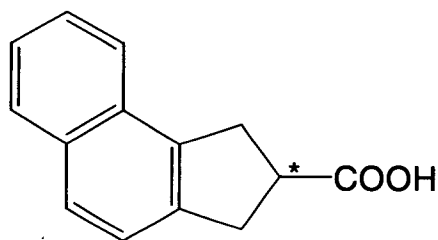


Experimental procedures

Nuclear magnetic resonance spectra were recorded on Varian Gemini 200, 300, and JOEL JNM-A500 spectrometers in the indicated solvents. Chemical shifts are reported in parts per million (δ unit) relative to tetramethylsilane. Melting points were recorded on a Yanaco MP-S3 model melting point apparatus and are uncorrected. Electrospray ionization (ESI) mass spectra were recorded on a micromass Quattro II and Q-Toff-2 instrument. Elemental analyses were performed on CE instruments EA 1108 Automatic Elemental Analyzer and are within 0.4% of theoretical values. Flash chromatography was performed with Merck silica gel 60 (230–400 mesh). Air-and/or moisture-sensitive reactions were carried out in commercially available anhydrous solvents under an atmosphere of nitrogen in flame dried glassware. All reagents were obtained from commercial suppliers and were used without further purification. Analytical HPLC analyses were performed under the following conditions: Wakopak combi ODS fast (30 x 2.0 mmI.D.) with liner gradient system of H₂O-CH₃CN-TFA 95 : 5 : 0.1 to 5 : 95 : 0.1 over 6 min and at a flow rate of 0.8 mL/min.



(-)-2,3-dihydro-1H-cyclopenta[a]naphthalene-2-carboxylic acid ((-)-10). To a stirred suspension of 60% oil dispersed sodium hydride (23 g, 0.57 mol) in 9 L of tetrahydrofuran was added diethyl malonate (15.9 mL, 0.11 mol) one portion at room temperature. After 30 min, **11** (30 g, 0.096 mol) was added one portion, and the mixture was stirred at room temperature for 15 h. The reaction was quenched by the addition of acetic acid (55 mL, 0.96 mol). After being stirred for an additional 3 h, the resulting precipitate was filtered, and the filtrate was concentrated. The residue was partitioned between

500 mL of ethyl acetate and 300 mL of saturated aqueous sodium bicarbonate, and the biphasic mixture was stirred vigorously for 10 min at room temperature. The layers were separated, and the organic layer was washed with 300 mL of water and 300 mL of brine, dried over sodium sulfate, and concentrated. The crude ester was dissolved in 350 mL of ethanol and treated with 350 mL of 2 N aqueous potassium hydroxide at room temperature. The mixture was heated to 80°C for 3h. After being cooled, the mixture was concentrated to a half of the original volume. The residual solution was diluted with 750 mL of water and extracted with 200 mL of dichloromethane twice. The aqueous layer was acidified with ca. 70 mL of 12 N hydrochloric acid. The resulting precipitate was collected by suction filtration, washed with H₂O, and dried on the paper for 1 h. Washing of the solid with 100 mL of dichloromethane in several portions gave the crude diacid, which was heated to 200°C for 10 min while evolution of carbon dioxide from the melted solid ceased. The mixture was cooled to afford 15.59 g (77%) of (±)-10.

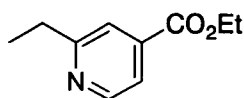
Chiral resolution

Crude (±)-10 (15.59 g, 0.074 mol) and (*R*)-(+)-1-(naphthyl)ethylamine (12.57 g, 0.074 mol) were combined in 390 mL of 1,4-dioxane at room temperature, and the mixture was kept at room temperature for 15 h. The resulting crystal was collected and washed with acetonitrile to give 11.87 g of the salt, which was recrystallized from 350 mL of hot 1,4-dioxane to give 6.81 g of the salt. The de of the salt was determined to be >98% by HPLC analysis of the corresponding amide generated by the condensation of the salt. The salt was suspended in 150 mL of 1 N hydrochloric acid and extracted with 500 mL of dichloromethane three times. The combined organic layers were washed with 1 N hydrochloric acid, dried over sodium sulfate, and concentrated to give 3.82 g of (-)-10 as a white solid: mp 139-140°C; $[\alpha]_D^{25} = -95.0$ (c 1.00, CHCl₃); ¹H NMR (CDCl₃) δ 3.42-3.65 (5H, m), 7.33-7.55 (3H, m), 7.69-7.87 (3H, m); MS (ESI-) *m/e* [M-H]⁻ 211 .

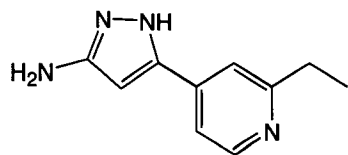
The determination of the de of the salt

A portion of the salt (< 5 mg) was dissolved in ca 0.5 mL of chloroform and treated with a spatulafull of EDCI at room temperature. After 5 min, the resulting solution was washed with water three times and dried over sodium sulfate. The chloroform solution was analyzed by HPLC for the de (Senshupack 1201N, 25:75 ethyl acetate/hexanes; 1 mL/min, 254 nm; minor isomer, $r_t = 6.9$ min; major isomer, $r_t = 7.7$ min)

(+)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene-2-carboxylic acid ((+)-10). Resolution of crude (\pm)-10 with (*S*)-(-)-1-(naphthyl)ethylamine by using the above procedure gave (+)-10 as a white solid:
 $[\alpha]_D^{25} = +94.0$ (c 1.00, CHCl₃)

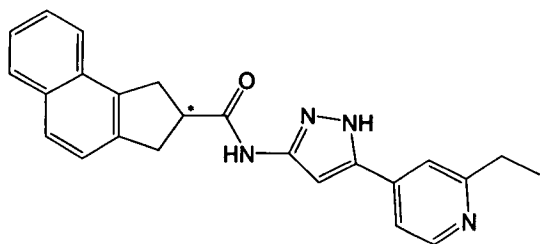


Ethyl 2-ethylisonicotinate. To a stirred solution of ethyl 2-chloroisonicotinate (2 g, 10.8 mmol) in 30 mL of tetrahydrofurane were added dichlorobis(triphenylphosphine)palladium(II) (758 mg, 1.08 mmol), a 1.0 M solution of diethyl zinc in tetrahydrofurane (15 mL, 15.0 mmol), and 2-dimethylaminoethanol (193 mg, 2.16 mmol) at room temperature, and the mixture was heated to 85°C for 1 h. After being cooled, the resulting solution was poured into saturated aqueous ammonium chloride, filtered through celite, and washed with ethyl acetate. The layers of the filtrate were separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with H₂O and brine, dried over sodium sulfate, and concentrated. Purification by flash-chromatography with hexanes/ethyl acetate = 9/1 to afford 1.66 g (86%) of ethyl 2-ethylisonicotinate as a colorless oil: ¹H NMR (CDCl₃) δ 1.33 (3H, t, $J = 7.6$ Hz), 1.40 (3H, t, $J = 7.1$ Hz), 2.90 (2H, q, $J = 7.6$ Hz), 4.38 (2H, q, $J = 7.1$ Hz), 7.24 (1H, d, $J = 8.1$ Hz), 8.20 (1H, dd, $J = 2.1, 8.1$ Hz), 9.13 (1H, d, $J = 2.1$ Hz).



5-(2-ethyl-4-pyridinyl)-1H-pyrazole-3-amine (9).

To a stirred solution of a 1.6 M solution of n-butyl lithium in hexanes (10.4 mL, 16.6 mmol) in 15 mL of tetrahydrofuran was added acetonitrile (0.87 mL, 16.6 mmol) at -78°C dropwise, and the mixture was stirred at -78°C for 1 h. Ethyl 2-ethylisonicotinate (2.70 g, 15.1 mmol) in 15 mL of tetrahydrofuran was added dropwise at -78°C . The reaction mixture was kept at -78°C for 2 h and allowed to warm to room temperature. After being stirred for an additional 2 h, the reaction was quenched by addition of H_2O and extracted with ether. The aqueous layer was acidified to pH 5 with 1 N hydrochloric acid and extracted with ethyl acetate three times. The combined organic layers were dried over sodium sulfate and concentrated to give the ketonitrile as a brown solid. The crude product was dissolved in 5 mL of ethanol and treated with hydrazine monohydrate (1.13 g, 22.5 mmol) at room temperature. The mixture was heated to reflux for 13 h and concentrated. The residue was directly purified by flash-chromatography with 10% methanol in chloroform to give 1.77 g (62%) of **9** as a brown foam: ^1H NMR (CDCl_3) δ 1.26 (3H, t, $J = 7.5$ Hz), 2.79 (2H, q, $J = 7.5$ Hz), 5.55 (3H, brs), 5.99 (1H, s), 7.27 (1H, d, $J = 5.2$ Hz), 7.33 (1H, s), 8.46 (1H, d, $J = 5.2$ Hz).



N-[5-(2-ethyl-4-pyridinyl)-1H-pyrazol-3-yl]-2,3-dihydro-1H-cyclopenta[*a*]naphthalene-2-carboxamide ((-)-7). **9** (1.02 g, 5.44 mmol) and (-)-**10** (1.14g, 5.38 mmol) were dissolved in 18 mL of pyridine and treated with EDCI at room temperature. The mixture was stirred at room temperature for 15 h and quenched by addition of H_2O . The resulting aqueous solution was extracted with chloroform three

times. The combined organic layers were dried over sodium sulfate, and concentrated. The residue was flash-chromatographed with ethyl acetate on silica gel to give 1.67 g (81%) of (-)-7. The ee was determined to be 98.6% by chiral HPLC analysis (DAICEL CHIRALCEL OJ-R, 55:45 H₂O/CH₃CN; 0.7 mL/min, 230 nm; (+)-7, r_t = 18.1; (-)-7, r_t = 21.1 min): white solid, mp 115–125°C; $[\alpha]_D^{25}$ = -104 (c 0.10, DMSO); ¹H NMR (Acetone-*d*₆) δ 1.30 (3H, t, J = 7.7 Hz), 2.82 (2H, q, J = 7.7 Hz), 3.30-3.81 (5H, m), 7.00 (1H, s), 7.41-7.55 (4H, m), 7.63 (1H, s), 7.77 (1H, d, J = 8.2 Hz), 7.83 (1H, d, J = 8.2 Hz), 7.97 (1H, d, J = 7.6 Hz), 8.51 (1H, d, J = 5.3 Hz), 9.98 (1H, brs), 12.22 (1H, brs); ¹³C NMR (Acetone-*d*₆) δ 14.1, 31.9, 35.9, 39.0, 45.4, 117.6, 118.3, 123.8, 124.9, 125.8, 127.0, 128.1, 129.2, 131.2, 133.8, 138.1, 140.0, 150.7, 165.0, 173.8; HRMS (ESI+) m/z [M+H]⁺ 383.1870 (C₂₄H₂₃N₄O requires: 383.1872). Anal. (C₂₄H₂₂N₄O): C, 75.37; H, 5.80; N, 14.65. Found: C, 75.37; H, 5.96; N, 14.99.

Hydrochloride of (-)-7. 1.60 g of (-)-7 was dissolved in a minimum amount of methanol and treated with 3 mL of a 4N HCl solution in ethyl acetate. The mixture was concentrated, and the residual solid suspended in acetone was sonicated for few minutes, filtered, washed with acetone, and vacuum-dried to give 1.45 g of the hydrochloride of (-)-7.

***N*-[5-(2-ethyl-4-pyridinyl)-1*H*-pyrazol-3-yl]-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene-2-carboxamide ((+)-7).** Using a procedure for (-)-7, **9** (8 mg, 0.043 mmol) and (+)-10 (11 mg, 0.049 mmol) were condensed. The crude product obtained was flash-chromatographed with ethyl acetate → 10% methanol in chloroform to give 13 mg (79%) of (+)-7. The ee was determined to be >99.9% by chiral HPLC analysis (DAICEL CHIRALCEL OJ-R, 55:45 H₂O/CH₃CN; 0.7 mL/min, 230 nm; (+)-7, r_t = 18.1; (-)-7, r_t = 21.1 min): white solid, mp 112–119°C; $[\alpha]_D^{25}$ = +92 (c 0.10, DMSO).

***N*-[5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]-2-indanecarboxamide (1).** Using a procedure for (-)-7, 2-indanecarboxylic acid (252 mg, 1.55 mmol) and 5-(4-chlorophenyl)-1*H*-pyrazole-3-amine (300 mg, 1.55 mmol) were condensed. The crude solid product obtained was suspended in ethyl acetate, filtered,

and vacuum-dried to give 331 mg (63%) of **1**: white solid, mp 269–270°C; ¹H NMR (CDCl₃) δ 3.20–3.45 (5H, m), 6.71 (1H, brs), 7.15–7.29 (4H, m), 7.39 (2H, d, *J* = 8.7 Hz), 7.56 (2H, d, *J* = 8.7 Hz), 7.92 (1H, brs); HRMS (ESI+) *m/z* [M+H]⁺ 338.1049 (C₁₉H₁₇N₃OCl requires: 338.1060).

***N*-(5-phenyl-1*H*-pyrazol-3-yl)-2-indanecarboxamide (2a)**. Using a procedure for (–)-7, 2-indanecarboxylic acid (16 mg, 0.1 mmol) and 5-phenyl-1*H*-pyrazole-3-amine (16 mg, 0.1 mmol) were condensed. The crude product obtained was flash-chromatographed with 75% ethyl acetate in hexanes to afford 30 mg (99%) of **2a**: white solid; ¹H NMR (CDCl₃) δ 3.20–3.40 (5H, m), 6.87 (1H, brs), 7.15–7.60 (9H, m), 8.40 (1H, brs); HRMS (ESI+) *m/z* [M+H]⁺ 304.1436 (C₁₉H₁₈N₃O requires: 304.1450).

***N*-[5-(3-chlorophenyl)-1*H*-pyrazol-3-yl]-2-indanecarboxamide (2b)**. Using a procedure for (–)-7, 2-indanecarboxylic acid (84 mg, 0.52 mmol) and 5-(3-chlorophenyl)-1*H*-pyrazole-3-amine (100 mg, 0.52 mmol) were condensed to give 122 mg (70%) of **2b**: beige solid, mp 200–203°C; ¹H NMR (CDCl₃) δ 3.20–3.42 (5H, m), 6.70 (1H, brs), 7.15–7.38 (6H, m), 7.52 (1H, m), 7.62 (1H, s), 8.09 (1H, brs); HRMS (ESI+) *m/z* [M+H]⁺ 338.1072 (C₁₉H₁₇N₃OCl requires: 338.1060).

***N*-[5-(2-chlorophenyl)-1*H*-pyrazol-3-yl]-2-indanecarboxamide (2c)**. Using a procedure for (–)-7, 2-indanecarboxylic acid (150 mg, 0.93 mmol) and 5-(2-chlorophenyl)-1*H*-pyrazole-3-amine hydrochloride (212 mg, 0.93 mmol) were condensed. The crude product was flash-chromatographed with 20% → 50% ethyl acetate in hexanes to give 112 mg (36%) of **2c**: pale yellow solid; ¹H NMR (CDCl₃) δ 3.18–3.42 (5H, m), 7.03 (1H, brs), 7.13–7.38 (6H, m), 7.45 (1H, m), 7.64 (1H, m), 8.13(1H, s); HRMS (ESI+) *m/z* [M+H]⁺ 338.1067 (C₁₉H₁₇N₃OCl requires: 338.1060).

***N*-[5-(4-methylphenyl)-1*H*-pyrazol-3-yl]-2-indanecarboxamide (2d)**. Using a procedure for (–)-7, 2-indanecarboxylic acid (33 mg, 0.20 mmol) and 5-(4-methylphenyl)-1*H*-pyrazole-3-amine (35 mg, 0.20 mmol) were condensed. The crude product obtained was flash-chromatographed with 75% ethyl acetate in hexanes to afford 45 mg (71%) of **2d**: beige solid; ¹H NMR (CDCl₃) δ 2.38 (3H, s),

3.20–3.40 (5H, m), 6.87 (1H, brs), 7.10–7.50 (8H, m); HRMS (ESI+) m/z $[M+H]^+$ 318.1605 ($C_{20}H_{20}N_3O$ requires: 318.1606).

***N*-[5-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]-2-indanecarboxamide (2e).** Using a procedure for (–)-7, 2-indanecarboxylic acid (98 mg, 0.60 mmol) and 5-(4-methoxyphenyl)-1*H*-pyrazole-3-amine (115 mg, 0.61 mmol) were condensed. The crude solid product obtained was suspended in ethyl acetate, filtered, and vacuum-dried to give 71 mg (35%) of **2e**: white solid, mp 199–203°C; 1H NMR ($CDCl_3$) δ 3.20–3.40 (5H, m), 3.84 (3H, s), 6.84 (1H, brs), 6.95 (2H, d, $J = 8.8$ Hz), 7.10–7.30 (4H, m), 7.52 (2H, d, $J = 8.8$ Hz), 8.05 (1H, brs), 9.75 (1H, brs); HRMS (ESI+) m/z $[M+H]^+$ 334.1554 ($C_{20}H_{20}N_3O_2$ requires: 334.1556).

***N*-[5-(4-isopropoxyphenyl)-1*H*-pyrazol-3-yl]-2-indanecarboxamide (2f).** Using a procedure for (–)-7, 2-indanecarboxylic acid (150 mg, 0.92 mmol) and 5-(4-isopropoxyphenyl)-1*H*-pyrazole-3-amine (200 mg, 0.92 mmol) were condensed. The crude product obtained was flash-chromatographed with 0% → 30% ethyl acetate in hexanes to give 153 mg (47%) of **2f**: pale yellow solid; 1H NMR ($CDCl_3$) δ 1.27 (6H, d, $J = 6.0$ Hz), 3.13 (4H, d, $J = 8.5$ Hz), 3.38–3.47 (1H, m), 4.65 (1H, sept, $J = 6.0$ Hz), 6.81 (1H, brs), 6.96 (2H, d, $J = 8.6$ Hz), 7.12–7.23 (4H, m), 7.60 (2H, d, $J = 8.6$ Hz), 10.51 (1H, brs), 12.63 (1H, brs); HRMS (ESI+) m/z $[M+H]^+$ 362.1867, ($C_{22}H_{24}N_3O_2$ requires: 362.1869).

***N*-[5-(3,4-dimethoxyphenyl)-1*H*-pyrazol-3-yl]-2-indanecarboxamide (2g).** Using a procedure for (–)-7, 2-indanecarboxylic acid (100 mg, 0.62 mmol) and 5-(3,4-dimethoxyphenyl)-1*H*-pyrazole-3-amine (135 mg, 0.62 mmol) were condensed. The crude solid product obtained was suspended in ethyl acetate, filtered, and vacuum-dried to give 21 mg (9%) of **2g**: white solid, mp 195–197°C; 1H NMR ($CDCl_3$) δ 3.18–3.42 (5H, m), 3.90 (3H, s), 3.91 (3H, s), 6.81 (1H, brs), 6.89 (1H, m), 7.09–7.27 (6H, m), 8.11 (1H, brs); HRMS (ESI+) m/z $[M+H]^+$ 364.1654 ($C_{21}H_{22}N_3O_3$ requires: 364.1661).

2-(2-naphthyl)-N-[5-(4-chlorophenyl)-1H-pyrazol-3-yl]acetamide (3). Using a procedure for (-)-7, 2-naphthaleneacetic acid (112 mg, 0.60 mmol) and 5-(4-chlorophenyl)-1H-pyrazole-3-amine (97 mg, 0.50 mmol) were condensed. The crude solid product obtained was suspended in ethyl acetate, filtered, and vacuum-dried to give 51 mg (28%) of **3**: white solid, mp 227–230°C; ¹H NMR (DMSO-*d*₆) δ 3.81 (2H, s), 6.90 (1H, brs), 7.42–7.56 (5H, m), 7.71 (2H, d, *J* = 8.3 Hz), 7.82–7.91 (4H, m), 10.76 (1H, brs), 12.91 (1H, brs); HRMS (ESI+) *m/z* [M+H]⁺ 362.1053 (C₂₁H₁₇N₃OCl requires: 362.1060).

2-(2-naphthyl)-N-[5-(3,4-dimethoxyphenyl)-1H-pyrazol-3-yl]acetamide (4). Using a procedure for (-)-7, 2-naphthaleneacetic acid (128 mg, 0.69 mmol) and 5-(3,4-dimethoxyphenyl)-1H-pyrazole-3-amine (150 mg, 0.69 mmol) were condensed. The crude solid product obtained was suspended in ethyl acetate, filtered, and vacuum-dried to give 164 mg (61%) of **4**: white solid, mp 202–205°C; ¹H NMR (DMSO-*d*₆) δ 3.76 (3H, s), 3.79 (5H, s), 6.80 (1H, brs), 6.98 (1H, d, *J* = 8.5 Hz), 7.18–7.30 (2H, m), 7.42–7.55 (3H, m), 7.80–7.92 (4H, m), 10.70 (1H, brs), 12.66 (1H, brs); HRMS (ESI+) *m/z* [M+H]⁺ 388.1666 (C₂₃H₂₂N₃O₃ requires: 388.1661).

N-[5-(3,4-dimethoxyphenyl)-1H-pyrazol-3-yl]-2,3-dihydro-1H-cyclopenta[*a*]naphthalene-2-carboxamide ((±)-5). Using a procedure for (-)-7, (±)-10 (36 mg, 0.17 mmol) and 5-(3,4-dimethoxyphenyl)-1H-pyrazole-3-amine (37 mg, 0.17 mmol) were condensed. The crude product was flash-chromatographed with 30% → 100% ethyl acetate in hexanes to give 15 mg (21%) of (±)-5: colorless amorphous; ¹H NMR (CDCl₃) δ 3.18 (1H, m), 3.30–3.55 (4H, m), 3.72 (3H, s), 3.76 (3H, s), 6.64 (1H, d, *J* = 8.4 Hz), 6.84 (1H, s), 7.03 (1H, d, *J* = 8.4 Hz), 7.07 (1H, s), 7.18 (1H, d, *J* = 8.4 Hz), 7.37 (2H, m), 7.56 (2H, m), 7.74 (1H, m), 9.13 (1H, brs); HRMS (ESI+) *m/z* [M+H]⁺ 414.1825 (C₂₅H₂₄N₃O₃ requires: 414.1818).

N-[5-(4-pyridinyl)-1H-pyrazol-3-yl]-2,3-dihydro-1H-cyclopenta[*a*]naphthalene-2-carboxamide ((±)-6). Using a procedure for (-)-7, (±)-10 (164 mg, 0.77 mmol) and 5-(4-pyridinyl)-

1*H*-pyrazole-3-amine (125 mg, 0.78 mmol) were condensed. The crude solid product was triturated with methanol and vacuum-dried to give 210 mg (77%) of (\pm)-**6**: white solid; ^1H NMR (CDCl_3) δ 3.40–3.65 (5H, m), 6.68 (1H, s), 7.33 (1H, d, $J = 8.4$ Hz), 7.40–7.50 (2H, m), 7.54 (2H, d, $J = 6.3$ Hz), 7.71 (2H, t, $J = 7.5$ Hz), 7.83 (1H, d, $J = 7.5$ Hz), 8.60 (2H, d, $J = 5.7$ Hz), 8.65 (1H, s); HRMS (ESI+) m/z $[\text{M}+\text{H}]^+$ 355.1552 ($\text{C}_{22}\text{H}_{19}\text{N}_4\text{O}$ requires: 355.1559).

Purity for the compounds in Table 1 and 3 by HPLC^a

Comopund	HPLC(Area%)
1	98.4
2a	99.5
2b	99.7
2c	97.9
2d	98.9
2e	>99.9
2f	98.6
2g	99.5
3	98.5
4	98.8
(±)-5	99.5
(±)-6	99.4
(±)-7	99.8
(+)-7	99.8 (98.4%ee) ^b
(-)-7	99.8 (>99.9%ee)

^a Wakopak combi ODS fast (30 x 2.0 mmI.D.) with liner gradient system of H₂O-CH₃CN-TFA 95 : 5 : 0.1 to 5 : 95 : 0.1 over 6 min and at a flow rate of 0.8 mL/min.

^b DAICEL CHIRALCEL OJ-R (150 x 4.6 mmI.D.), 55:45 H₂O/CH₃CN; 0.7 mL/min, 230 nm; (+)-7, *r*_t = 18.1; (-)-7, *r*_t = 21.1 min

Parallel Synthesis Library

Procedure: 0.06 mmol of the carboxylic acids and 0.02 mmol of 3-(4-chlorophenyl)-1*H*-pyrazol-3-amine were reacted in 110 μ L of pyridine in the presence of 0.03 mmol of 1,3-diisopropylcarbodiimide (DIPCI) at rt for 20 h. The resultant mixture diluted with 1890 μ L of DMSO was tested for Y5 binding. TLC and MS were used for the characterization of the compounds. Since the yields of the reactions were generally very high, the IC_{50} values were determined, assuming quantitative chemical yield. Before the library was constructed, the authors examined whether the reaction residues affected the binding data. It turned out that the binding data were not significantly influenced by the reaction residues. For instance, compound **1** prepared in this manner showed an IC_{50} value of 49 nM, and the confirmation of the activity of compound **3** is shown in the main text.