Supporting information

Cushing's Syndrome: Development of Highly Potent and Selective CYP11B1 Inhibitors of the (Pyridylmethyl)pyridine Type

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1. Synthetic procedures and characterization of compounds **33**–**35, 42**, **55**, **56** and intermediates **3**, **4**, **6**–**14**, **25**–**32**, **53**, **54**; as well as ^{13}C-NMR spectra of all compounds.

General Experimental

^{1}H NMR and ^{13}C spectra were recorded on a Bruker DRX-500 instrument. Chemical shifts are given in parts per million (ppm) and spectra are obtained from DMSO-d_6 or $CDCl_3$ solutions (reported in ppm), using chloroform as the reference standard (7.26 ppm) or DMSO-d_6 (2.50 ppm). The following abbreviations are used to denote signal multiplicities: s = singlet, d = doublet, t = triplet and m = multiplet. All coupling constants (*J*) are given in Hertz (Hz). Mass spectra (LC/MS) were measured on an MSQ® electro spray mass spectrometer (ThermoFisher, Dreieich, Germany). An RP-C18 NUCLEODUR® 100-5 (125x3 mm) column (Macherey-Nagel GmbH, Düren, Germany) was used as stationary phase and water/ acetonitrile mixtures as eluents. The purity of all compounds was ≥95%. Reagents and solvents were used as obtained from commercial suppliers without further purification or drying. Yields refer to purified products and are not optimized. Flash chromatography was performed on silica gel 40 (35/40−63/70 μM) with petroleum ether/ethyl acetate mixtures as eluents, and the reaction progress was determined by thin-layer chromatography analyses on Alugram SIL G/UV254 (Macherey Nagel). Visualization was accomplished with UV light.

Method A: Suzuki-Coupling

The corresponding brominated aromatic compound (1 eq) and the boronic acid (1.5 eq) were dissolved in toluene (20 mL), ethanol (20 mL) and aq. Na_2CO_3 (2.0 M, 5.0 mL). The mixture was deoxygenated under reduced pressure and flushed with N_2. After having repeated this cycle three times, $Pd(PPh_3)_4$ (5 mol %) was added. The resulting suspension was heated under reflux for 4 h. After cooling, the phases were separated and the aqueous phase was extracted two times with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The purification was performed by flash chromatography using SiO_2.

Method B: Grignard Reaction

To a solution of the Grignard reagent (2 eq) in dry diethyl ether (10 mL) the corresponding carbonyl compound (1 eq) in dry diethyl ether (5 mL) was added dropwise. The reaction mixture was heated to reflux for 2 hours. Afterwards ice was added followed by the addition of HCl (1 M) until the resulting precipitate disappeared. The phases were separated and the aqueous phase was extracted twice with diethyl ether. The combined organic layers were washed with saturated sodium hydrogen carbonate solution and brine. After drying over $MgSO_4$ and concentration under vacuum the crude product was purified by flash chromatography on silica-gel.

Method C: CDI Reaction

To a solution of the corresponding alcohol (1 eq) in NMP, CDI (5 eq) was added. Then the solution was heated to reflux for 16 hours. After cooling to room temperature the reaction mixture was diluted with EtOAc and washed with water and brine. The organic phase was

dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography on silica-gel.

Method D: Wohl Ziegler Bromination

The methyl heteroaromatic compound was dissolved in 20 mL of dry carbon tetrachloride. To this solution *N*-bromsuccinimide (NBS) (1.1eq) and benzoyl peroxide (5 mol%) were added and the mixture was refluxed overnight. After cooling, the succinimide was removed by filtration and the filtrate was concentrated under vacuum. The crude product was purified by flash chromatography on silica-gel.

Method E: S_N-Reaction

K_2CO_3 (5 eq), imidazole (4 eq) and the corresponding methyl heteroaromatic bromide were suspended in DMF (1 mL / mmol) or acetonitrile (1 mL / mmol). The resulting mixture was heated to 120°C for 2 h. After cooling, water (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by column chromatography using SiO_2.

Method F: Suzuki-Coupling using microwave

A mixture of brominated aromatic compound (1 eq), corresponding boronic acid or boronic acid pinacolester (1.2 eq), Cs_2CO_3 (3 eq) and $PdCl_2$(dppf) (5 mol %) were dissolved in DME/ H_2O/ EtOH (1 mL/ 1 mL/ 1 mL). The reaction mixture was stirred for 20 min at 150°C, 150 W and 18 bar in the microwave. After addition of H_2O (10 mL) and ethyl acetate (15 mL) further extraction with ethyl acetate (2 × 15 mL) were followed. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The purification was performed by flash chromatography using SiO_2. After flash chromatography the product was dissolved in ethyl acetate and a few drops of conc. HCl and water were added. After stirring for 30 minutes the phases were separated and aqueous phase was neutralized with aqueous Na_2CO_3 solution (2M). After extraction with ethyl acetate and drying over $MgSO_4$ the solvent was removed under vacuum.

6-Bromonicotinaldehyde (1). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) =129.0, 130.6, 137.5, 148.3, 152.5, 189.4.

6-Phenylnicotinaldehyde (2). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 120.5, 127.5, 129.0, 129.8, 130.4, 136.5, 138.0, 152.4, 162.2, 190.4.

6-(Thiophen-3-yl)nicotinaldehyde (3). Synthesized using compound **1** (840 mg, 4.52 mmol) and thiophen-3-ylboronic acid (867 g, 6.77 mmol) according to Method A. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (8:2) as eluent. Orange solid. Yield: 556 mg, 65 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 7.45 (dd, J = 5.0, 2.8 Hz, 1H), 7.72–7.80 (m, 2H), 8.11 (dd, J = 2.8, 1.3 Hz, 1H), 8.19 (dd, J = 8.2, 2.2 Hz, 1H), 9.06 (dd, J = 2.2, 0.9 Hz, 1H), 10.11 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 120.3, 126.3, 126.4, 126.9, 129.6, 136.5, 141.1, 152.6, 158.0, 190.2; (ESI): *m/z* = 190.27 $[M+H]^+$.

6-(naphthalen-1-yl)nicotinaldehyde (4). Synthesized using compound **1** (720 mg, 3.87 mmol) and 1-naphthalenboronic acid (1.00 g, 5.81 mmol) according to Method A. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (8:1) as eluent. Orange solid. Yield: 733 mg, 81 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 7.50–7.62 (m, 3H), 7.65–7.69 (m, 1H), 7.77–7.81 (m, 1H), 7.92–8.00 (m, 2H), 8.10–8.14 (m, 1H), 8.31 (dd, J = 7.9, 2.2 Hz, 1H), 9.25 (dd, J = 2.2, 0.9 Hz, 1H), 10.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 125.1, 125.2, 125.4, 126.2, 127.0, 128.0, 128.5, 129.7, 130.0, 130.7, 134.0, 136.1, 137.2, 152.1, 164.6, 190.5; MS (ESI): m/z = 234.29 $[M+H]^+$.

1-(6-phenylpyridin-3-yl)ethanol (5). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 25.0, 67.8, 120.4, 126.9, 128.7, 128.9, 134.0, 139.0, 139.5, 147.2, 156.6.

1-(6-phenylpyridin-3-yl)propan-1-ol (6). Synthesized using compound **2** (313 mg, 1.71 mmol) and ethylmagnesium bromide (3.42 mL, 3.42 mmol, 1 M in THF) according to Method B. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (3:1) as eluent. Light yellow solid. Yield: 298 mg, 82 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 0.90–0.95 (m, 3H), 1.71–1.88 (m, 2H), 4.62 (t, J = 6.62 Hz, 1H), 7.38–7.43 (m, 1H), 7.43–7.49 (m, 2H), 7.64–7.67 (m, 1H), 7.69–7.73 (m, 1H), 7.92–7.96 (m, 2H), 8.54 (d, J = 2.21 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 9.9, 31.7, 73.2, 120.3, 126.8, 128.7, 128.8, 134.5, 138.3, 139.0, 147.7, 156.5; MS (ESI): m/z = 214.28 $[M+H]^+$.

Cyclopropyl(6-phenylpyridin-3-yl)methanol (7). Synthesized using compound **2** (227 mg, 1.24 mmol) and cyclopropylmagnesium bromide (4.96 mL, 2.48 mmol, 0.5 M in THF) according to Method B. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (3:1) as eluent. Light yellow solid. Yield: 234 mg, 84 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 0.35–0.44 (m, 1H), 0.49 (dq, J = 9.4, 4.7 Hz, 1H), 0.55–0.68 (m, 2H), 1.21 (qt, J = 8.1, 5.0 Hz, 1H), 3.00 (br, s, 1H), 4.05 (d, J = 8.2 Hz, 1H), 7.38–7.44 (m, 1H), 7.44–7.50 (m, 2H), 7.66–7.70 (m, 1H), 7.80–7.85 (m, 1H), 7.94–8.00 (m, 2H), 8.64–8.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 2.8, 3.6, 19.0, 75.9, 120.3, 126.8, 128.7, 128.8, 134.5, 137.7, 139.1, 147.6, 156.5; MS (ESI): m/z = 226.28 $[M+H]^+$.

2-Methyl-1-(6-phenylpyridin-3-yl)propan-1-ol (8). Synthesized using compound **2** (283 mg, 1.55 mmol) and isopropylmagnesium chloride (1.55 mL, 3.10 mmol, 2 M in THF) according to Method B. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (4:1) as eluent. Orange solid. Yield: 138 mg, 40 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 0.82–0.93 (m, 3H), 1.02 (d, J = 6.6 Hz, 3H), 1.95–2.08 (m, 1H), 4.46 (d, J = 6.6 Hz, 1H), 7.39–7.44 (m, 1H), 7.45–7.50 (m, 2H), 7.68–7.75 (m, 2H), 7.96–8.01 (m, 2H), 8.57 (d, J = 1.9 Hz, H); MS (ESI): m/z = 228.26 $[M+H]^+$.

Furan-2-yl(6-phenylpyridin-3-yl)methanol (9). Synthesized using compound **2** (650 mg, 3.75 mmol) and furan-2-ylmagnesium bromide (1.85 g, 10.8 mmol, 2 M in THF) according to Method B. Crude product was purified by flash chromatography on silica-gel using a mixture

of hexane / ethyl acetate (6:1) as eluent. Yellow solid. Yield: 631 mg, 67 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 3.62 (br. s., 1H), 5.86 (s, 1H), 6.17 (d, *J* = 3.4 Hz, 1H), 6.33 (dd, *J* = 3.0, 1.8 Hz, 1H), 7.33–7.51 (m, 4H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.83 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.88–7.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 66.7, 106.7, 109.3, 119.4, 126.0, 127.7, 128.0, 134.0, 134.3, 137.9, 141.8, 147.1, 154.1, 156.1; (ESI): *m/z* = 251.87 $[M+H]^+$.

Phenyl(6-phenylpyridin-3-yl)methanol (10). Synthesized using compound **2** (300 mg, 1.73 mmol) and phenylmagnesium bromide (1.73 mL, 3.46 mmol, 2 M in THF) according to Method B. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (3:1) as eluent. Yellow solid. Yield: 138 mg, 42 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 5.91 (s, 1H), 7.29–7.34 (m, 1H), 7.35–7.50 (m, 7H), 7.68 (dd, *J* = 8.2, 0.6 Hz, 1H), 7.73–7.78 (m, 1H), 7.94–7.99 (m, 2H), 8.68 (dd, *J* = 1.6, 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 74.1, 120.3, 126.5, 126.9, 128.0, 128.7, 128.7, 128.9, 135.0, 137.6, 139.0, 143.0, 148.2, 156.7; (ESI): *m/z* = 261.97 $[M+H]^+$.

1-(6-(Thiophen-3-yl)pyridin-3-yl)ethanol (11). Synthesized using compound **3** (260 mg, 1.37 mmol) and methylmagnesium bromide (2.74 mL, 2.74 mmol, 1 M in THF) according to Method B. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (1:1) as eluent. Yellow solid. Yield: 240 mg, 85 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 1.50 (d, *J* = 6.6 Hz, 3H), 4.90 (q, *J* = 6.3 Hz, 1H), 7.38 (dd, *J* = 5.0, 2.8 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.61 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.70 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.85 (dd, *J* = 2.8, 1.3 Hz, 1H), 8.48 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 25.2, 68.0, 120.4, 123.6, 126.4, 126.5, 134.3, 139.5, 142.0, 147.4, 152.9; (ESI): *m/z* = 206.29 $[M+H]^+$.

Cyclopropyl(6-(thiophen-3-yl)pyridin-3-yl)methanol (12). Synthesized using compound **3** (270 mg, 1.43 mmol) and cyclopropylmagnesium bromide (5.72 mL, 2.86 mmol, 0.5 M in THF) according to Method B. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (1:1) as eluent. Yellow solid. Yield: 138 mg, 42 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 0.37–0.45 (m, 1H), 0.50 (dq, *J* = 9.7, 4.8 Hz, 1H), 0.57–0.71 (m, 2H), 1.18–1.29 (m, 1H), 2.48 (br. s., 1H), 4.06 (d, *J* = 8.2 Hz, 1H), 7.39 (dd, *J* = 5.0, 3.2 Hz, 1H), 7.60 (dd, *J* = 8.2, 0.6 Hz, 1H), 7.64–7.68 (m, 1H), 7.78–7.85 (m, 1H), 7.89 (dd, *J* = 3.0, 1.4 Hz, 1H), 8.60–8.64 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 2.8, 3.6, 19.1, 76.1, 120.0, 123.4, 126.2, 126.3, 134.5, 137.2, 141.9, 147.6, 152.8; (ESI): *m/z* = 232.26 $[M+H]^+$.

1-(6-(naphthalen-1-yl)pyridin-3-yl)ethanol (13). Synthesized using compound **4** (231 mg, 0.99 mmol) and methylmagnesium bromide (1.98 mL, 1.98 mmol, 1 M in THF) according to Method B. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (2:1) as eluent. White solid. Yield: 172 mg, 70 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 1.59 (d, *J* = 6.1 Hz, 3H), 5.00 (m, 1H), 7.44–7.62 (m, 5H), 7.80–7.86 (m, 1H), 7.90–7.96 (m, 2H), 8.07 (d, *J* = 7.9 Hz, 1H), 8.74 (s, 1H); (ESI): *m/z* = 250.29 $[M+H]^+$.

Cyclopropyl(6-(naphthalen-1-yl)pyridin-3-yl)methanol (14). Synthesized using compound **4** (253 mg, 1.09 mmol) and cyclopropylmagnesium bromide (4.34 mL, 2.17 mmol, 0.5 M in THF) according to Method B. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (3:1) as eluent. Light yellow solid. Yield: 239 mg, 80 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 0.39–0.54 (m, 2H), 0.60–0.72 (m, 2H), 1.22–1.29 (m, 1H), 4.04–4.14 (m, 1H), 7.42–7.60 (m, 5H), 7.86–7.92 (m, 3H), 8.04–8.08 (m, 1H), 8.77 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 3.3, 3.9, 14.4, 60.6, 125.0, 125.5, 125.9, 126.1, 126.7, 127.7, 128.6, 129.1, 134.2, 137.8, 138.5, 147.8, 158.5, 171.4; MS (ESI): m/z = 276.34 $[M+H]^+$.

5-(1-(1*H*-imidazol-1-yl)ethyl)-2-phenylpyridine (15). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 21.8, 54.2, 117.7, 120.5, 126.9, 128.8, 129.3, 129.9, 134.3, 135.3, 135.9, 138.5, 147.5, 157.4.

5-(1-(1*H*-imidazol-1-yl)propyl)-2-phenylpyridine (16). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 10.9, 28.4, 60.8, 117.4, 120.4, 126.8, 128.8, 129.2, 130.0, 134.1, 134.7, 136.3, 138.5, 148.0, 157.4.

5-(Cyclopropyl(1*H*-imidazol-1-yl)methyl)-2-phenylpyridine (17). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 4.9, 5.2, 16.2, 63.8, 118.2, 120.4, 126.8, 128.8, 129.2, 129.7, 134.0, 134.9, 136.4, 138.5, 148.0, 157.4.

5-(1-(1*H*-imidazol-1-yl)-2-methylpropyl)-2-phenylpyridine (18). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 19.9, 20.2, 32.4, 66.6, 117.2, 120.5, 126.8, 128.8, 129.3, 130.0, 133.2, 135.3, 136.4, 138.5, 148.8, 157.4.

5-(Furan-2-yl(1*H*-imidazol-1-yl)methyl)-2-phenylpyridine (19). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 56.6, 110.7, 110.8, 118.6, 120.4, 126.9, 128.8, 129.4, 129.9, 131.6, 135.4, 136.8, 138.4, 143.9, 148.4, 150.1, 157.8.

5-((1*H*-imidazol-1-yl)(phenyl)methyl)-2-phenylpyridine (20). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 62.6, 119.0, 120.2, 126.8, 127.8, 128.7, 128.8, 129.0, 129.3, 129.8, 133.1, 136.1, 137.2, 138.0, 138.3, 149.2, 157.4.

5-(1-(1*H*-imidazol-1-yl)ethyl)-2-(thiophen-3-yl)pyridine (21). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 21.7, 54.2, 117.6, 120.2, 123.9, 126.1, 126.5, 129.9, 134.3, 134.9, 135.9, 141.4, 147.5, 153.5.

5-(Cyclopropyl(1*H*-imidazol-1-yl)methyl)-2-(thiophen-3-yl)pyridine (22). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 4.9, 5.2, 16.2, 63.8, 118.2, 120.2, 123.9, 126.1, 126.5, 129.8, 133.7, 134.9, 136.4, 141.4, 148.0, 153.5.

5-(1-(1*H*-imidazol-1-yl)ethyl)-2-(naphthalen-1-yl)pyridine (23). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 22.1, 54.5, 117.9, 125.3, 125.5, 125.6, 126.2, 126.8, 127.8, 128.6, 129.4, 130.2, 131.2, 134.1, 134.1, 135.6, 136.2, 137.9, 147.6, 159.4.

5-(Cyclopropyl(1*H*-imidazol-1-yl)methyl)-2-(naphthalen-1-yl)pyridine (24). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 5.1, 5.2, 16.4, 64.0, 118.2, 125.0, 125.2, 125.4, 125.9, 126.6, 127.6, 128.4, 129.2, 129.8, 131.0, 133.9, 134.1, 134.5, 136.4, 137.7, 147.8, 159.3.

3-Methyl-6-Phenylpyridazine (25). Synthesized using 3-chloro-6-methylpyridazine (1.00 g, 7.78 mmol) and phenylboronic acid (1.42 g, 11.67 mmol) according to Method A. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (2:1) as eluent. White solid. Yield: 1.00 g, 76 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 2.76 (s, 3H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.46–7.55 (m, 3H), 7.76 (d, *J* = 8.5 Hz, 1H), 8.03–8.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 22.0, 123.9, 126.9, 127.2, 128.9, 129.7, 134.4, 136.4, 157.2, 158.5; (ESI): *m/z* = 170.96 $[M+H]^+$.

2-Methyl-5-phenylpyrazine (26). To a stirred solution of propylenediamine (2.94 g, 0.04 mol) in ethanol (50 mL) was added phenylglyoxal-monohydrate (5.00 g, 0.03 mol) at 0°C within 30 minutes. After stirring for 1.5 hours at room temperature KOH (2.10 g, 0.04 mol) was added and the reaction mixture was refluxed for 12 hours. Then the solvent was removed under vacuum and the residue was extracted with ether. The organic phases were washed with brine and dried over $MgSO_4$. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (7:3→3:7) as eluent. After flash chromatography the product was recrystallized from hexane. White solid. Yield: 780 mg, 15 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 2.57 (s, 3H), 7.38–7.50 (m, 3H), 7.91–7.99 (m, 2H), 8.43–8.49 (m, 1H), 8.87 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 21.2, 126.6, 128.9, 129.4, 136.5, 140.9, 143.8, 149.8, 151.9; (ESI): *m/z* = 170.94 $[M+H]^+$.

5-Methyl-2-phenylpyrimidine (27). To a solution of benzamidine hydrochloride (500 mg, 3.19 mmol) and 3-ethoxy-2-methylacrylaldehyde (400 mg, 3.51 mmol) in methanol (10 mL) was added a NaOMe solution (30% in methanol) dropwise under stirring over 30 minutes. After stirring for 4 hours water (20 mL) was added and mixture was stirred for further 30 minutes at room temperature. After filtration the obtained precipitate was washed with water and dried. White solid. Yield: 220 mg, 41 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 2.34 (s, 3H), 7.44–7.54 (m, 3H), 8.37–8.45 (m, 2H), 8.64 (d, *J* = 0.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 15.7, 128.1, 128.5, 128.8, 130.6, 137.9, 157.6, 162.7; (ESI): *m/z* = 170.97 $[M+H]^+$.

4-Methyl-1-phenylisoquinoline (28). Under nitrogen atmosphere methoxymethyl-triphenylphosphoniumchlorid (11.0 g, 0.03 mol) was suspensed in THF (40 mL) and cooled to -40°C. Then KOtBu (4.50 g, 0.04 mol) was added so that temperature not rised over -10°C. After complete addition of KOtBu immediately 2'-bromacetophenon (4.00 g, 2.71 mL, 0.02 mol) in THF (25 mL) was added dropwise at less then -10°C. The reaction mixture was stirred for 1 h at -10°C and afterwards 18 h at room temperature. Then addition of H_2O (100 mL) and extraction with hexane (10 × 20 mL) were followed. The organic phases were dried over $MgSO_4$ and concentrated under vacuum. The residue was dissolved in methanol (100 mL) and water (75 mL) followed by extraction with hexane (10 × 20 mL). Again the organic phases were dried over $MgSO_4$ and concentrated under vacuum. The obtained 1-Bromo-2-(1-

methoxyprop-1-en-2-yl)benzene (orange liquid, 4.05 g) was used directly in the next step without further purification and characterization. To a stirred solution of 1-Bromo-2-(1-methoxyprop-1-en-2-yl)benzene (3.13 g, 13.8 mmol) in diethyl ether (30 mL) at 0°C was added *n*-BuLi (1.6M in hexane, 8.60 mL, 13.8 mmol) dropwise. After 1 h PhCN (1.56 g, 1.56 mL, 15.2 mmol) was added and the reaction temperature was raised to room temperature. H_2O (40 mL) was added and the organic materials were extracted with diethyl ether (2 × 30 mL). The combined extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under vacuum. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (10:1→5:1) as eluent. Yellow oil. Yield: 1.10 g, 36 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 2.66 (d, *J* = 0.9 Hz, 3 H), 7.44–7.54 (m, 4 H), 7.64–7.68 (m, 2 H), 7.72 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1 H), 8.00 (m, 1 H), 8.09 (m, 1 H), 8.45 (d, *J* = 0.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 16.0, 123.5, 126.1, 126.7, 128.1, 128.3, 128.3, 129.8, 129.9, 136.1, 139.8, 142.1, 159.3; (ESI): *m/z* = 219.92 $[M+H]^+$.

3-(Bromomethyl)-6-phenylpyridazine (29). Synthesized using compound **25** (982 mg, 5.77 mmol), NBS (1.13 g, 6.35 mmol) and DBPO (70 mg, 0.29 mmol) in carbon tetrachloride according to Method D. Crude product was purified by flash chromatography on silica-gel using hexane / ethyl acetate (4:1) as eluent. Product was used directly in the next step without further characterization. Orange solid. Yield: 53 mg, 4 %. (ESI): *m/z* = 250.67 $[M+H]^+$.

2-(Bromomethyl)-5-phenylpyrazine (30). Synthesized using compound **26** (724 mg, 4.25 mmol), NBS (832 mg, 4.68 mmol) and DBPO (52 mg, 0.21 mmol) in carbon tetrachloride according to Method D. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (3:1) as eluent. Product was used directly in the next step without further characterization. Yellow solid. Yield: 571 mg, 54 %. (ESI): *m/z* = 250.80 $[M+H]^+$.

5-(Bromomethyl)-2-phenylpyrimidine (31). Synthesized using compound **27** (205 mg, 1.20 mmol), NBS (236 mg, 1.32 mmol) and DBPO (14.6 mg, 0.06 mmol) in carbon tetrachloride according to Method D. Crude product was purified by flash chromatography on silica-gel using hexane / ethyl acetate (10:1) as eluent. Product was used directly in the next step without further characterization. White solid. Yield: 89 mg, 30 %. (ESI): *m/z* = 250.68 $[M+H]^+$.

4-(Bromomethyl)-1-phenylisoquinoline (32). Synthesized using compound **28** (4.21 g, 19.2 mmol), NBS (3.76 g, 21.1 mmol) and DBPO (233 mg, 0.96 mmol) in carbon tetrachloride according to Method D. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (8:1→2:1) as eluent. Light yellow solid. Yield: 710 mg, 12 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 4.94 (s, 2 H), 7.47–7.54 (m, 3 H), 7.57 (ddd, *J* = 8.4, 7.0, 1.1 Hz, 1 H), 7.64–7.67 (m, 2 H), 7.82 (ddd, *J*=8.4, 7.0, 1.3 Hz, 1 H), 8.14 (m, 1 H), 8.18 (m, 1 H), 8.64 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 28.5, 123.3, 126.1, 126.7, 127.4, 128.4, 128.4, 128.5, 128.9, 129.9, 130.0, 130.6, 134.6, 139.2, 142.6, 162.3; (ESI): *m/z* = 299.59 $[M+H]^+$.

3-((1*H*-imidazol-1-yl)methyl)-6-phenylpyridazine (33). Synthesized using compound **29** (40 mg, 0.16 mmol), imidazole (44 mg, 0.64 mmol) and K_2CO_3 (111 mg, 0.80 mmol) in acetonitrile according to Method E. The crude product was purified by flash chromatography on silica-gel using ethyl acetate as eluent. After flash chromatography the solid was washed with ethyl acetate. Light orange solid. Yield: 22 mg, 58 %. Mp: 145–148 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 5.58 (s, 2H), 7.08 (s, 1H), 7.17–7.26 (m, 2H), 7.55–7.61 (m, 3H), 7.72 (s, 1H), 7.88 (d, *J* = 8.8 Hz, 1H), 8.09–8.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 50.9, 119.6, 125.1, 125.5, 127.4, 129.4, 130.7, 130.8, 135.8, 137.8, 157.2, 159.3; MS (ESI): *m/z* = 236.91 $[M+H]^+$.

2-((1*H*-imidazol-1-yl)methyl)-5-phenylpyrazine (34). Synthesized using compound **30** (100 mg, 0.40 mmol), imidazole (109 mg, 1.60 mmol) and K_2CO_3 (276 mg, 2.00 mmol) in DMF according to Method E. Crude product was purified by flash chromatography on silica-gel using ethyl acetate as eluent. Light yellow solid. Yield: 69 mg, 73 %. Mp: 152–154 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 5.50 (s, 2H), 7.24 (t, *J* = 1.3 Hz, 1H), 7.33 (t, *J* = 1.1 Hz, 1H), 7.64–7.74 (m, 3H), 7.86 (s, 1H), 8.17–8.23 (m, 2H), 8.63 (d, *J* = 1.3 Hz, 1H), 9.18 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 50.0, 119.2, 126.9, 129.1, 130.2, 130.3, 135.7, 137.5, 141.5, 142.3, 152.3; MS (ESI): *m/z* = 236.91 $[M+H]^+$.

5-((1*H*-imidazol-1-yl)methyl-2-phenylpyrimidine (35). Synthesized using compound **31** (70 mg, 0.28 mmol), imidazole (76 mg, 1.12 mmol) and K_2CO_3 (195 mg, 1.41 mmol) in acetonitrile according to Method E. Crude product was purified by flash chromatography on silica-gel using ethyl acetate as eluent. After flash chromatography the product was recrystallized in ethyl acetate. Light yellow solid. Yield: 62 mg, 94 %. Mp: 155–157 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 5.17 (s, 2H), 6.94 (t, *J* = 1.3 Hz, 1H), 7.15 (t, *J* = 1.1 Hz, 1H), 7.47–7.54 (m, 3H), 7.61 (s, 1H), 8.41–8.46 (m, 2H), 8.63 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 46.0, 118.8, 127.0, 128.2, 128.7, 130.7, 131.1, 136.8, 137.2, 156.2, 164.8; MS (ESI): *m/z* = 236.92 $[M+H]^+$.

4-((1*H*-Imidazol-1-yl)methyl)-1-phenylisoquinoline (36). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 46.5, 119.1, 122.0, 123.4, 126.5, 127.4, 128.3, 128.7, 128.9, 129.8, 129.8, 131.0, 134.7, 137.1, 139.0, 142.5, 162.4.

5-Methyl-2-phenylpyridine (37). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 18.1, 120.0, 126.7, 128.6, 128.7, 131.5, 137.3, 139.4, 150.1, 154.8.

5-(Bromomethyl)-2-phenylpyridine (38). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 29.7, 120.6, 127.0, 128.4, 128.8, 130.1, 137.6, 138.5, 149.6, 157.36.

2-Phenyl-5-(pyridin-3-ylmethyl)pyridine (39). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 35.9, 120.4, 123.6, 126.8, 128.7, 128.9, 133.6, 135.4, 136.2, 137.0, 139.0, 148.1, 149.9, 150.1, 155.9.

2-Phenyl-5-(pyridin-4-ylmethyl)pyridine (40). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 38.0, 120.3, 124.0, 126.7, 128.7, 128.9, 132.7, 137.1, 138.9, 148.7, 149.9, 150.0, 156.0.

4-((6-Phenylpyridin-3-yl)methyl)isoquinoline (41). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 33.2, 120.3, 123.1, 126.7, 127.2, 128.4, 128.6, 128.6, 128.7, 128.9, 130.7, 133.6, 134.6, 136.7, 139.0, 143.7, 149.7, 152.3, 155.7.

5-((6-Phenylpyridin-3-yl)methyl)pyrimidine (42). Synthesized using compound **38** (219 mg, 0.88 mmol) and pyrimidine-5-boronic acid (164 mg, 1.32 mmol) according to Method A. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (1:1) as eluent. After flash chromatography the product was dissolved in ethyl acetate and a few drops of conc. HCl and water were added. After stirring for 30 minutes the phases were separated and aqueous phase was neutralized with aqueous Na_2CO_3 solution (2M). After extraction with ethyl acetate and drying over $MgSO_4$ the solvent was removed under vacuum. White solid. Yield: 43 mg, 20 %. Mp: 128–130 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 4.02 (s, 2H), 7.39–7.44 (m, 1H), 7.44–7.56 (m, 3H), 7.70 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.95–8.00 (m, 2H), 8.58–8.67 (m, 3 H), 9.13 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 33.4, 120.5, 126.8, 128.8, 129.1, 132.2, 133.3, 136.9, 138.7, 149.7, 156.4, 156.9, 157.3; MS (ESI): *m/z* = 247.83 $[M+H]^+$.

5-((4-Methylpyridin-3-yl)methyl)-2-phenylpyridine (43). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 19.3, 33.8, 120.5, 125.7, 126.9, 129.0, 129.1, 133.2, 133.8, 136.8, 139.2, 146.1, 148.7, 149.9, 150.7, 155.9.

5-((5-Methylpyridin-3-yl)methyl)-2-phenylpyridine (44). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 18.3, 35.7, 120.4, 126.7, 128.7, 128.9, 133.1, 133.8, 134.8, 136.8, 137.0, 139.0, 147.2, 148.6, 149.8, 155.8.

5-((6-Phenylpyridin-3-yl)methyl)nicotinamide (45). ^{13}C NMR (DMSO-d_6, 125 MHz): δ_C (ppm) = 34.5, 120.1, 126.4, 128.7, 128.9, 129.6, 134.5, 135.2, 135.9, 137.4, 138.4, 146.6, 149.7, 152.0, 154.3, 166.3.

5-((5-Fluoropyridin-3-yl)methyl)-2-phenylpyridine (46). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 35.6, 120.7, 123.1, 123.3, 127.0, 129.0, 129.2, 133.0, 136.6, 136.8, 137.3, 137.4, 137.4, 139.1, 146.0, 146.1, 150.1, 156.4, 158.8, 160.8.

2-Phenyl-5-((5-(trifluoromethyl)pyridin-3-yl)methyl)pyridine (47). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 35.7, 120.6, 126.8, 128.8, 129.1, 132.4, 133.1, 133.1, 135.7, 137.0, 138.8, 144.9, 145.0, 149.8, 153.3, 153.3, 156.4.

5-((5-Methoxypyridin-3-yl)methyl)-2-phenylpyridine (48). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 35.7, 55.5, 120.4, 120.9, 126.7, 128.7, 128.9, 133.6, 135.7, 136.0, 137.0, 139.0, 142.3, 149.8, 155.8, 155.9.

5-((6-Phenylpyridin-3-yl)methyl)pyridin-3-ol (49). ^{13}C NMR (DMSO-d_6, 125 MHz): δ_C (ppm) = 34.4, 120.0, 122.0, 126.3, 128.7, 128.8, 134.9, 136.1, 136.7, 137.3, 138.5, 140.4, 149.6, 153.6, 154.2.

2-Bromo-5-((5-bromopyridin-3-yl)methyl)pyridine (51). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 35.0, 121.1, 128.3, 133.7, 136.5, 138.9, 138.9, 140.8, 147.8, 149.3, 150.2.

2-Phenyl-5-((5-phenylpyridin-3-yl)methyl)pyridine (52). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 35.8, 120.4, 126.7, 127.1, 128.1, 128.7, 128.9, 129.0, 133.5, 134.6, 135.2, 136.6, 137.0, 137.4, 138.9, 146.6, 148.6, 149.8, 155.9.

5-Bromo-2-Phenylpyridine (53). Synthesized using 2-iodo-5-bromopyridine (1.79 g, 6.3 mmol) and phenylboronic acid (1 eq, 770 mg, 6.3 mmol) according to Method A. Crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (50:1→30:1) as eluent. Product was used directly in the next step without further characterization. White solid. Yield: 841 mg, 57 %. MS (ESI): *m/z* = 235.83 $[M+H]^+$.

5-Iodo-2-Phenylpyridine (54). To a mixture of NaI (2.20 g, 14.8 mmol) and CuI (71.0 mg, 0.37 mmol) *N*,*N*′-dimethylethylendiamin (65.0 mg, 0.74 mmol), **55** (1.74 g, 7.42 mmol) and dioxan (30 mL) were added under nitrogen atmosphere. The reaction mixture was stirred for 21 h at 110°C followed by the addition of an ammonia solution (30 % in water, 5 mL) and water (20 mL). The aqueous phase was extracted with DCM (4 × 30 mL) and then the combined organic phases were dried over $MgSO_4$. The solvent was removed under vacuum and the crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (40:1) as eluent. Product was used directly in the next step without further characterization. Light yellow solid. Yield: 860 mg, 41 %. (ESI): *m/z* = 281.86 $[M+H]^+$.

2-Phenyl-5-(pyridine-3-yloxy)pyridine (55). A mixture of **54** (230 mg, 0.82 mmol), copper(I) iodide (8.00 mg, 0.04 mmol), 2-picolinic acid (10.0 mg, 0.08 mmol), 3-hydroxypyridine (94.0 mg, 0.98 mmol) and K_3PO_4 (348 mg, 1.64 mmol) was dissolved in DMSO (5 mL) under nitrogen atmosphere. The reaction mixture was stirred for 24 h at 80°C. After cooling down to room temperature ethyl acetate (10 mL) and H_2O (1mL) were added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 10 mL) and the combined organic phases were dried over $MgSO_4$. After filtration the solvent was evaporated under vacuum and the resulting crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (2:1) as eluent. Light yellow solid. Yield: 38 mg, 19 %. Mp: 150–152 °C (ethyl acetate). ^1H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 7.29–7.33 (m, 1 H), 7.34–7.43 (m, 3 H), 7.45–7.50 (m, 2 H), 7.73 (m, 1 H), 7.95–7.99 (m, 2 H), 8.43 (dd, *J* = 4.6, 1.4 Hz, 1 H), 8.49 (d, *J* = 2.8 Hz, 1 H), 8.51 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 121.1, 124.2, 125.4, 126.5, 126.6, 128.8, 128.8, 138.5, 141.1, 141.4, 145.1, 151.9, 153.2; MS (ESI): *m/z* = 249.04 $[M+H]^+$.

6-Phenyl-*N*-(pyridin-3-yl)pyridin-3-amine (56). A mixture of **54** (91.0 mg, 0.32 mmol), 3-aminopyridine (37.0 mg, 0.38 mmol) and Cs_2CO_3 (521 mg, 1.60 mmol) was dissolved in toluene (15 mL) under nitrogen atmosphere. Then a fresh solution of $Pd(OAc)_2$-BINAP (under nitrogen atmosphere $Pd(OAc)_2$ (2.00 mg, 0.01 mmol) and (±)-BINAP (6.00 mg, 0.01 mmol) were dissolved in toluene (5 mL) and stirred for 20 min at room temperature) in

toluene was added. The resulting reaction mixture was heated under reflux overnight. After mixture was cooled down to room temperature the solid material was filtered off and washed with DCM (100 mL). The filtrate was evaporated and the resulting crude product was purified by flash chromatography on silica-gel using a mixture of hexane / ethyl acetate (1:1→1:2→EE) as eluent. Orange solid. Yield: 47 mg, 52 %. Mp: 157–159 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H (ppm) = 6.50 (s, 1 H), 7.21 (dd, *J* = 8.2, 4.7 Hz, 1 H), 7.34–7.40 (m, 1 H), 7.42–7.51 (m, 4 H), 7.65 (d, *J* = 8.5 Hz, 1 H), 7.92–7.96 (m, 2 H), 8.23 (dd, *J* = 4.7, 1.3 Hz, 1 H), 8.43 (d, *J* = 2.5 Hz, 1 H), 8.46–8.50 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C (ppm) = 120.7, 123.8, 123.9, 124.8, 126.2, 128.3, 128.7, 137.5, 138.9, 139.0, 140.2, 140.3, 142.6, 150.7; MS (ESI): *m/z* = 247.97 $[M+H]^+$.

2. HPLC purity control of final compounds

A SpectraSystems® LC system consisting of a pump, an autosampler, and a PDA detector was employed. Mass spectra (LC/MS) were measured on an MSQ® electro spray mass spectrometer (ThermoFisher, Dreieich, Germany). An RP-C18 NUCLEODUR® 100-5 (125x3 mm) column (Macherey-Nagel GmbH, Düren, Germany) was used as stationary phase. All solvents were HPLC grade. The system was operated by the standard software Xcalibur®. In a gradient run the percentage of acetonitrile (containing 0.1 % trifluoroacetic acid) was increased from an initial concentration of 0 % at 0 min to 100 % at 15 min and kept at 100 % for 5 min. The injection volume was 10 µL and the flow rate was set to 800 µL/min. MS analysis was carried out at a spray voltage of 3800 V, a capillary temperature of 350°C and a source CID of 10 V. Spectra were acquired in positive mode from 100 to 1000 m/z and at 254 nm for the UV trace. The relative peak area in the UV chromatogram was used to determine the purity of the compounds. The purity of all compounds was ≥95 %.

Comp.	RT (min)	Purity [%]
15	5.68	99
16	6.31	98
17	6.09	97
18	6.92	98
19	7.28	99
20	7.82	99
21	4.99	99
22	5.98	98
23	7.88	99
24	8.68	97
33	4.39	99
34	6.45	99
35	6. 37	98
36	6. 09	99
39	6.24	99
40	7.70	99
41	5.91	99
42	5.86	99
43	5.22	98
44	5.31	99
45	5.75	99
46	7.14	98
47	7.97	99
48	6.18	99
49	5.52	98
52	7.33	99
55	5.92	99
56	6.13	98

3. The predicted and determined pIC_{50} values of both training and test compounds.

Compd.	Determined values pIC_{50}	Predicted values pIC_{50}	Residuals
15	7.4815	7.8396	0.3581
16	7.5528	6.8537	-0.6991
18	7.9208	8.5233	0.6025
19	7.1612	7.3917	0.2305
20	6.9066	6.3829	-0.5237
21	7.6778	8.0133	0.3355
22	7.9586	7.7962	-0.1624
23	7.2218	7.1768	0.0450
24	6.8210	6.4598	-0.3612
33	5.7667	5.5085	-0.2582
34	6.2147	6.5369	0.3222
36	7.0605	6.8567	-0.2038
39	7.4949	7.0042	-0.4907
40	7.0088	6.8937	-0.1151
42	6.6198	6.4217	-0.1981
43	8.0969	8.2794	0.1825
45	6.3696	6.5782	0.2086
47	7.4202	7.2071	-0.2131
48	8.3010	8.6746	0.3736
49	7.2924	7.4117	0.1193
52	8.8861	8.6316	-0.2545
55	5.9935	5.8853	-0.1082
56	5.3010	5.0805	-0.2205
Ref 1	6.9706	7.2548	0.2842
Ref 3	6.7423	6.6688	0.0735
Ref 4	7.1675	7.0217	-0.1458
17	7.6778	7.8170	0.1392
35	5.9500	6.1245	0.1745
41	8.2218	8.3607	0.1389
44	8.6990	8.8357	0.1367
46	6.9031	7.1548	0.2517

The formulas used to calculate the statistic parameters:

$$r^2 = 1 - \frac{\Sigma(y_p - y_a)^2}{\Sigma(y_a - y_a)^2}$$

$$q^2 = 1 - \frac{\Sigma(y_a - y_a)^2}{\Sigma(y_a - y_a)^2}$$

$$SDEP = \sqrt{\frac{\Sigma(y_p - y_a)^2}{N}}$$

$$SDEC = \sqrt{\frac{\Sigma(y_c - y_a)^2}{N}}$$

4. The alignment of training set compounds.