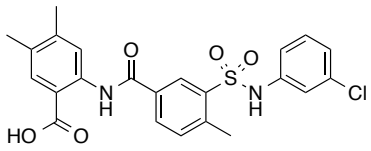
2-(3-(*N*-(3-chlorophenyl)sulfamoyl)-4-methylbenzamido)-5-fluorobenzoic acid 18f: Synthesized according to procedure for **11** in 42%. ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 10.89 (broad s, 1 H), 8.63 (dd, *J* = 5.2 Hz, 9.2 Hz, 1 H), 8.55 (d, *J* = 1.9 Hz, 1 H), 8.08 (dd, *J* = 1.9 Hz, 7.8 Hz, 1 H), 7.78 (dd, *J* = 1.9 Hz, 7.8 Hz, 1 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 7.56 (m, 1 H), 7.27 (t, *J* = 8.0 Hz, 1 H), 7.13 (t, *J* = 2.0 Hz, 1 H), 7.10 (m, 1H), 7.05 (m, 1H), 2.67 (s, 3 H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 168.8, 162.9, 158.1, 156.2, 141.2, 138.8, 137.8, 137.1, 133.6, 132.3, 131.4, 131.1, 128.3, 123.5, 122.5, 121.0, 119.7, 118.1, 117.2, 116.9, 19.7. MS (ESI) $[M+H]^+$ m/z = 463.2.



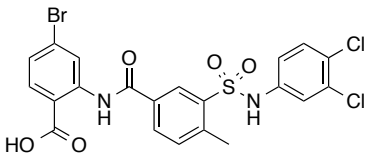
2-(3-(*N*-(3-chlorophenyl)sulfamoyl)-4-methylbenzamido)-5-methylbenzoic acid 18g: Synthesized according to procedure for **11** in 25%. ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 10.88 (broad s, 1 H), 8.55-8.54 (m, 2 H), 8.05 (dd, *J* = 1.9 Hz, 7.8 Hz, 1 H), 7.95 (d, *J* = 8.1 Hz, 1 H), 7.62 (d, *J* = 8.1 Hz, 1 H), 7.26 (t, *J* = 8.1 Hz, 1 H), 7.12 (t, *J* = 2.0 Hz, 1 H), 7.10 (m, 1 H) 7.05-7.02 (m, 2 H), 2.66 (s, 3 H), 2.39 (s, 3 H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 170.2, 162.8, 145.0, 141.2, 140.9, 138.8, 137.8, 133.7, 133.5, 132.4, 131.4, 131.3, 131.1, 128.2, 124.1, 123.5, 120.2, 118.1, 116.9, 113.9, 21.7, 19.8. MS (ESI) $[M+H]^+$ m/z = 459.1.



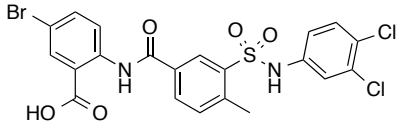
2-(3-(*N*-(3-chlorophenyl)sulfamoyl)-4-methylbenzamido)-6-methylbenzoic acid 18h: Synthesized according to procedure for **11** in 17%. ^{1}H-NMR (400 MHz, CD_3OD): δ = 8.57 (s, 1 H), 8.04 (t, *J* = 8.7 Hz, 1 H), 7.52 (d, *J* = 7.2 Hz, 1 H), 7.40 (t, *J* = 7.9 Hz, 1 H), 7.21-7.08 (m, 4 H), 6.99 (d, *J* = 7.6 Hz, 1 H), 2.70 (s, 3 H), 2.54 (s, 3H). MS (ESI) $[M+H]^+$ m/z = 459.0.



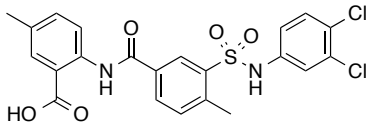
2-(3-(*N*-(3-chlorophenyl)sulfamoyl)-4-methylbenzamido)-4,5-dimethylbenzoic acid 18i: Synthesized according to procedure for **11** in 14%. ^{1}H-NMR (400 MHz, CD_3OD): δ = 8.60 (s, 1 H), 8.10 (s, 1 H), 7.78 (broad s, 1 H), 7.49 (m, 1 H), 7.23-7.16 (m, 2 H), 7.11 (s, 1 H), 7.05 (d, *J* = 7.7 Hz, 1 H), 6.99 (d, *J* = 7.3 Hz, 1 H), 2.69 (s, 3H), 2.38 (s, 3H), 2.18 (s, 3H). MS (ESI) $[M+H]^+$ m/z = 473.1.



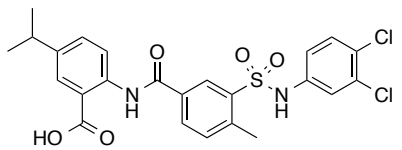
4-bromo-2-(3-(*N*-(3,4-dichlorophenyl)sulfamoyl)-4-methylbenzamido)benzoic acid 20c: Synthesized according to procedure for **11** in 42%. ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 11.05 (s, 1 H), 8.92 (d, *J* = 2.1 Hz 1 H), 8.53 (d, *J* = 1.9 Hz, 1 H), 8.06 (dd, *J* = 1.9 Hz, 7.9 Hz, 1 H), 7.98 (d, *J* = 8.5 Hz 1 H), 7.64 (d, *J* = 8.2 Hz, 1 H), 7.50 (d, *J* = 8.8 Hz 1 H), 7.43 (dd, *J* = 2.1 Hz, 8.5 Hz, 1 H), 7.28 (d, *J* = 2.6 Hz 1 H), 7.12 (dd, *J* = 2.6 Hz, 8.9 Hz, 1 H), 3.39 (broad s, 1 H), 2.67 (s, 3 H). ^{13}C-NMR (150 MHz, DMSO-d_6): δ = 169.6, 163.1, 141.8, 141.5, 137.6, 137.4, 133.8, 133.0, 132.1, 131.6, 131.6, 131.4, 128.2, 127.7, 126.1, 125.6, 122.2, 119.8, 118.3, 115.8, 19.7. MS (ESI) $[M+H]^+$ m/z = 556.9.



5-bromo-2-(3-(*N*-(3,4-dichlorophenyl)sulfamoyl)-4-methylbenzamido)benzoic acid 20d: Synthesized according to procedure for **11** in 36%. ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 11.04 (s, 1 H), 8.60 (d, *J* = 9.0 Hz, 1 H), 8.54 (d, *J* = 2.0 Hz, 1 H), 8.12 (d, *J* = 2.6 Hz, 1 H), 8.06 (dd, *J* = 2.0 Hz, 7.9 Hz, 1 H), 7.86 (dd, *J* = 2.5 Hz, 8.8 Hz, 1 H), 7.63 (d, *J* = 8.1 Hz, 1 H), 7.50 (d, *J* = 8.9 Hz, 1 H), 7.28 (d, *J* = 2.6 Hz, 1 H), 7.12 (dd, *J* = 2.5 Hz, 8.9 Hz, 1 H), 2.66 (s, 3 H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 168.8, 163.0, 141.4, 139.9, 137.6, 137.5, 136.8, 133.8, 133.3, 132.3, 131.6, 131.6, 131.4, 128.3, 125.6, 122.2, 119.9, 119.2, 118.4, 114.8, 19.8. MS (ESI) $[M+H]^+$ m/z = 556.9.



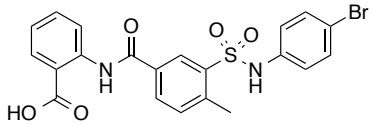
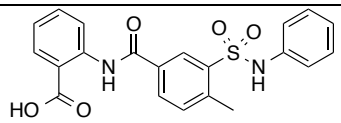
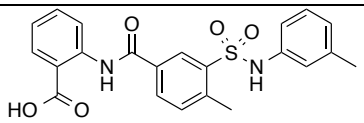
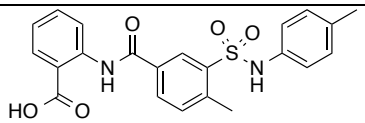
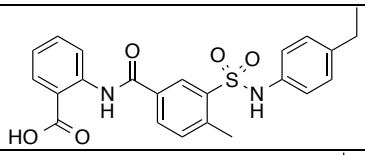
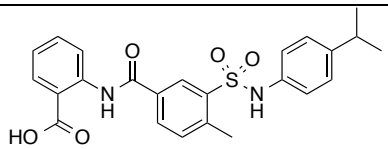
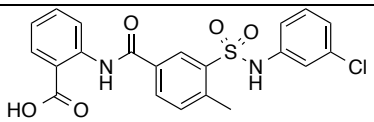
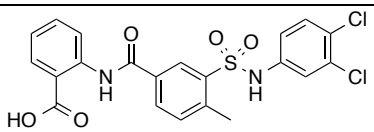
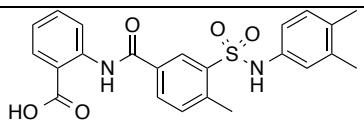
2-(3-(*N*-(3,4-dichlorophenyl)sulfamoyl)-4-methylbenzamido)-5-methylbenzoic acid 20g: Synthesized according to procedure for **11** in 31%. ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 11.05 (broad s, 1 H), 8.56-8.55 (m, 2 H), 8.08 (dd, *J* = 1.9 Hz, 7.9 Hz, 1 H), 7.96 (d, *J* = 8.1 Hz, 1 H), 7.65 (d, *J* = 8.1 Hz, 1 H), 7.51 (d, *J* = 8.9 Hz, 1 H), 7.29 (d, *J* = 2.6 Hz, 1 H), 7.13 (dd, *J* = 2.6 Hz, 8.9 Hz, 1 H), 7.06 (m, 1H), 2.68 (s, 3 H), 2.41 (s, 3H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 170.2, 162.8, 145.0, 141.2, 140.9, 137.5, 137.5, 133.8, 132.6, 131.6, 131.5, 131.4, 131.3, 128.1, 125.6, 124.1, 120.2, 119.8, 118.3, 114.0, 21.7, 19.7. MS (ESI) $[M+H]^+$ m/z = 493.0.

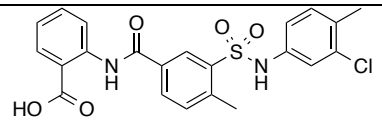
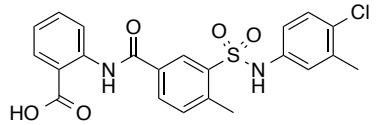
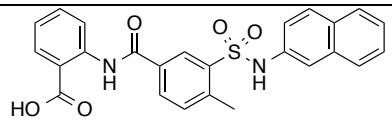
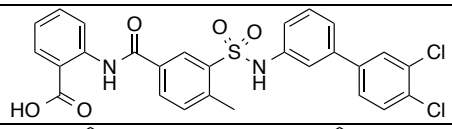
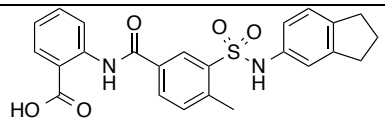
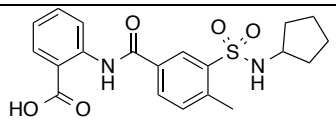
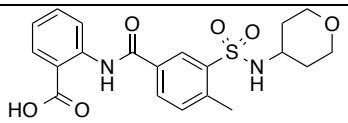
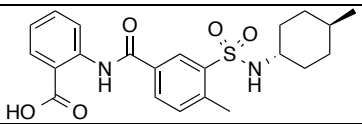
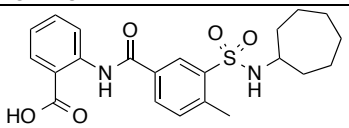
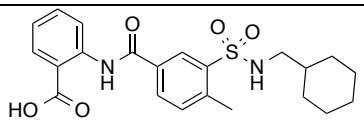
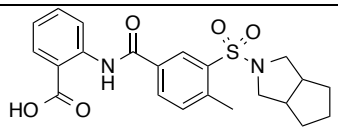
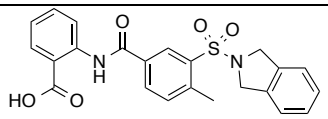
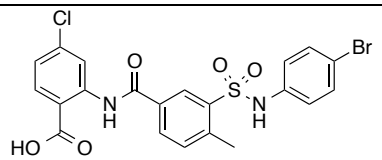


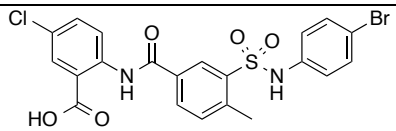
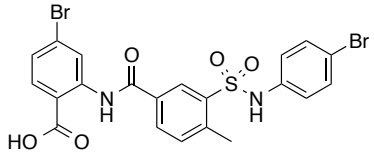
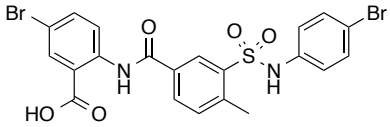
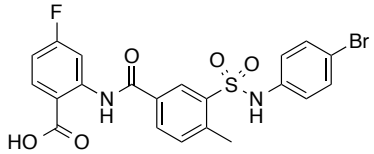
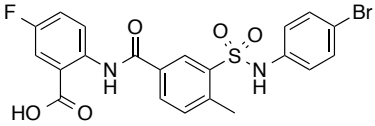
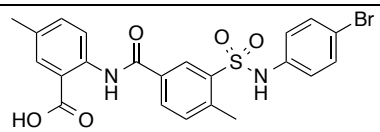
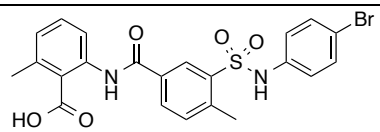
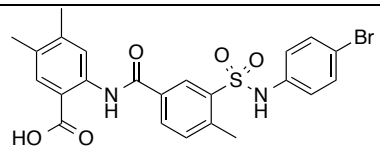
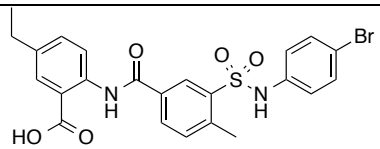
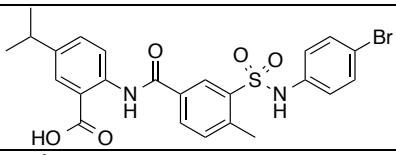
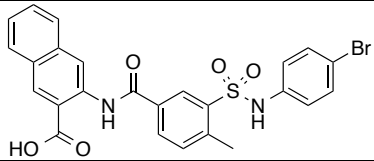
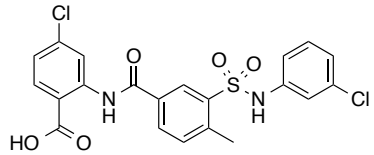
2-(3-(*N*-(3,4-dichlorophenyl)sulfamoyl)-4-methylbenzamido)-5-isopropylbenzoic acid 20k: Synthesized according to procedure for **11** in 29%. ^{1}H-NMR (400 MHz, CD_3OD): δ = 8.67 (d, *J* = 8.6 Hz, 1 H), 8.63 (d, *J* = 1.7 Hz, 1H), 8.08 (d, *J* = 7.9 Hz, 1 H), 8.02 (d, *J* = 1.9 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.50 (dd, *J* = 1.9 Hz, 8.7 Hz, 1 H), 7.35 (d, *J* = 8.8 Hz, 1 H), 7.24

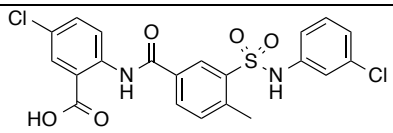
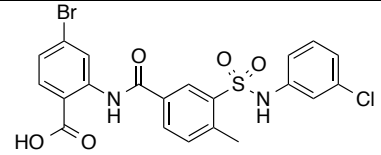
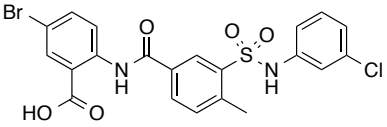
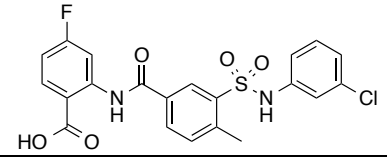
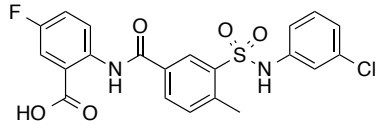
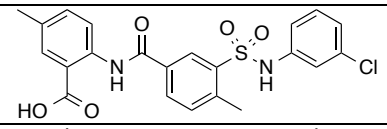
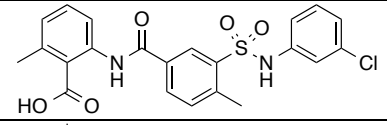
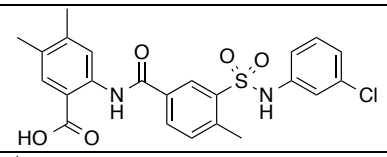
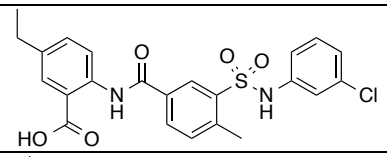
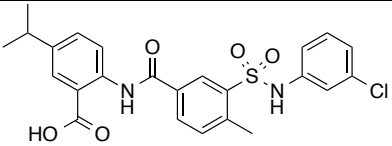
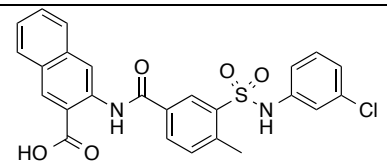
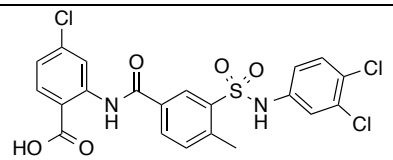
(d, *J* = 4.2 Hz, 1 H), 7.13 (dd, *J* = 2.6 Hz, 8.8 Hz, 1 H), 2.95 (m, 1 H), 2.70 (s, 3 H), 1.28 (d, *J* = 6.9 Hz, 6 H). MS (ESI) $[M+H]^+$ m/z = 521.1.

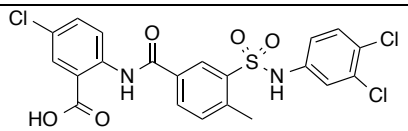
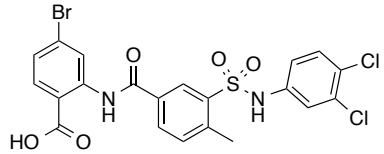
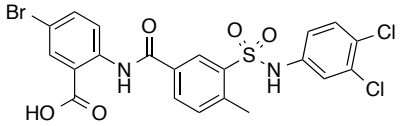
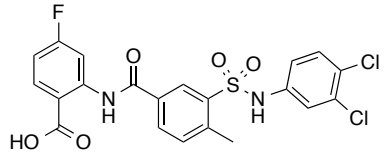
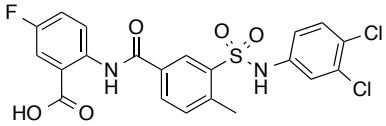
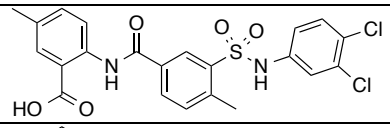
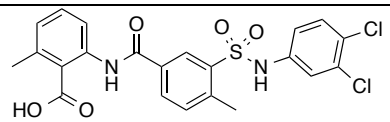
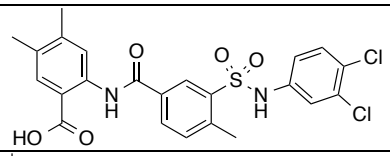
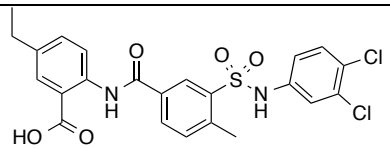
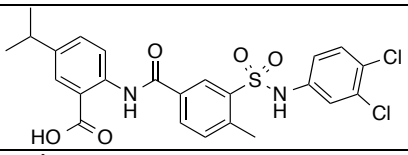
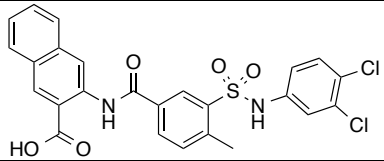
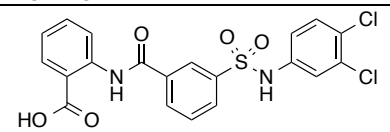
Table S1: LC-MS purity data for library analogs. [a]Purity by UV analysis at 214nM and/or 254 nM. [b]Purity by analysis of ELSD. [c]Where ^{1}H-NMR data was collected, a spectrum consistent with the structure was obtained, and a purity of >95% by integration was established. Compounds **15**, **19**, **28**, **33**, and **34** were purchased >95% pure from commercial vendors and tested without further purification.

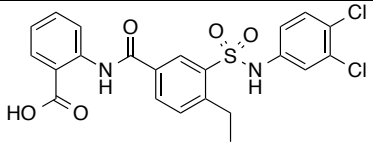
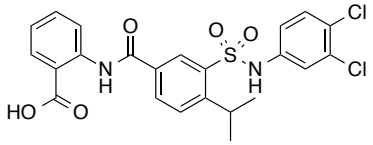
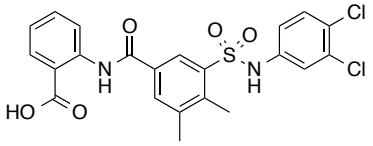
Cpd	Structure	Rt	m/z $[M+H]^+$	Purity (UV)[a],(ELSD)[b]	^{1}H-NMR[c]
11		1.40	489.1	>95%[a,b]	Y
12		1.27	411.1	>95%[a,b]	N
13		1.34	425.2	>95%[a,b]	Y
14		1.35	425.2	>95%[a,b]	N
16		1.45	439.1	>95%[a,b]	N
17		1.50	453.1	>95%[a,b]	N
18		1.37	445.2	95% [a,b]	Y
20		1.45	479.1	>95%[a,b]	Y
21		1.42	439.2	>95%[a,b]	N

22		1.46	459.1	>95%[a,b]	N
23		1.47	459.1	>95%[a,b]	N
24		1.40	461.2	>95% [a,b]	N
25		1.65	555.0	>95% [a,b]	N
26		1.46	451.2	>95% [a,b]	N
27		1.35	430.2	>95% [a]	Y
29		1.15	419.2	>95% [a]	Y
30		1.48	431.2	>95% [a,b]	Y
31		1.47	431.2	>95% [a]	Y
32		1.51	431.2	>95% [a]	Y
35		1.51	429.3	>95% [a]	Y
36		1.40	437.2	>95% [a,b]	N
11a		1.52	523.0	>95% [a,b]	N

11b		1.50	523.0	>95% [a,b]	N
11c		1.54	568.9	>95% [a,b]	Y
11d		1.52	568.9	>95% [a,b]	N
11e		1.45	507.0	95% [a,b]	N
11f		1.41	507.1	95% [a,b]	Y
11g		1.45	503.0	95% [a,b]	Y
11h		1.60	503.1	>95% [a,b]	Y
11i		1.57	517.0	>95% [a,b]	N
11j		1.78	517.0	>95% [a,b]	N
11k		1.84	531.1	>95% [a,b]	Y
11l		1.79	539.1	>95% [a,b]	N
18a		1.50	479.1	>95% [a,b]	Y

18b		1.48	479.0	>95% [a,b]	N
18c		1.51	523.0	>95% [a,b]	Y
18d		1.50	523.0	>95% [a,b]	Y
18e		1.42	463.1	>95% [a,b]	N
18f		1.39	463.2	>95% [a]	Y
18g		1.45	459.1	>95% [a,b]	Y
18h		1.58	459.0	>95% [a,b]	Y
18i		1.54	473.1	>95% [a,b]	Y
18j		1.76	473.1	>95% [a,b]	N
18k		1.82	487.2	>95% [a,b]	N
18l		1.76	495.1	>95% [a,b]	N
20a		158	513.0	>95% [a,b]	N

20b		1.56	513.0	>95% [a,b]	N
20c		1.59	556.9	>95% [a,b]	Y
20d		1.58	556.9	>95% [a,b]	Y
20e		1.51	497.1	>95% [a,b]	N
20f		1.47	497.1	>95%[a,b]	N
20g		1.53	493.0	>95%[a]	Y
20h		1.67	493.0	>95% [a,b]	N
20i		1.64	507.1	>95% [a,b]	N
20j		1.86	507.1	>95% [a,b]	N
20k		1.92	521.1	>95% [a,b]	Y
20l		1.85	529.0	>95% [a,b]	N
20m		1.68	465.0	>95% [a,b]	N

20n		1.77	493.0	>95% [a,b]	N
20o		1.83	507.1	>95% [a,b]	N
20p		1.76	493.0	>95% [a,b]	N

Fluorescence Polarization Anisotropy (FPA) Assays. 90,000 compounds from the Vanderbilt Institute of Chemical Biology compound collection were screened at the High Throughput Screening core at a single concentration of 30 μM for their ability to disrupt the binding of an ATRIP-based probe to RPA70N. The protocol is described in full detail in Souza-Fagundes, E.M., et al., *Anal Biochem*, 2012.[2]

FPA competition and DNA binding assays were conducted as previously described with minor modifications.[2-4] For the FPA competition assays, compounds were diluted in a 10-point, 3-fold serial dilution scheme in DMSO for a final concentration range of 500 - 0.025 μM. Compounds were added to assay buffer (50 mM HEPES, 75 mM NaCl, 5 mM DTT, pH 7.5) containing FITC-labeled probe and appropriate RPA70 protein in a final reaction volume of 50 μL containing 5% DMSO. All assays were conducted using a protein concentration equal to 1X K_d for the protein/probe interaction. Therefore, competition for binding to RPA70N was measured using either the FITC-ATRIP peptide (FITC-Ahx-DFTADDLEELDTLAS-NH_2; 50 nM with 6 μM RPA70N) or the FITC-ATRIP2 peptide (FITC-Ahx-DFTADDLEEWFAL-NH_2; 25 nM with 350 nM RPA70N). Binding to RPA70NAB was measured using 200 nM RPA70NAB and 25 nM FITC-ATRIP2. Following incubation for 1h, emission anisotropy was measured using the EnVision plate reader (Perkin Elmer). IC_{50} values were generated using a four-parameter dose-response (variable slope) equation in XLfit and were converted to K_d values. Reported K_d values are the average of two independent experiments, run in duplicate.

X-ray crystal structures of complexes with RPA70N. Crystals of the E7R mutant of RPA70N were grown as described previously.[5] X-ray diffraction data were collected at sector 21 (Life Sciences Collaborative Access Team, LS-CAT) of the Advanced Photon Source (Argonne, IL). All data were processed by HKL-2000.[6] E7R crystallized in space group $P2_12_12_1$ and contained one molecule in the asymmetric unit. Initial phases were obtained by molecular replacement with PHASER[7] using the structure of the free protein (4IPC) as a search model. Iterative cycles of model building and refinement were performed using COOT[8] and PHENIX.[9] The structure of compound **20c** bound to E7R are deposited at the Protein Data Bank under accession code 5E7N. The program Pymol (Schrödinger) was used to visualize and analyze the structures.

Table S2: X-ray Collection Statistics

Data Collection	
Wavelength	0.97872
Space Group	$P2_12_12_1$
Cell dimensions	38.56, 53.26, 54.48
α, β, γ (º)	90, 90, 90
Resolution (Å)	50 – 1.3
R_{sym} (%)	6.4 (5.6)
$I/\delta I$	22.49 (2.77)
Completeness (%)	99.8 (98.0)
Redundancy	5.8
Refinement	
Resolution	31.47 – 1.21
No. reflections	34513
R_{work}	0.1959
R_{free}	0.2155
No. atoms	2152
Protein	1920
Ligand	30
Water	16
B-factors (Å)	

Average	21.60
Protein	19.43
Water	24.73
RMS	
Bond lengths (Å)	0.006
Bond angles (º)	1.19
Ramachandran plot	
Favored (%)	98%
Allowed (%)	2 %
Disallowed (%)	0 %
Values in parentheses refer to the highest resolution shell	

Protein Binding Assays. Compound **20c** was assayed for binding to human plasma proteins by by Absorption Systems, a preclinal contract research organization. The procedure for this assay is as follows: Studies were carried out in human plasma (Lot# BRH622380). All plasma was obtained from Bioreclamation and collected on sodium heparin. A Pierce Rapid Equilibrium Dialysis Device (RED) was used for all experiments. Stock solutions of the test and control compounds were first prepared in DMSO. Aliquots of the DMSO solutions were dosed into 1.5 mL of plasma at a dosing concentration of 1 µg/mL for the test compounds and 10 µM for the co-dosed control compound warfarin. Plasma (300 µL) containing the test and control compounds was loaded into two wells of the 96-well dialysis plate. Blank PBS (500 µL) was added to each corresponding receiver chamber. The device was then placed into an enclosed heated rocker that was pre-warmed to 37°C, and allowed to incubate for four hours. After 4 hours of incubation, both sides were sampled. Aliquots (50 µL for donor, 200 µL for receiver) were removed from the chambers and placed into a 96-well plate. Plasma (50 µL) was added to the wells containing the receiver samples, and 200 µL of PBS was added to the wells containing the donor samples. Two volumes of acetonitrile were added to each well, and the plate was mixed and then centrifuged at 3,000 rpm for 10 minutes. Aliquots of the supernatant were removed, diluted 1:1 into distilled water, and analyzed by LC-MS/MS. Protein binding values were calculated as follows:

$$\% \text{ Bound} = [(\text{PARR in Donor} - \text{PARR in Receiver}) / (\text{PARR in Donor})] \times 100\%$$

Where: PARR = peak area response ratio of compound to internal standard, including applicable dilution factors.

Caco-2 Cellular Permeability Assays. Compound **20c** was assayed in a bidirectional Caco-2 permeability assay conducted by Absorption Systems, a preclinal contract research

organization. The procedure for this assay is as follows: Cell monolayers were grown to confluence on collagen-coated, microporous, polycarbonate membranes in 12-well Costar Transwell® plates. Details of the plates and their certification are shown below. The permeability assay buffer was Hanks Balanced Salt Solution containing 10 mM HEPES and 15 mM glucose at a pH of 7.4. The buffer in the receiver chamber also contained 1% bovine serum albumin. The dosing solution concentration was 5 μM test compound in the assay buffer. Cell monolayers were dosed on the apical side (A-to-B) or basolateral side (B-to-A) and incubated at 37°C with 5% CO_2 in a humidified incubator. Samples were taken from the donor and receiver chambers at 120 minutes. Each determination was performed in duplicate. The co-dosed lucifer yellow flux was also measured for each monolayer to ensure no damage was inflicted to the cell monolayers during the flux period. All samples were assayed by LC-MS/MS using electrospray ionization. The apparent permeability, P_{app}, and percent recovery were calculated as follows:

$$P_{app} = (dC_r / dt) \times V_r/(A \times CA)$$

$$\text{Percent Recovery} = 100 \times ((V_r \times C_r^{final}) + (V_d \times C_d^{final}))/(V_d \times C_N)$$

Where:

dCr/dt is the slope of the cumulative concentration in the receiver compartment versus time in μM s^{-1};

V_r is the volume of the receiver compartment in cm^3;

V_d is the volume of the donor compartment in cm^3;

A is the area of the insert (1.13 cm^2 for 12-well Transwell®);

C_A is the average of the nominal dosing concentration and the measured 120 minute donor concentration in μM;

C_N is the nominal concentration of the dosing solution in μM;

C_r^{final} is the cumulative receiver concentration in μM at the end of the incubation period;

C_d^{final} is the concentration of the donor in μM at the end of the incubation period.

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