Supporting Information

Design, Synthesis, and in Vitro Evaluation of Novel Aminomethyl-pyridines as DPP-4 Inhibitors

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Supporting information includes experimental procedures and characterization of new compounds.

Biological screening.

In vitro DPP-4 inhibition assay: The screening of the compounds for DPP-4 inhibitory activity was performed by using a DPP-4 drug discovery kit (AK499-0001, Enzo Life Sciences). The inhibition of the human recombinant DPP-4 activity was measured by following the increase of absorbance upon cleavage of the chromogenic substrate Gly-Pro-pNA according to the protocol of the manufacturer.

In order to determine the range over which the reaction was linear, the absorbance at 405 nm was continuously measured for 60 min. As an optimal time for the experiment 16 min were chosen. Reactions were carried out at 37 ˚C in Tris buffer (50 mM, pH 7.5) containing 0.18 mU/well of enzyme, 50 μM of substrate (the final substrate concentration was chosen around K_m value obtained under the assay conditions) and variable concentration of the inhibitor. For the compound dilutions DMSO was used and its final solvent concentration did not exceed 1%. Enzyme DPP-4 was first preincubated with the compounds for 10 min prior the substrate addition. After preincubation period the substrate was added and the reaction was followed by continuous absorbance measurement at 405 nm for 16 min using a MRX Revelation plate reader (Dynex Technologies). The experiment was repeated 3 times for each test compound and the values were averaged.

To obtain the IC_{50} values the active compounds were titrated up to eight concentrations. The IC_{50} values were calculated from the trend line of the curve generated after plotting the percentage of activity versus inhibitor concentration (Table S1). Percent remaining activity in presence of the inhibitor was calculated using the equation: $\%Activity = \frac{V_i}{V} \cdot 100$,

where V_i is the initial velocity in presence of the inhibitor at concentration i, V is the initial velocity of the negative control (enzyme without inhibitor).

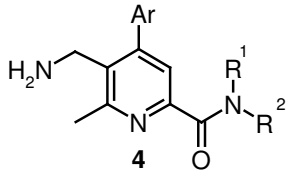
The type of inhibition was determined by measuring the rate of hydrolysis of Gly-Pro-pNA at four different concentrations of substrate and inhibitor. To calculate the initial rate of pNA formation the absorption at 405 nm was converted to nanomoles of pNA using a standard calibration curve. For each concentration of inhibitor the initial rates were used for Lineweaver-Burk plots. The inhibition constant K_i was obtained from the expression:

$$K_i = \frac{i}{\left[\left(\frac{K_p}{K_m}\right) - 1\right]}$$

where K_m is concentration of substrate that leads to half-maximal velocity, and K_p is the effective Michaelis constant in presence of the inhibitor at concentration i.

In vitro DPP-8 inhibition assay: The screening of the compounds for DPP-8 inhibitory activity was performed using human recombinant DPP-8, supplied by Enzo Life Sciences. The substrate used for the screening was Gly-Pro-pNA at 300 μM. Other parameters and conditions of the assay were identical as previously described for DPP-4 (Table S1).

Table S2. Selectivity of the novel DPP-4 inhibitors **4** over DPP-8 in comparison to IPI.



4

Compd	Ar	R^1	R^2	DPP-4	DPP-8	LC_{50} (µM)
				IC_{50}/K_i (nM)[a]	IC_{50}/K_i (µM)[a]	
4e-1	2,4-Dichloro-phenyl	H	H	16 ± 2	33 ± 0.5	> 10
4e-2	2,4-Dichloro-phenyl	Me	H	11 ± 0.5 (5.5 ± 2)	39 ± 1	> 10
4e-7	2,4-Dichloro-phenyl	Cyanomethyl	H	10 ± 0.7	66 ± 0.3	> 10
4e-4	2,4-Dichloro-phenyl	Pyrrolidin-1-yl		44 ± 5	25 ± 0.5	> 10
4b-1	4-Fluoro-phenyl	Cyclopropyl	H	80 ± 6	106 ± 2.5	> 10
4b-2	4-Fluoro-phenyl	Pyrrolidin-1-yl		686 ± 45	137 ± 1.5	> 10
4c-1	2,4-Difluoro-phenyl	Cyclopropyl	H	937 ± 11	182 ± 0.9	> 10
4c-5	2,4-Difluoro-phenyl	5-Methyl-isoxazol-3-yl	H	674 ± 1.6	179 ± 3.4	> 10
	IPI			3000	39 ± 5.4	

[a]Measured in three independent experiments. Results given as the mean ± SD.

Toxicity of the compounds: The toxicity of the compounds at 10 µM was investigated with HeLa cells (Human cervix carcinoma [ATCC Cat.No. CCL-2]) at the Fraunhofer Institute in Stuttgart.

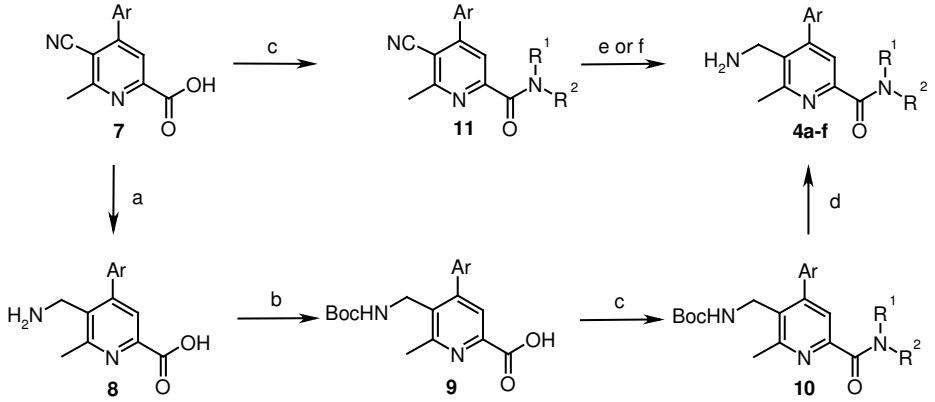
Synthesis of compound collections.

General.

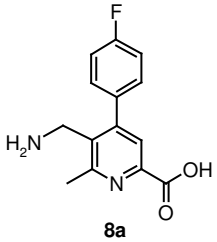
The chemicals were used as purchased from commercial suppliers. Analytical TLC were performed with ALUGRAM silica gel 60 F254 plate. Column chromatographies were carried out using MN silica gel 60 (70-230 mesh ASTM). The mass spectra were measured on a Waters LC/MS system (Alliance 2795 HPLC, SQD mass detector, PDA 996 detector; Grom-Sil 80 ODS-7 PH 4 µm, 2.0 x 40 mm; ionizing voltage 10 eV). Ion mass (m/z) signals are reported as values in atomic mass units. For FT-ICR-MS measurements the APEX II Bruker Daltonics (4.7 Tesla) spectrometer was used. ^1H, and ^{13}C NMR analyses were performed on a Bruker 400 Ultra Shield instrument. NMR spectra were performed as DMSO-D_6 or $CDCl_3$ solutions (reported in ppm), using solvent peak or TMS as the reference. Other NMR solvents were used as needed. When peak multiplets are given, the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, bs = broad singlet, dd = doublet of doublets, dt = doublet of triplets. Coupling constants, when given, are reported in Hz.

Synthesis of 5-aminomethyl-pyridines 4.

Scheme S1

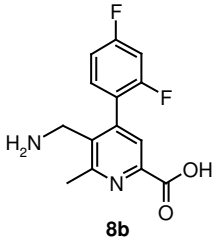


5-Aminomethyl-4-aryl-6-methyl-pyridine-2-carboxylic acids 8 – general procedure (Scheme S1, conditions a): 5-Cyano-4-aryl-6-methyl-pyridine-2-carboxylic acid **7** (1 eq, 0.25 mmol) was dissolved in acetic acid (0.25 mL) and 10% Pd/C (10% m/m) was added. The mixture was degassed and hydrogenated under 1.0 atm pressure of H_2 for 24 h at 60 ˚C. The catalyst was filtered off and the solvent was removed on vacuum. The residue was taken up in water and extracted with DCM. Aqueous layer was lyophilized to give a solid product **8** that was used in the next step without further purification.



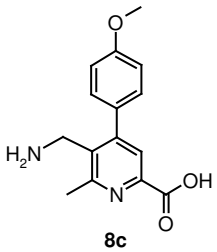
8a

8a; orange solid; 52% yield, $C_{14}H_{13}FN_2O_2$, M = 260.27 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 261 *m/z*.



8b

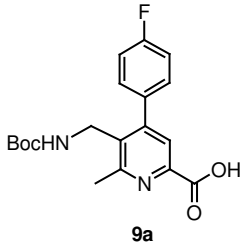
8b; pale solid; 69% yield, $C_{14}H_{12}F_2N_2O_2$, M = 278.26 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 279 *m/z*.



8c

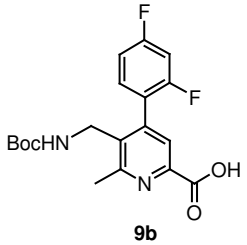
8c; pale solid; 72% yield, $C_{15}H_{16}N_2O_3$, M = 272.31 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 273 *m/z*.

5-(*tert*-Butoxycarbonylamino-methyl)-4-aryl-6-methyl-pyridine-2-carboxylic acids 9 - general procedure (Scheme S1, conditions b): Boc_2O (1.5 eq, 0.225 mmol, 0.049 g) was added to a solution of **8** (1 eq, 0.15 mmol, 0.041 g) in dioxane/water (10:1, 5.5 mL) and the mixture was stirred for 16 h. The solvent was removed under reduced pressure and the product **9** was isolated by column chromatography with DCM/MeOH (40:1) as eluent.



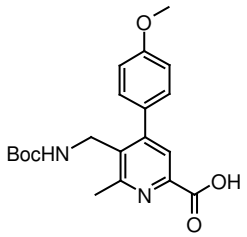
9a

9a; colorless solid; 68% yield, $C_{19}H_{21}FN_2O_4$, M = 360.39 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 361 *m/z*.



9b

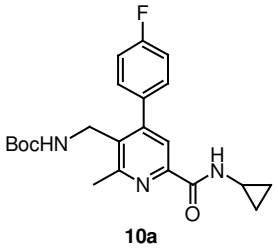
9b; colorless solid; 62% yield, $C_{19}H_{20}F_2N_2O_4$, M = 378.38 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 379 *m/z*.



9c

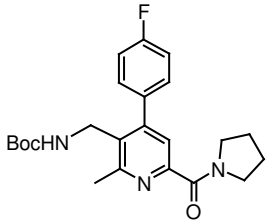
9c; colorless solid; 79% yield, $C_{20}H_{24}N_2O_5$, M = 372.43 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 373 *m/z*.

General procedure for the synthesis of 10 (Scheme S1, conditions c): The carboxylic acid **9** (1 eq, 0.15 mmol) was dissolved in 5 mL DCM. Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (1.1 eq, 0.17 mmol 0.864 g) and triethylamine (2 eq, 0.30 mmol, 41 µl) were successively added followed by addition of amine or 1-hydroxybenzotriazol ammonium salt (1.5 eq, 0.23 mmol, 0.035 g). After 3-16 h stirring at room temperature (the reaction monitored by TLC), the solvent was removed and the product **9** was isolated by filtration on silica gel.



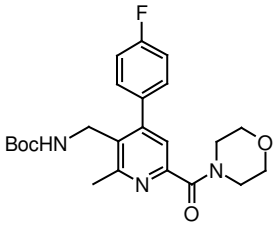
10a

10a; colorless solid; 57% yield, $C_{22}H_{26}FN_3O_3$, M = 399.47 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 400 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (m, 2 H), 0.86 (m, 2 H), 1.39 (s, 9 H), 2.64 (s, 3 H), 2.91 (m, 1 H), 4.27 (d, J = 4.6 Hz, 2 H), 4.62 (s, 1 H), 7.11 (m, 2 H), 7.23 (m, 2 H), 7.81 (s, 1 H), 8.07 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.5 (CH_2), 22.7 (CH_3), 23.9 (CH), 28.3 (CH_3), 39.0 (CH_2), 79.8 (C), 115.7 (d, $^2J_{C\text{-}F}$ = 22.0 Hz, CH), 121.1 (CH), 130.2 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, CH), 131.7 (C), 134.2 (d, $^4J_{C\text{-}F}$ = 3.7 Hz, C), 147.5 (C), 151.0 (C), 155.2 (C), 157.8 (C), 162.8 (d, $^1J_{C\text{-}F}$ =248.8, C), 165.5 (C).



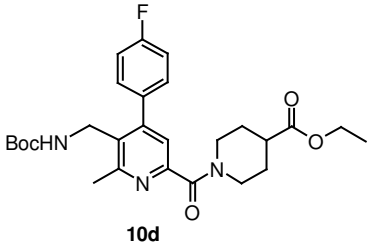
10b

10b; colorless solid; 92% yield, $C_{23}H_{28}FN_3O_3$, M = 413.50 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 414 *m/z*.



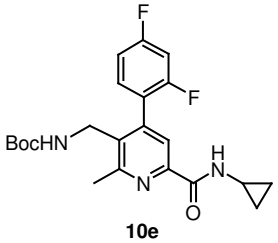
10c

10c; colorless solid; 84% yield, $C_{23}H_{28}FN_3O_4$, M = 429.50 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 430 *m/z*.



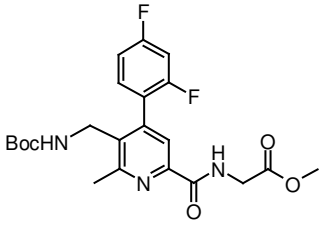
10d

10d; colorless solid; 92% yield, $C_{30}H_{34}FN_3O_5$, M = 499.59 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 501 *m/z*.



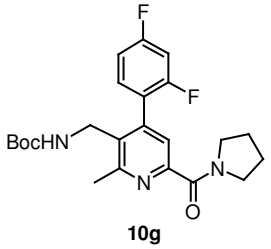
10e

10e; colorless solid; 46% yield, $C_{22}H_{25}F_2N_3O_3$, M = 417.46 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 418 *m/z*.



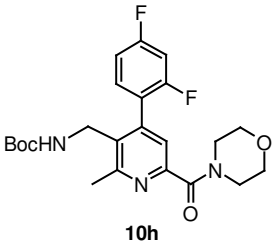
10f

10f; colorless solid; 67% yield, $C_{22}H_{25}F_2N_3O_5$, M = 449.46 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 450 *m/z*.



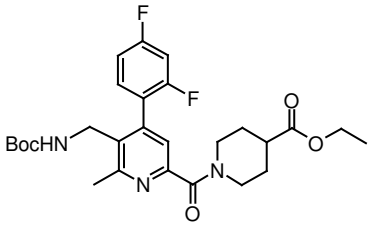
10g

10g; colorless solid; 92% yield, $C_{23}H_{27}F_2N_3O_3$, M = 431.49 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 432 *m/z*.



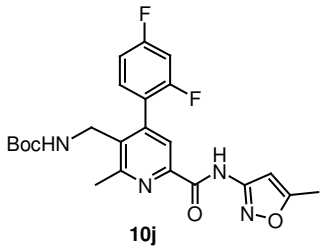
10h

10h; colorless solid; 91% yield, $C_{23}H_{27}F_2N_3O_4$, M = 447.49 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 448 *m/z*.



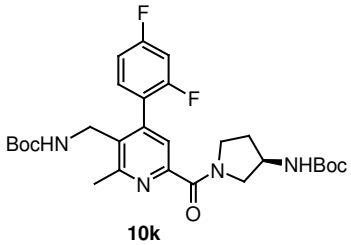
10i

10i; colorless solid; 76% yield, $C_{27}H_{33}F_2N_3O_5$, M = 517.58 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 519 *m/z*.



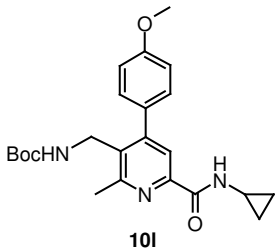
10j

10j; colorless solid; 58% yield, $C_{23}H_{24}F_2N_4O_4$, M = 458.47 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 459 *m/z*.



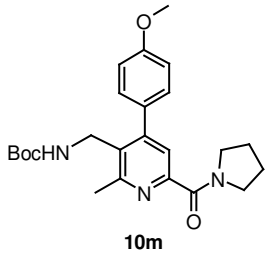
10k

10k; colorless solid; 92% yield, $C_{29}H_{37}F_2N_3O_5$, M = 545.64 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 547 *m/z*.



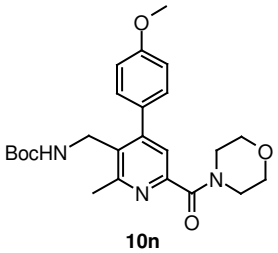
10l

10l; colorless solid; 74% yield, $C_{23}H_{29}N_3O_4$, M = 411.51 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 412 *m/z*.



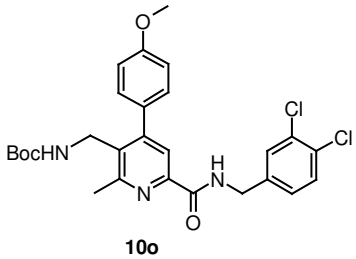
10m

10m; colorless solid; 72% yield, $C_{24}H_{31}N_3O_4$, M = 425.53 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 426 *m/z*.



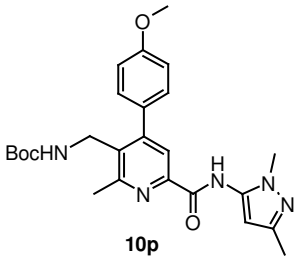
10n

10n; colorless solid; 92% yield, $C_{24}H_{31}N_4O_5$, M = 441.43 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 442 *m/z*.



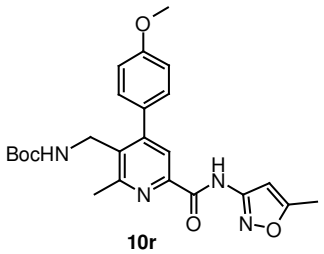
10o

10o; colorless solid; 88% yield, $C_{27}H_{29}Cl_2N_3O_4$, M = 530.46 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 531 *m/z*.



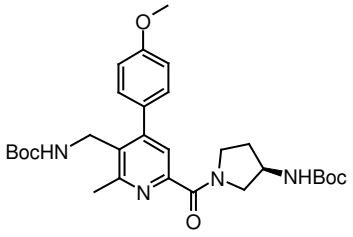
10p

10p; colorless solid; 62% yield, $C_{25}H_{31}N_5O_4$, M = 465.56 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 467 *m/z*.



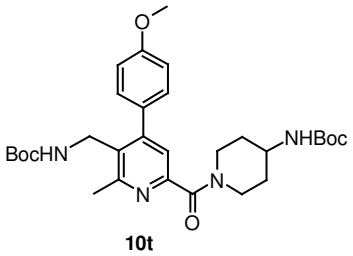
10r

10r; colorless solid; 57% yield, $C_{24}H_{28}N_4O_5$, M = 452.52 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 454 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9 H), 2.42 (s, 3 H), 2.66 (s, 3 H), 3.84 (s, 3 H), 4.33 (d, J = 4.3 Hz, 2 H), 4.61 (s, 1 H), 6.85 (s, 1 H), 6.95 (m, 2 H), 7.20 (m, 2 H), 7.88 (s, 1 H), 10.50 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7 (CH_3), 22.5 (CH_3), 28.3 (CH_3), 39.1 (CH_2), 55.3 (CH_3), 79.7 (C), 96.0 (CH), 114.2 (CH), 121.8 (CH), 129.7 (CH), 130.1 (C), 132.8 (C), 146.0 (C), 152.0 (C), 155.0 (C), 157.6 (C), 158.3 (C), 159.8 (C), 162.1 (C), 170.0 (C).



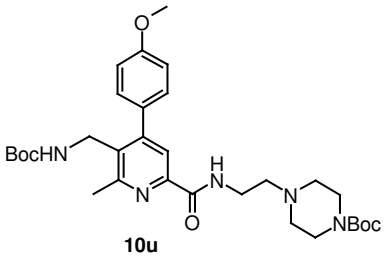
10s

10s; colorless solid; 89% yield, $C_{30}H_{41}N_3O_6$, M = 539.68 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 541 *m/z*.



10t

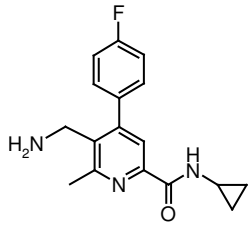
10t; colorless solid; 53% yield, $C_{30}H_{42}N_4O_4$, M = 554.70 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 556 *m/z*.



10u

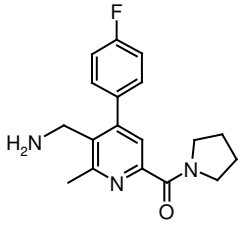
10u; colorless solid; 92% yield, $C_{32}H_{46}N_4O_6$, M = 539.68 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 541 *m/z*.

5-Aminomethyl-4-aryl-6-methyl-pyridine-2-carboxylic acid amides 4 – general procedure (Scheme S1, conditions d): The Boc - protected aminomethyl-pyridine **10** (0.10 mmol) was treated with 25% TFA/DCM (5 mL) at rt. After 1 h the solvent was removed under reduced pressure, the residue was taken up in water and extracted with DCM/EA. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated. The product **4** was isolated by column chromatography with DCM/MeOH (40:1) as eluent.



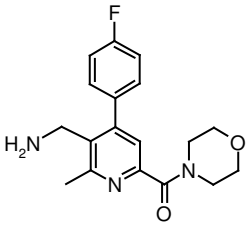
4b-1

4b-1; colorless solid; 99% yield, $C_{17}H_{18}FN_3O$, M = 299.35 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 300 *m/z*. ^{1}H NMR (400 MHz, Methanol-D_4) δ 0.55 (m, 2 H), 0.70 (m, 2 H), 2.62 (s, 3 H), 2.74 (m, 1 H), 3.98 (s, 2 H), 7.13 (m, 2 H), 7.28 (m, 2 H), 7.65 (s, 1 H). ^{13}C NMR (100 MHz, Methanol-D_4) δ 6.7 (CH_2), 22.8 (CH_3), 23.6 (CH), 38.2 (CH_2), 117.0 (d, $^2J_{C\text{-}F}$ = 22.7 Hz, CH), 122.2 (CH), 131.2 (C), 131.9 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, CH), 135.3 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, C), 149.8 (C), 153.1 (C), 159.8 (C), 164.5 (d, $^1J_{C\text{-}F}$ =247.4 Hz, C), 167.7 (C). FT-ICR-MS: calculated for $C_{17}H_{18}FN_3OH^+$: 300.1507, found: 300.1505.



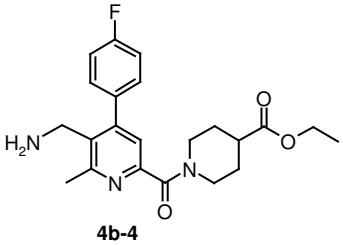
4b-2

4b-2; colorless solid; 95% yield, $C_{18}H_{20}FN_3O$, M = 313.38 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 314 *m/z*. ^{1}H NMR (400 MHz, Methanol-D_4) δ 1.96 (m, 4 H), 2.74 (s, 3 H), 3.61 (m, 2 H), 3.69 (m, 2 H), 3.95 (s, 2 H), 7.25 (m, 2 H), 7.44 (m, 3 H). ^{13}C NMR (100 MHz, Methanol-D_4) δ 22.5 (CH_3), 25.0 (CH_2), 27.3 (CH_2), 39.1 (CH_2), 47.9 (CH_2), 50.3 (CH_2), 116.8 (d, $^2J_{C\text{-}F}$ = 22.0 Hz, CH), 123.5 (CH), 131.9 (d, $^3J_{C\text{-}F}$ = 8.8 Hz, CH), 132.9 (C), 135.6 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, C), 152.3 (C), 153.6 (C), 159.2 (C), 164.4 (d, $^1J_{C\text{-}F}$ = 247.4 Hz, C), 168.2 (C). FT-ICR-MS: calculated for $C_{18}H_{20}FN_3OH^+$: 314.1663, found: 314.1662.



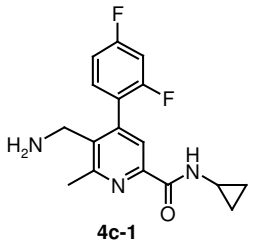
4b-3

4b-3; colorless solid; 89% yield, $C_{18}H_{20}FN_3O_2$, M = 329.38 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 330 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 3 H), 3.68 (s, 2 H), 3.79 (m, 6 H), 7.12 (m, 2 H), 7.35 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5 (CH_3), 39.8 (CH_2), 42.7 (CH_2), 47.8 (CH_2), 66.8 (CH_2), 67.0 (CH_2), 115.5 (d, $^2J_{C\text{-}F}$ = 21.2 Hz, CH), 123.0 (CH), 130.3 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, CH), 134.2 (C), 134.5 (d, $^4J_{C\text{-}F}$ = 3.7 Hz, C), 150.0 (C), 151. 0 (C), 157.1 (C), 162.7 (d, $^1J_{C\text{-}F}$ = 248.1 Hz, C), 167.4 (C). FT-ICR-MS: calculated for $C_{18}H_{20}FN_3O_2H^+$: 330.1612, found: 330.1611.



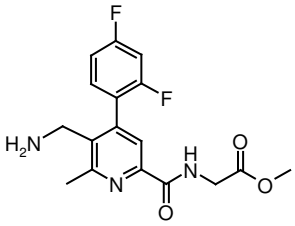
4b-4

4b-4; colorless solid; 99% yield, $C_{22}H_{26}FN_3O_3$, M = 399.47 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 400 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (m, 3 H), 1.82 (m, 3 H), 2.07 (m, 3 H), 2.59 (m, 1 H), 2.72 (s, 3 H), 3.05 (m, 1 H), 3.21 (m, 1 H), 3.83 (s, 2 H), 3.98 (m, 1 H), 4.16 (q, J = 7.1 Hz, 2 H), 4.53 (m, 1 H), 7.14 (m, 2 H), 7.28 (s, 1 H), 7.37 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.4 (CH_3), 27.7 (CH_2), 28.4 (CH_2), 39.6 (CH_2), 41.0 (CH), 41.6 (CH_2), 46.5 (CH_2), 60.6 (CH_2), 115.5 (d, $^2J_{C\text{-}F}$ = 21.2 Hz, CH), 122.2 (CH), 130.3 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, CH), 133.5 (C), 134.5 (d, $^4J_{C\text{-}F}$ = 3.7 Hz, C), 149.9 (C), 151.7 (C), 157.3 (C), 162.6 (d, $^1J_{C\text{-}F}$ = 248.1 Hz, C), 167.5 (C), 174.1 (C). FT-ICR-MS: calculated for $C_{22}H_{26}FN_3O_3H^+$: 400.2031, found: 400.2032.



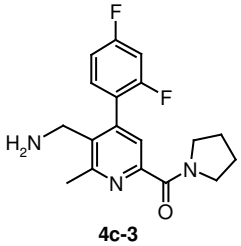
4c-1

4c-1; colorless solid; 86% yield, $C_{17}H_{17}F_2N_3O$, M = 317.34 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 318 *m/z*. ^{1}H NMR (400 MHz, Methanol-D_4) δ 0.70 (m, 2 H), 0.86 (m, 2 H), 2.78 (s, 3 H), 2.89 (m, 1 H), 4.15 (s, 2 H), 7.20 (m, 2 H), 7.45 (m, 1 H), 7.84 (s, 1 H). FT-ICR-MS: calculated for $C_{17}H_{17}F_2N_3OH^+$: 318.1413, found: 318.1412.



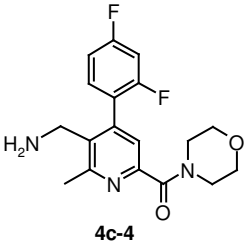
4c-2

4c-2; colorless solid; 99% yield, $C_{17}H_{17}F_2N_3O_3$, M = 349.34 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 350 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (s, 3 H), 3.74 (s, 2 H), 3.78 (s, 3 H), 4.26 (d, J = 5.6 Hz, 1 H), 6.95 (m, 2 H), 7.23 (m, 1 H), 7.85 (s, 1 H), 8.52 (t, J = 5.5 Hz, 1 H). FT-ICR-MS: calculated for $C_{17}H_{17}F_2N_3O_3H^+$: 350.1311, found: 350.1309.



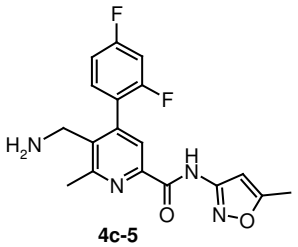
4c-3

4c-3; colorless solid; 95% yield, $C_{18}H_{19}F_2N_3O$, M = 331.37 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 332 *m/z*. FT-ICR-MS: calculated for $C_{18}H_{19}F_2N_3OH^+$: 332.1569, found: 332.1569.



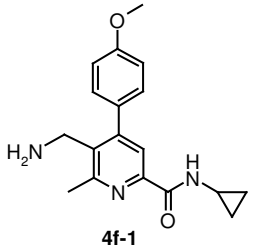
4c-4

4c-4; colorless solid; 91% yield, $C_{18}H_{19}F_2N_3O_2$, M = 347.37 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 348 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3 H), 3.69 (m, 10 H), 6.90 (m, 2 H), 7.22 (m, 2 H). FT-ICR-MS: calculated for $C_{18}H_{19}F_2N_3O_2H^+$: 348.1518, found: 348.1519.



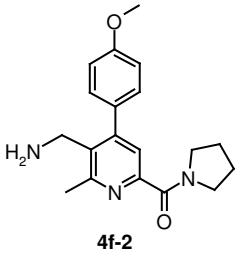
4c-5

4c-5; colorless solid; 98% yield, $C_{18}H_{16}F_2N_4O_2$, M = 358.35 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 359 *m/z*. ^{1}H NMR (400 MHz, Methanol-D_4) δ 2.44 (s, 3 H), 2.85 (s, 3 H), 4.19 (s, 2 H), 6.77 (s, 1 H), 7.23 (m, 2 H), 7.48 (m, 1 H), 7.98 (s, 1 H). FT-ICR-MS: calculated for $C_{18}H_{16}F_2N_4O_2H^+$: 359.1314, found: 359.1311.



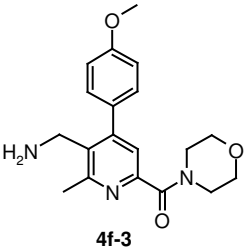
4f-1

4f-1; colorless solid; 87% yield, $C_{18}H_{21}N_3O_2$, M = 311.39 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 312 *m/z*. FT-ICR-MS: calculated for $C_{18}H_{21}N_3O_2H^+$: 312.1707, found: 312.1708.



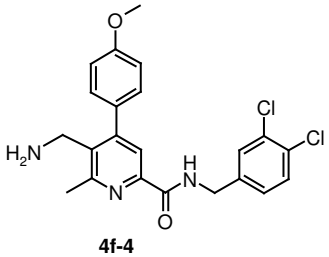
4f-2

4f-2; colorless solid; 78% yield, $C_{19}H_{23}N_3O_2$, M = 325.41 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 326 *m/z*. FT-ICR-MS: calculated for $C_{19}H_{23}N_3O_2H^+$: 326.1863, found: 326.1864.



4f-3

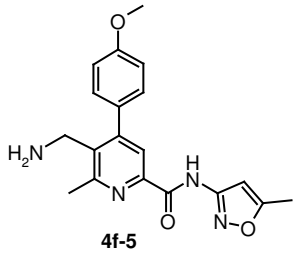
4f-3; colorless solid; 99% yield, $C_{19}H_{23}N_3O_3$, M = 341.41 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 342 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 3 H), 3.73 (m, 13 H), 6.91 (m, 2 H), 7.23 (m, 3 H). FT-ICR-MS: calculated for $C_{19}H_{23}N_3O_3H^+$: 342.1812, found: 342.1811.



4f-4

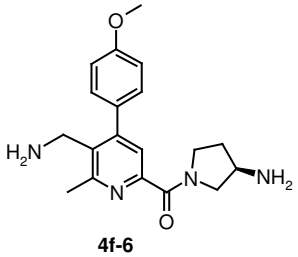
4f-4; colorless solid; 99% yield, $C_{22}H_{21}Cl_2N_3O_2$, M = 430.34 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 431 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (s, 3 H), 3.86 (s, 3 H), 4.62 (d, *J* = 6.4 Hz, 2 H), 6.98 (m, 2 H), 7.21 (m, 1 H), 7.29 (m, 2 H), 7.42 (m, 2 H), 7.94 (s, 1 H), 8.54 (t, *J* = 6.2

Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5 (CH_3), 39.8 (CH_2), 42.2 (CH_2), 55.3 (CH_3), 114.0 (CH), 121.8 (CH), 127.1 (CH), 129.6 (CH), 129.7 (CH), 130.5 (CH), 130.8 (C), 131.3 (C), 132.6 (C), 138.8 (C), 146.7 (C), 151.1 (C), 157.0 (C), 159.7 (C), 164.6 (C). FT-ICR-MS: calculated for $C_{22}H_{21}Cl_2N_3O_2H^+$: 430.1084, found: 430.1084.



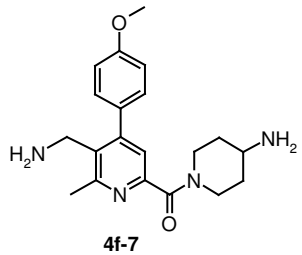
4f-5

4f-5; colorless solid; 87% yield, $C_{19}H_{20}N_4O_3$, M = 352.40 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 353 *m/z*. ^{1}H NMR (400 MHz, Methanol-D_4) δ 2.43 (s, 3 H), 2.95 (s, 3 H), 3.88 (s, 3 H), 4.41 (s, 2 H), 6.73 (s, 1 H), 7.14 (m, 2 H), 7.47 (m, 2 H), 8.16 (s, 1 H). ^{13}C NMR (100 MHz, Methanol-D_4) δ 12.4 (CH_3), 21.5 (CH_3), 37.7 (CH_2), 56.1 (CH_3), 97.4 (CH), 115.9 (CH), 124.7 (CH), 129.6 (C), 131.5 (CH), 146.3 (C), 158.1 (C), 158.9 (C), 159.7 (C), 161.5 (C), 162.5 (C), 171.9 (C). FT-ICR-MS: calculated for $C_{19}H_{20}N_4O_3H^+$: 353.1608, found: 353.1608.



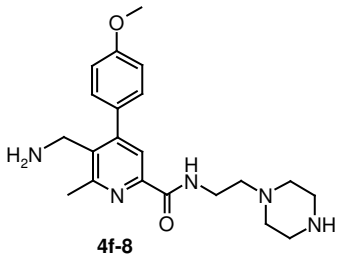
4f-6

4f-6; colorless solid; 82% yield, $C_{19}H_{24}N_4O_2$, M = 340.43 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 340 *m/z*. FT-ICR-MS: calculated for $C_{19}H_{24}N_4O_2H^+$: 341.1972, found: 341.1972.



4f-7

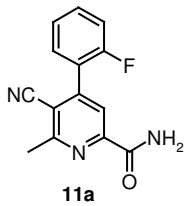
4f-7; colorless solid; 79% yield, $C_{20}H_{26}N_4O_2$, M = 354.46 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 355 *m/z*. FT-ICR-MS: calculated for $C_{20}H_{26}N_4O_2H^+$: 355.2129, found: 355.2128.



4f-8

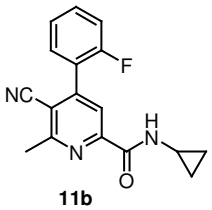
4f-8; colorless solid; 88% yield, $C_{21}H_{29}N_5O_2$, M = 383.50 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 383 *m/z*. FT-ICR-MS: calculated for $C_{21}H_{29}N_5O_2H^+$: 384.2394, found: 384.2400.

4-Aryl-5-cyano-6-methyl-pyridine-2-carboxylic acid amides 11 – general procedure (Scheme S1, conditions c): These compounds were prepared according to the procedure for **10**, using compound **7** as a starting material.



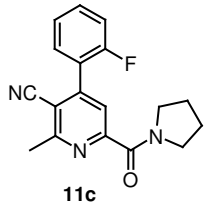
11a

11a; pale solid; 90% yield, $C_{14}H_{10}FN_3O$, M = 255.25 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 256 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (s, 3 H), 6.08 (s, 1 H), 7.22 (m, 2 H), 7.37 (m, 1 H), 7.45 (m, 1 H), 7.81 (s, 1 H), 8.11 (s, 1 H).



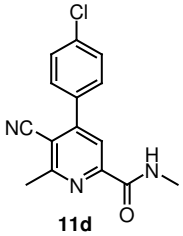
11b

11b; pale solid; 99% yield, $C_{17}H_{14}FN_3O$, M = 295.32 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 296 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (m, 2 H), 0.91 (m, 2 H), 2.85 (s, 3 H), 2.95 (m, 1 H), 7.28 (m, 2 H), 7.41 (m, 1 H), 7.51 (m, 1 H), 8.04 (s, 1 H), 8.15 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.6 (CH_2), 22.7 (CH), 23.9 (CH_3), 111.5 (C), 115.8 (C), 116.5 (d, $^2J_{C\text{-}F}$ = 21.95 Hz, CH), 120.6 (CH), 123.6 (d, $^2J_{C\text{-}F}$ = 14.64 Hz, C), 124.8 (d, $^3J_{C\text{-}F}$ = 3.66 Hz, CH), 130.6 (d, $^4J_{C\text{-}F}$ = 2.19 Hz, CH), 132.3 (d, $^3J_{C\text{-}F}$ = 8.78 Hz, CH), 149.8 (C), 150.9 (C), 159.1 (d, $^1J_{C\text{-}F}$ =251.03, C), 161.2 (C), 164.03 (C).



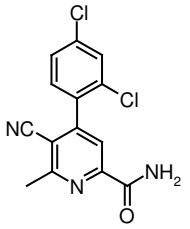
11c

11c; colorless solid; 95% yield, $C_{18}H_{16}FN_3O$, M = 209.35 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 310 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95 (m, 4 H), 2.86 (s, 3 H), 3.68 (m, 2 H), 3.76 (m, 2 H), 7.23 (m, 1 H), 7.29 (m, 1 H), 7.42 (m, 1 H), 7.49 (m, 1 H), 7.78 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9 (CH_3), 24.0 (CH_2), 26.6 (CH_2), 47.1 (CH_2), 49.1 (CH_2), 109.9 (C), 115.9 (C), 116.4 (d, $^2J_{C\text{-}F}$ = 21.22 Hz, CH), 122.3 (CH), 123.7 (d, $^2J_{C\text{-}F}$ = 14.64 Hz, C), 124.7 (d, $^3J_{C\text{-}F}$ = 3.66 Hz, CH), 130.6 (d, $^4J_{C\text{-}F}$ = 2.19 Hz, CH), 132.1 (d, $^3J_{C\text{-}F}$ = 8.78 Hz, CH), 148.9 (C), 155.9 (C), 159.1 (d, $^1J_{C\text{-}F}$ =251.02, C), 161.2 (C), 164.7 (C).



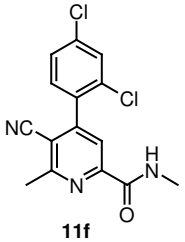
11d

11d; colorless solid; 79% yield, $C_{15}H_{12}ClN_3O$, M = 285.74 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 286 *m/z*.



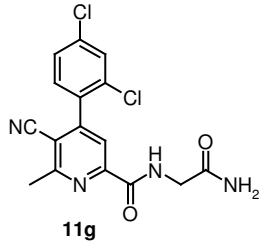
11e

11e; colorless solid; 80% yield, $C_{14}H_9Cl_2N_3O$, M = 306.15 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 306 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88 (s, 3 H), 6.14 (s, 1 H), 7.26 (d, *J* = 8.1 Hz, 1 H), 7.40 (dd, *J* = 8.1, 2.0 Hz, 1 H), 7.57 (d, *J* = 2.0 Hz, 1 H), 7.84 (s, 1 H), 8.10 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9 (CH_3), 112,0 (C), 115.3 (C), 120.9 (CH), 127.7 (CH), 130.3 (CH), 131.1 (CH), 133.1 (C), 133.2 (C), 136.8 (C), 150.7 (C), 151.9 (C), 161.5 (C), 164.9 (C).



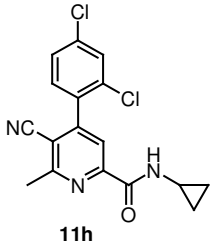
11f

11f; colorless solid; 83% yield, $C_{15}H_{11}Cl_2N_3O$, M = 320.18 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 320 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (s, 3 H), 3.06 (d, *J* = 5.1 Hz, 3 H), 7.25 (d, *J* = 8.1 Hz, 1 H), 7.39 (dd, *J* = 8.3, 1.9 Hz, 1 H), 7.56 (d, *J* = 2.0 Hz, 1 H), 8.03 (m, 1 H), 8.09 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9 (CH_3) 26.3 (CH_3) 111.6 (C) 115.4 (C) 120.6 (CH) 127.7 (CH) 130.2 (CH) 131.1 (CH) 133.2 (C) 133.2 (C) 136.7 (C) 151.1 (C) 151.9 (C) 161.1 (C) 163.2 (C).



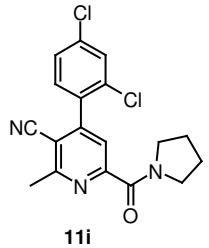
11g

11g; colorless solid; 99% yield, $C_{16}H_{12}Cl_2N_4O_2$, M = 363.21 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 363 *m/z*.



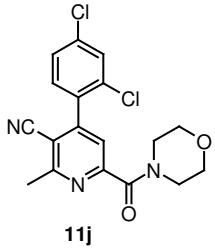
11h

11h; colorless solid; 88% yield, $C_{17}H_{13}Cl_2N_3O$, M = 346.22 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 346 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69 (m, 2 H), 0.91 (m, 2 H), 2.84 (s, 3 H), 2.94 (m, 1 H), 7.24 (d, *J* = 8.1 Hz, 1 H), 7.39 (dd, *J* = 8.1, 2.0 Hz, 1 H), 7.56 (d, *J* = 2.0 Hz, 1 H), 8.03 (s, 1 H), 8.08 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.6 (CH_2), 22.7 (CH), 23.8 (CH_3), 111.7 (C), 115.4 (C), 120.4 (CH), 127.7 (CH), 130.2 (CH), 131.1 (CH), 133.2 (C), 133.1 (C), 136.8 (C), 151.0 (C), 151.9 (C), 161.1 (C), 163.9 (C).



11i

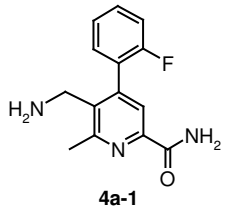
11i; colorless solid; 78% yield, $C_{18}H_{15}Cl_2N_3O$, M = 360.25 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 360 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95 (m, 4 H), 2.85 (s, 3 H), 3.68 (t, *J* = 6.5 Hz, 2 H), 3.78 (m, 2 H), 7.26 (d, *J* = 8.4 Hz, 1 H), 7.39 (dd, *J* = 8.3, 1.9 Hz, 1 H), 7.56 (d, *J* = 2.0 Hz, 1 H), 7.72 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9 (CH_2), 23.9 (CH_3), 26.6 (CH_2), 47.2 (CH_2), 49.1 (CH_2), 110.0 (C), 115.5 (C), 122.2 (CH), 127.7 (CH), 130.2 CH), 131.2 (CH), 133.1 (C), 133.3 (C), 136.6 (C), 151.0 (C), 155.8 (C), 161.1 (C), 164.4 (C).



11j

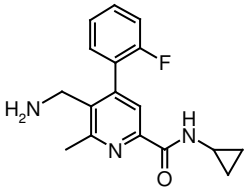
11j; colorless solid; 81% yield, $C_{18}H_{15}Cl_2N_3O_2$, M = 376.25 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 376 *m/z*.

5-Aminomethyl-4-aryl-6-methyl-pyridine-2-carboxylic acid amides 4 – general procedure (Scheme S1, conditions e): Raney Nickel (6 mL, 50% slurry in water) was added to a solution of **11** (1 eq, 0.15 mmol, 0.048 g) in AcOH (5 mL). Upon disappearance of the starting material (3-24 h), the catalyst was filtered off through celite and the solvent was removed under reduced pressure. The residue was taken up in water, using 4M NaOH the solution was adjusted to pH = 8 and extracted with DCM/EA. The product **4** was purified by column chromatography with DCM/MeOH (10:1) as eluent.



4a-1

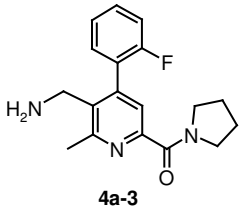
4a-1; colorless solid; 64% yield, $C_{14}H_{14}FN_3O$, M = 259.29 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 260 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.35 (s, 2 H), 2.75 (s, 3 H), 3.76 (s, 2 H), 5.98 (s, 1 H), 7.21 (m, 3 H), 7.41 (m, 1 H), 7.93 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 22.5 (CH_3), 40.7 (CH_2), 115.7 (d, $^2J_{C\text{-}F}$ = 22.0 Hz, CH), 122.0 (CH), 124.5 (d, $^3J_{C\text{-}F}$ = 3.7 Hz, CH), 126.1 (d, $^2J_{C\text{-}F}$ = 16.8 Hz, C), 130.4 (d, $^3J_{C\text{-}F}$ = 8.8 Hz, CH), 130.8 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, CH), 137.6 (C), 144.7 (C), 146.9 (C), 157.1 (C), 158.9 (d, $^1J_{C\text{-}F}$ = 245.2 Hz, C), 166.8 (C).



4a-2

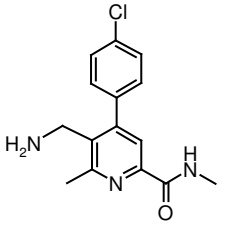
4a-2; colorless solid; 53% yield, $C_{17}H_{18}FN_3O$, M = 299.35 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 300 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 0.64 (m, 2 H), 0.83 (m, 2 H), 1.50 (s, 2 H), 2.67 (s, 3

H), 2.88 (m, 1 H), 3.69 (s, 2 H), 7.12 (m, 1 H), 7.19 (m, 2 H), 7.37 (m, 1 H), 7.86 (s, 1 H), 8.10 (s, 1 H).[13]C NMR (100 MHz, $CDCl_3$) δ 6.5 (CH_2), 22.3 (CH_3), 22.4 (CH), 40.6 (CH_2), 116.2 (d, $^2J_{C\text{-}F}$ = 22.0 Hz, CH), 121.4 (CH), 124.4 (d, $^3J_{C\text{-}F}$ = 3.7 Hz, CH), 126.1 (d, $^2J_{C\text{-}F}$ = 16.8 Hz, C), 130.3 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, CH), 130.8 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, CH), 137.1 (C), 144.7 (C), 147.1 (C), 156.7 (C), 158.9 (d, $^1J_{C\text{-}F}$ = 245.9 Hz, C), 165.5 (C).



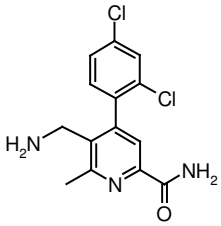
4a-3

4a-3; colorless solid; 48% yield, $C_{18}H_{20}FN_3O$, M = 313.38 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 314 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (m, 6 H), 2.70 (s, 3 H), 3.63 (m, 2 H), 3.74 (m, 4 H), 7.13 (m, 1 H), 7.22 (m, 2 H), 7.38 (m, 1 H), 7.47 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4 (CH_3), 24.0 (CH_2), 26.5 (CH_2), 40.5 (CH_2), 46.8 (CH_2), 49.1 (CH_2), 115.7 (d, $^2J_{C\text{-}F}$ = 21.96 Hz, CH), 123.0 (CH), 124.4 (d, $^3J_{C\text{-}F}$ = 3.7 Hz, CH), 126.2 (d, $^2J_{C\text{-}F}$ = 16.8 Hz, C), 130.3 (d, $^3J_{C\text{-}F}$ = 8.8 Hz, CH), 130.9 (d, $^4J_{C\text{-}F}$ = 3.7 Hz, CH), 135.1 (C), 144.3 (C), 152.0 (C), 156.6 (C), 158.9 (d, $^1J_{C\text{-}F}$ = 245.9 Hz, C), 166.3 (C).



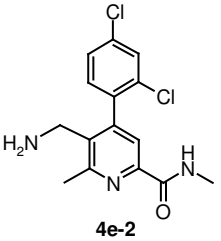
4d

4d; colorless solid; 38% yield, $C_{15}H_{16}ClN_3O$, M = 289.77 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 290 *m/z*. FT-ICR-MS: calculated for $C_{15}H_{16}ClN_3OH^+$: 290.1055, found: 290.1054.



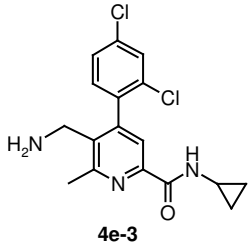
4e-1

4e-1; colorless solid; 45% yield, $C_{14}H_{13}Cl_2N_3O$, M = 310.19 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 310 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.72 (s, 3 H), 3.38 (d, *J* = 13.2 Hz, 1 H), 3.63 (d, *J* = 13.2 Hz, 1 H), 7.49 (d, *J* = 8.1 Hz, 1 H), 7.54 (m, 1 H), 7.57 (s, 1 H), 7.67 (s, 1 H), 7.78 (d, *J* = 1.5 Hz, 1 H), 8.06 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.3 (CH_3), 39.8 (CH_2), 120.5 (CH), 127.5 (CH), 128.9 (CH), 132.1 (CH), 132.6 (C), 133.9 (C), 136.1 (C), 136.8 (C), 146.3 (C), 147.4 (C), 157.7 (C), 165.8 (C). FT-ICR-MS: calculated for $C_{14}H_{13}Cl_2N_3OH^+$: 310.0508, found: 310.0508.



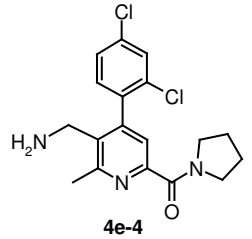
4e-2

4e-2; colorless solid; 51% yield, $C_{15}H_{15}Cl_2N_3O$, M = 324.21 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 324 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (s, 3 H), 3.02 (d, *J* = 5.1 Hz, 3 H), 3.60 (d, *J* = 13.5 Hz, 1 H), 3.71 (d, *J* = 13.5 Hz, 1 H), 7.14 (d, *J* = 8.4 Hz, 1 H), 7.32 (dd, *J* = 8.1, 2.0 Hz, 1 H), 7.50 (d, *J* = 2.0 Hz, 1 H), 7.79 (s, 1 H), 8.07 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4 (CH_3), 26.1 (CH_3), 40.4 (CH_2), 121.0 (CH), 127.3 (CH), 129.6 (CH), 131.1 (CH), 133.3 (C), 135.0 (C), 136.1 (C), 136.6 (C), 147.1 (C), 147.4 (C), 157.0 (C), 164.8 (C). FT-ICR-MS: calculated for $C_{15}H_{15}Cl_2N_3OH^+$: 324.0665, found: 324.0666.



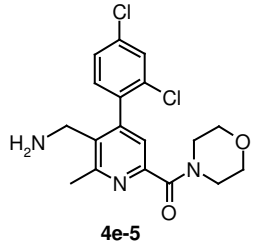
4e-3

4e-3; colorless solid; 34% yield, $C_{17}H_{17}Cl_2N_3O$, M = 350.25 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 350 *m/z*. ^{1}H NMR (400 MHz, Methanol-D_4) δ 0.69 (m, 2 H), 0.84 (m, 2 H), 2.75 (s, 3 H), 2.88 (m, 1 H), 3.61 (d, *J* = 13.7 Hz, 1 H), 3.82 (d, *J* = 14.0 Hz, 1 H), 7.37 (d, *J* = 8.1 Hz, 1 H), 7.49 (m, 1 H), 7.66 (d, *J* = 2.0 Hz, 1 H), 7.68 (s, 1 H). ^{13}C NMR (100 MHz, Methanol- D_4) δ 6.6 (CH_2), 22.6 (CH_3), 23.6 (CH), 40.0 (CH_2), 121.9 (CH), 128.9 (CH), 130.6 (CH), 132.9 (CH), 134.4 (C), 136.5 (C), 137.2 (C), 148.9 (C), 149.1 (C), 159.4 (C), 167.8 (C). FT-ICR-MS: calculated for $C_{17}H_{17}Cl_2N_3OH^+$: 350.0821, found: 350.0821.



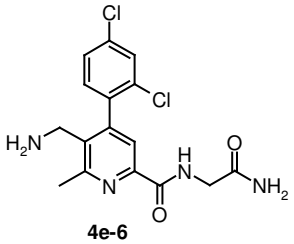
4e-4

4e-4; colorless solid; 48% yield, $C_{18}H_{19}Cl_2N_3O$, M = 364.28 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 364 *m/z*. ^{1}H NMR (400 MHz, Methanol-D_4) δ 1.96 (m, 4 H), 2.75 (s, 3 H), 3.62 (t, *J* = 6.4 Hz, 2 H), 3.72 (m, 3 H), 3.98 (d, *J* = 14.2 Hz, 1 H), 7.40 (m, 2 H), 7.51 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.68 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR (100 MHz, Methanol-D_4) δ 22.5 (CH_3), 25.0 (CH_2), 27.4 (CH_2), 39.1 (CH_2), 48.0 (CH_2), 50.4 (CH_2), 123.4 (CH), 129.0 (CH), 130.7 (CH), 132.4 (C), 133.0 (CH), 134.4 (C), 136.6 (C), 136.8 (C), 149.5 (C), 154.2 (C), 159.4 (C), 167.8 (C). FT-ICR-MS: calculated for $C_{18}H_{19}Cl_2N_3OH^+$: 364.0978, found: 364.0980.



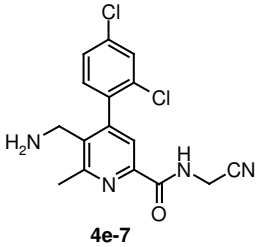
4e-5

4e-5; colorless solid; 44% yield, $C_{18}H_{19}Cl_2N_3O_2$, M = 380.28 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 380.28 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (s, 3 H), 3.70 (m, 8 H), 3.79 (s, 2 H), 7.22 (m, 2 H), 7.35 (dd, *J* = 8.1, 1.5 Hz, 1 H), 7.51 (d, *J* = 1.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5 (CH_3), 40.2 (CH_2), 42.7 (CH_2), 47.8 (CH_2), 66.7 (CH_2), 66.9 (CH_2), 122.6 (CH), 127.3 (CH), 129.6 (CH), 131.1 (CH), 133.2 (C), 135.1 (C), 135.8 (C), 146.8 (C), 151.1 (C), 157.3 (C), 167.1 (C). FT-ICR-MS: calculated for $C_{18}H_{19}Cl_2N_3O_2H^+$: 380.0927, found: 380.0928.



4e-6

4e-6: To the degassed solution of **11g** (1 eq, 0.25 mmol, 0.091 g) in acetic acid (0.25 mL) Raney Nickel (6 mL, 50% slurry in water) was added and the mixture was stirred 48 h at 50 °C under argon. The catalyst was filtered off through celite and the solvent was removed under reduced pressure. The residue was taken up in water, using 4M NaOH the solution was adjusted to pH 8 and extracted with DCM/EA. The product, a colorless solid (0.055 g, 60%), was purified by column chromatography with DCM/MeOH (10:1) as eluent. $C_{16}H_{16}Cl_2N_4O_2$, M = 367.24 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 367 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 1.09 (s, 2 H), 2.75 (s, 3 H), 3.51 (m, 2 H), 3.91 (d, J = 5.1 Hz, 2 H), 7.13 (s, 1 H), 7.53 (m, 4 H), 7.78 (s, 1 H), 8.77 (t, J = 5.1 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2 (CH_3), 31.3 (CH_2), 42.0 (CH_2), 120.3 (CH), 127.5 (CH), 128.9 (CH), 132.1 (CH), 133.9 (C), 136.0 (C), 146.4 (C), 146.8 (C), 157.7 (C), 163.5 (C), 170.5 (C).

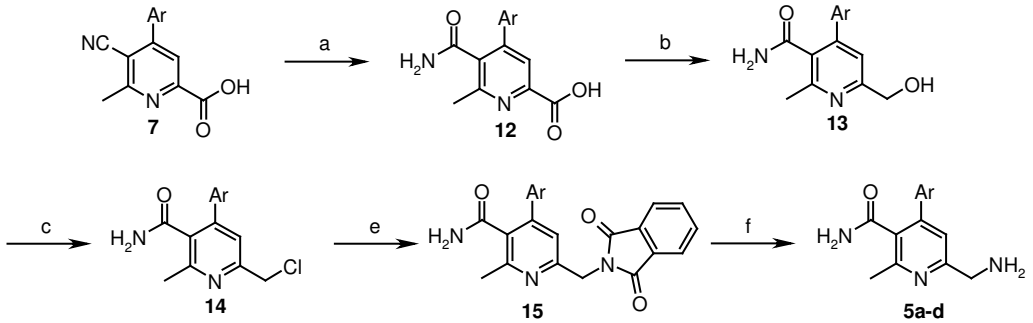


4e-7

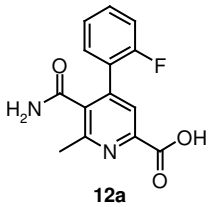
4e-7: 4e-6 (0.054 g, 0.15 mmol) was dissolved in $POCl_3$ (2 mL), and the mixture was heated at 70 ºC for 2 h. The excess of the reagent was removed in vacuo. The product as a yellow solid (0.037 g, 70%) was isolated by column chromatography (MeOH/DCM, 40:1). $C_{16}H_{14}Cl_2N_4O$, M = 349.22 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 349 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.75 (s, 3 H), 3.40 (m, 1 H), 3.66 (d, J = 12.0 Hz, 1 H), 4.31 (d, J = 5.6 Hz, 2 H), 7.54 (m, 2 H), 7.60 (s, 1 H), 7.80 (m, 1 H), 9.36 (t, J = 5.7 Hz, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.3 (CH_3), 27.7 (CH_2), 39.6 (CH_2), 117.5 (C), 120.8 (CH), 127.6 (CH), 129.0 (CH), 132.1 (CH), 132.6 (C), 134.0 (C), 135.8 (C), 137.2 (C), 146.1 (C), 146.6 (C), 158.2 (C), 164.3 (C). FT-ICR-MS: calculated for $C_{16}H_{14}Cl_2N_4OH^+$: 349.0617, found: 349.0620.

Synthesis of 6-aminomethyl-pyridines 5.

Scheme S2

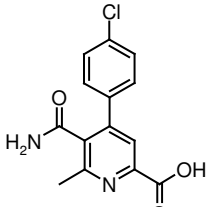


5-Carbamoyl-4-aryl-6-methyl-pyridine-2-carboxylic acids 12 – general procedure (Scheme S2, conditions a): *t*-BuOK (3 eq, 3.0 mmol, 0.336 g) was added to a suspension of 5-cyano-2-pyridine carboxylic acid **7** (1 eq, 1 mmol) in water (15 mL). The mixture was heated at 100 ˚C for 3 h. After cooling to room temperature the mixture was concentrated in vacuo, acidified with 1M HCl and extracted with DCM. The combined organic phases were dried over anhydrous Na_2SO_4, concentrated and the residue was used without further purification.



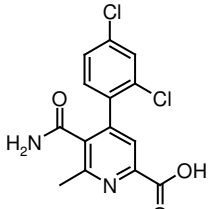
12a

12a; pale solid; 80% yield, $C_{14}H_{11}FN_2O_3$, M = 274.25 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 275 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.59 (s, 3 H), 7.29 (m, 2 H), 7.47 (m, 2 H), 7.64 (s, 1 H), 7.79 (s, 1 H), 7.97 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.3 (CH_3), 115.8 (d, $^2J_{C\text{-}F}$ = 21.22 Hz, CH), 123.4 (CH), 124.3 (d, $^3J_{C\text{-}F}$ = 3.66 Hz, CH), 124.7 (d, $^2J_{C\text{-}F}$ = 14.64 Hz, C), 130.8 (d, $^4J_{C\text{-}F}$ = 2.20 Hz, CH), 131.0 (d, $^3J_{C\text{-}F}$ = 8.05 Hz, CH), 135.8 (C), 141.1 (C), 146.8 (C), 154.9 (C), 158.8 (d, $^1J_{C\text{-}F}$ =246.64 Hz, C), 165.7 (C), 168.3 (C).



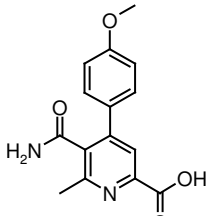
12b

12b; colorless solid; 65% yield, $C_{14}H_{11}ClN_2O_3$, M = 290.71 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 291 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.57 (s, 3 H), 7.54 (m, 4 H), 7.69 (s, 1 H), 7.81 (s, 1 H), 7.97 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.2 (CH_3), 122.5 (CH), 128.6 (CH), 130.1 (CH), 133.8 (C), 134.8 (C), 136.3 (C), 145.5 (C), 147.4 (C), 154.8 (C), 165.8 (C), 168.9 (C).



12c

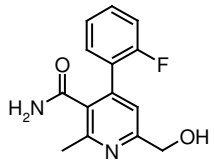
12c; colorless solid; 99% yield, $C_{14}H_{11}Cl_2N_2O_3$, M = 325.15 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 325 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.59 (s, 3 H), 7.42 (m, 1 H), 7.52 (m, 1 H), 7.64 (s, 1 H), 7.74 (m, 2 H), 7.93 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.3 (CH_3), 123.1 (CH), 127.0 (CH), 128.9 (CH), 132.0 (CH), 132.1 (C), 134.2 (C), 134.7 (C), 135.6 (C), 143.6 (C), 146.8 (C), 154.7 (C), 165.7 (C), 167.8 (C).



12d

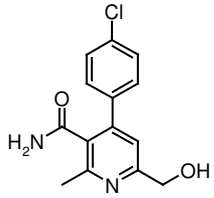
12d; colorless solid; 91% yield, $C_{15}H_{14}N_2O_4$, M = 286.29 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 287 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.55 (s, 3 H), 3.79 (s, 3 H), 7.02 (m, 2 H), 7.51 (d, 2 H), 7.65 (s, 1 H), 7.79 (s, 1 H), 7.93 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.2 (CH_3), 55.3 (CH_3), 114.1 (CH), 122.5 (CH), 129.6 (CH), 134.7 (C), 146.2 (C), 147.1 (C), 154.6 (C), 159.8 (C), 165.9 (C), 169.3 (C).

4-Aryl-6-hydroxymethyl-2-methyl-nicotinamide 13 – general procedure (Scheme S2, conditions b): Triethylamine (1.2 eq, 1.2 mmol, 0.167 mL) and ethyl chloroformate (1.2 eq, 1.2 mmol, 0.114 mL) were added successively to the solution of **12** (1 eq, 1 mmol) in THF (15 mL) and the mixture was stirred at rt for 30 minutes. After decreasing the temperature to 0 ˚C, the solution of sodium borohydride (10 eq, 10 mmol, 0.378 g) in water (5 mL) was added dropwise and the mixture was stirred at 0 ˚C for additional 30 minutes. The residue was acidified with 1M HCl, concentrated in vacuo and extracted with DCM/EA. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated. The product **13** was isolated by column chromatography with DCM/MeOH (10:1) as eluent.



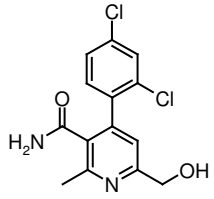
13a

13a; colorless solid; 61% yield, $C_{14}H_{13}FN_2O_2$, M = 260.27 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 261 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.50 (s, 3 H), 4.56 (d, J = 5.6 Hz, 2 H), 5.46 (t, J = 5.9 Hz, 1 H), 7.26 (m, 3 H), 7.44 (m, 3 H), 7.79 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.3 (CH_3), 63.9 (CH_2), 115.7 (d, $^2J_{C\text{-}F}$ = 22.0 Hz, CH), 118.5 (CH), 124.1 (d, $^3J_{C\text{-}F}$ = 3.7 Hz, CH), 125.9 (d, $^2J_{C\text{-}F}$ = 15.4 Hz, C), 130.5 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, CH), 130.9 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, CH), 131.3 (C), 140.7 (C), 153.3 (C), 158.8 (d, $^1J_{C\text{-}F}$ =246.6, C), 160.6 (C), 169.0 (C).



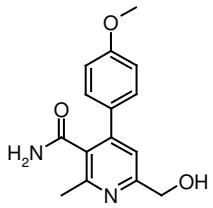
13b

13b; colorless solid; 71% yield, $C_{14}H_{13}ClN_2O_2$, M = 276.72 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 277 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.49 (s, 3 H), 4.57 (d, J = 5.6 Hz, 2 H), 5.49 (t, J = 5.3 Hz, 1 H), 7.25 (s, 1 H), 7.53 (m, 5 H), 7.83 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.2 (CH_3), 63.95 (CH_2), 117.6 (CH), 128.5 (CH), 1230.0 (CH), 130.4 (C), 133.3 (C), 137.4 (C), 144.9 (C), 153.3 (C), 161.1 (C), 169.7 (C).



13c

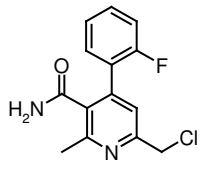
13c; colorless solid; 77% yield, $C_{14}H_{12}Cl_2N_2O_2$, M = 311.17 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 311 m/z. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.55 (s, 3 H), 4.63 (s, 2 H), 7.23 (s, 1 H), 7.27 (m, 1 H), 7.31 (m, 1 H), 7.50 (m, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.2 (CH_3), 65.2 (CH_2), 120.3 (CH), 128.0 (CH), 130.4 (CH), 132.3 (C), 133.1 (CH), 134.6 (C), 136.3 (C), 136.8 (C), 146.4 (C), 155.3 (C), 162.1 (C), 172.2 (C).



13d

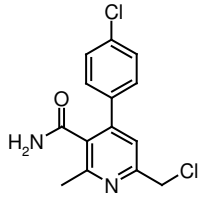
13d; colorless solid; 99% yield, $C_{15}H_{16}N_2O_3$, M = 272.31 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 273 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.47 (s, 3 H), 3.79 (s, 3 H), 4.55 (d, J = 5.9 Hz, 2 H), 5.43 (m, 1 H), 7.01 (m, 2 H), 7.23 (s, 1 H), 7.46 (m, 3 H), 7.77 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.1 (CH_3), 55.2 (CH_3), 64.0 (CH_2), 113.9 (CH), 117.6 (CH), 129.4 (CH), 130.4 (C), 130.8 (C), 145.7 (C), 153.1 (C), 159.4 (C), 160.7 (C), 170.1 (C).

General procedure for the synthesis of 14 (Scheme S2, conditions c): Thionyl chloride (4 eq, 2 mmol, 0.145 mL) was added to a suspension of **13** (1 eq, 0.5 mmol) in toluene (10 mL) and the mixture was stirred at 60 ˚C for 16 h. The solvent was removed under reduced pressure and the product **14** was isolated by column chromatography with DCM/MeOH gradient (40:1 to 10:1) as eluent.



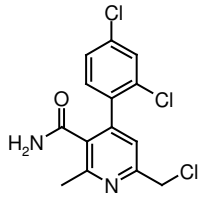
14a

14a; colorless solid; 85% yield, $C_{14}H_{12}Cl_2FN_2O$, M = 278.72 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 279 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (s, 3 H), 4.64 (s, 2 H), 5.61 (s, 1 H), 5.88 (s, 1 H), 7.18 (m, 2 H), 7.38 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6 (CH_3), 46.2 (CH_2), 115.9 (d, $^2J_{C\text{-}F}$ = 22.0 Hz, CH), 121.56 (CH), 124.5 (d, $^3J_{C\text{-}F}$ = 3.7 Hz, CH), 124.8 (d, $^2J_{C\text{-}F}$ = 15.4 Hz, C), 130.8 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, CH), 130.9 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, CH), 142.3 (C), 155.6 (C), 156.2 (C), 159.1 (d, $^1J_{C\text{-}F}$ =246.6, C), 160.3 (C), 169.5 (C).



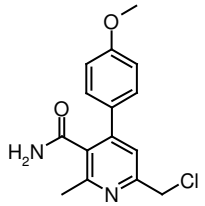
14b

14b; colorless solid; 76% yield, $C_{14}H_{12}Cl_2N_2O$, M = 295.17 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 295 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.51 (s, 3 H), 4.77 (s, 2 H), 7.39 (s, 1 H), 7.53 (m, 4 H), 7.59 (s, 1 H), 7.91 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.1 (CH_3), 46.5 (CH_2), 121.0 (CH), 128.5 (CH), 130.0 (CH), 131.7 (C), 133.6 (C), 136.6 (C), 145.5 (C), 154.4 (C), 155.4 (C), 169.2 (C).



14c

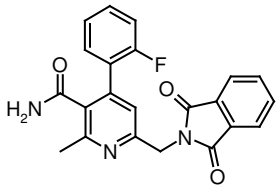
14c; colorless solid; 75% yield, $C_{14}H_{11}Cl_3N_2O$, M = 329.62 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 330 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.53 (s, 3 H), 4.78 (s, 2 H), 7.31 (s, 1 H), 7.40 (d, J = 8.1 Hz, 1 H), 7.50 (dd, J = 7.5, 2.0 Hz, 1 H), 7.54 (s, 1 H), 7.73 (d, J = 2.0 Hz, 1 H), 7.86 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.3 (CH_3), 46.3 (CH_2), 121.5 (CH), 127.0 (CH), 128.9 (CH), 132.0 (CH), 132.5 (C), 132.8 (C), 134.0 (C), 135.2 (C), 143.7 (C), 154.3 (C), 154.9 (C), 168.1 (C).



14d

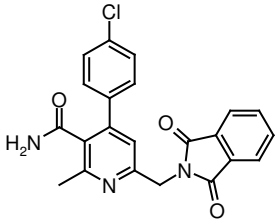
14d; colorless solid; 79% yield, $C_{15}H_{15}ClN_2O_2$, M = 290.75 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 291 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.50 (s, 3 H), 3.79 (s, 3 H), 4.76 (s, 2 H), 7.01 (m, 2 H), 7.36 (s, 1 H), 7.47 (m, 2 H), 7.55 (s, 1 H), 7.86 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.3 (CH_3), 46.3 (CH_2), 55.2 (CH_3), 114.0 (CH), 121.0 (CH), 129.5 (CH), 130.1 (C), 131.6 (C), 146.3 (C), 154.2 (C), 155.1 (C), 159.6 (C), 169.7 (C).

General procedure for the synthesis of 15 (Scheme S2, conditions e): 14 (1 eq, 0.5 mmol) was dissolved in dry DMF (2 mL) and a suspension of phthalimide (1.5 eq, 0.75 mmol, 0.110 g) and *t*-BuOK (1.5 eq, 0.75 mmol, 0.084 g) in DMF (2 mL) was added. The mixture was stirred at 60 ˚C for 4 h, then the solvent was removed under reduced pressure and the product **15** was isolated by column chromatography (DCM/MeOH, 40:1).



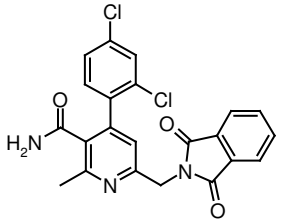
15a

15a; colorless solid; 65% yield, $C_{22}H_{16}FN_3O_3$, M = 389.39 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 390 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.42 (s, 3 H), 4.90 (s, 2 H), 7.23 (m, 3 H), 7.41 (m, 3 H), 7.87 (m, 4 H), 7.94 (s, 1 H).



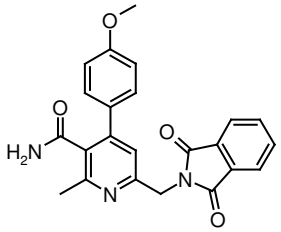
15b

15b; colorless solid; 82% yield, $C_{22}H_{16}ClN_3O_3$, M = 405.84 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 406 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.40 (s, 3 H), 4.90 (s, 2 H), 7.23 (s, 1 H), 7.48 (m, 4 H), 7.53 (s, 1 H), 7.88 (m, 5 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.7 (CH_3), 42.6 (CH_2), 119.1 (CH), 123.6 (CH), 128.7 (CH), 130.4 (CH), 131.4 (C), 132.1 (C), 133.8 (C), 134.9 (CH), 137.2 (C), 145.6 (C), 154.2 (C), 154.8 (C), 168.2 (C), 169.7 (C).



15c

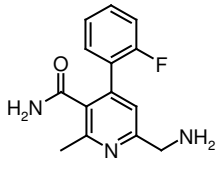
15c; colorless solid; 80% yield, $C_{22}H_{15}Cl_2N_3O_3$, M = 440.29 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 440 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.42 (s, 3 H), 4.90 (s, 2 H), 7.16 (s, 1 H), 7.35 (d, J = 8.4 Hz, 1 H), 7.46 (dd, J = 8.1, 1.8 Hz, 2 H), 7.67 (d, J = 1.8 Hz, 1 H), 7.79 (s, 1 H), 7.88 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.5 (CH_3), 46.2 (CH_2), 119.2 (CH), 123.3 (CH), 126.9 (CH), 128.8 (CH), 131.8 (C), 132.1 (CH), 132.8 (C), 133.8 (C), 134.6 (CH), 135.5 (C), 143.5 (C), 153.8 (C), 154.0 (C), 167.8 (C), 168.3 (C).



15d

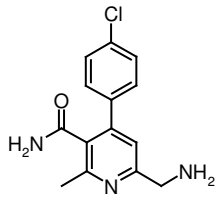
15d; colorless solid; 90% yield, $C_{23}H_{19}Cl_2N_3O_4$, M = 401.43 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 402 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.38 (s, 3 H), 3.76 (s, 3 H), 4.89 (s, 2 H), 6.98 (m, 2 H), 7.17 (s, 1 H), 7.42 (m, 2 H), 7.48 (s, 1 H), 7.80 (s, 1 H), 7.88 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.3 (CH_3), 42.2 (CH_2), 55.2 (CH_3), 113.9 (CH), 118.8 (CH), 123.3 (CH), 129.5 (CH), 130.2 (C), 131.0 (C), 131.8 (C), 134.6 (CH), 146.1 (C), 153.7 (C), 154.1 (C), 159.5 (C), 167.8 (C), 169.8 (C).

General procedure for the synthesis of 5 (Scheme S2, conditions f): 15 (1 eq, 0.5 mmol) was suspended in 30% KOH (5 mL) and the mixture was stirred at 110 ˚C for 4 h. After cooling to room temperature the product was extracted with DCM. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated. The product **5** was purified by column chromatography with DCM/MeOH (10:1) as eluent.



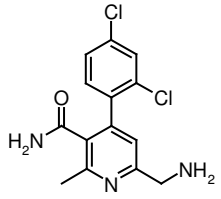
5a

5a; yellow solid; 91% yield, $C_{14}H_{14}FN_3O$, M = 259.29 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 260 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.50 (s, 3 H), 3.79 (s, 2 H), 7.27 (m, 3 H), 7.42 (m, 3 H), 7.76 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.4 (CH_3), 47.1 (CH_2), 115.6 (d, $^2J_{C\text{-}F}$ = 22.0 Hz, CH), 119.4 (CH), 124.1 (d, $^3J_{C\text{-}F}$ = 3.7 Hz, CH), 126.0 (d, $^2J_{C\text{-}F}$ = 15.4 Hz, C), 130.4 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, CH), 131.0 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, CH), 131.1 (C), 140.7 (C), 153.2 (C), 158.8 (d, $^1J_{C\text{-}F}$ =248.1, C), 161.8 (C), 169.1 (C).



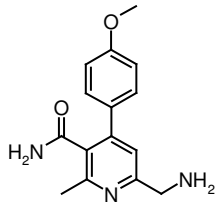
5b

5b; yellow solid; 89% yield, $C_{14}H_{14}ClN_3O$, M = 275.74 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 276 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.48 (s, 3 H), 7.27 (s, 1 H), 7.51 (m, 5 H), 7.81 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.2 (CH_3), 47.2 (CH_2), 118.4 (CH), 128.4 (CH), 130.0 (CH), 130.1 (C), 133.3 (C), 137.5 (C), 144.8 (C), 153.2 (C), 162.3 (C), 169.8 (C).



5c

5c; colorless solid; 84% yield, $C_{14}H_{13}Cl_2N_3O$, M = 310.19 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 310 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.50 (s, 3 H), 3.80 (s, 2 H), 7.18 (s, 1 H), 7.44 (m, 3 H), 7.72 (m, 2 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.4 (CH_3), 47.0 (CH_2), 118.9 (CH), 126.8 (CH), 128.8 (CH), 130.8 (C), 132.1 (CH), 132.8 (C), 133.6 (C), 136.0 (C), 143.1 (C), 153.1 (C), 161.7 (C), 168.7 (C).

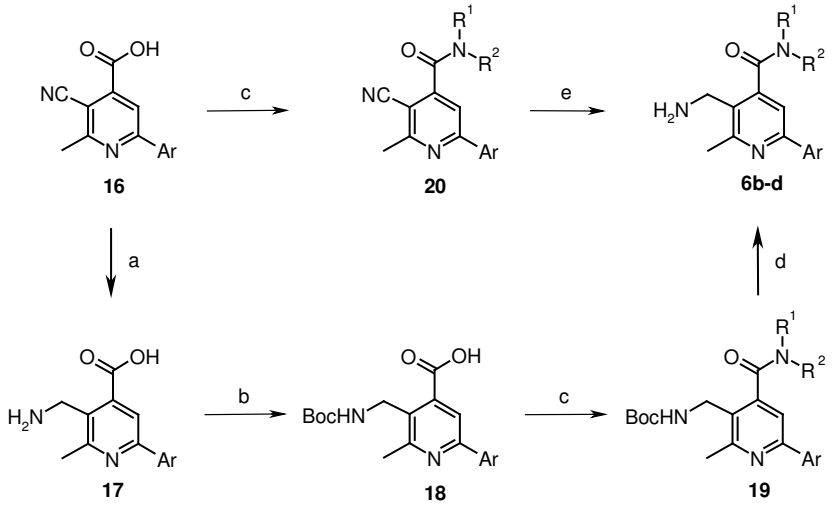


5d

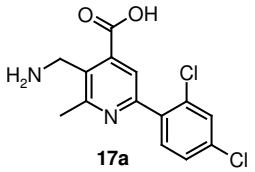
5d; yellow solid; 79% yield, $C_{15}H_{17}N_3O_2$, M = 271.32 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 272 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.46 (s, 3 H), 3.77 (s, 2 H), 3.78 (s, 3 H), 6.99 (d, J = 8.7 Hz, 2 H), 7.24 (s, 1 H), 7.46 (m, 3 H), 7.74 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 22.2 (CH_3), 47.2 (CH_2), 55.2 (CH_3), 113.8 (CH), 118.4 (CH), 129.5 (CH), 130.1 (C), 130.9 (C), 145.6 (C), 153.1 (C), 159.4 (C), 161.9 (C), 170.3 (C).

Synthesis of 3-aminomethyl-pyridines 6.

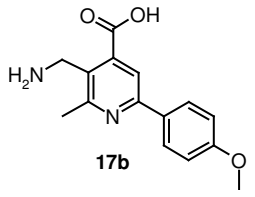
Scheme S3



Synthesis of 17 (Scheme S3, conditions a):
Synthesis of 17a: The 5-cyano-4-(2,4-dichloro-phenyl)-6-methyl-pyridine-2-carboxylic acid **16a** (1 eq, 0.2 mmol, 0.061 g) and nickel (II) chloride hexahydrat (1 eq, 0.2 mmol, 0.048 g) were dissolved in MeOH (5 ml). $NaBH_4$ (7 eq, 1.4 mmol, 0.053 g) was added very cautiously while stirring the solution vigorously. The progress of the reaction was monitored by LC/MS. After 24 h the reaction mixture was filtered through a celite pad and the solvent was removed under vacuum. The residue was taken up in water and extracted with DCM. The aqueous layer was lyophilized to give **17a** as a colorless solid product (0.040 g, 64% yield) that was used in the next step without further purification. $C_{14}H_{12}Cl_2N_2O_2$, M = 311.17 g/mol, HPLC-ESI-MS: $[M + H]^+ = 311$ *m/z*.

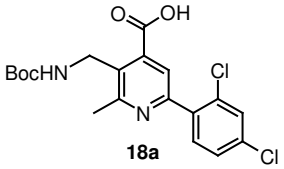


Synthesis of 17b: The 5-Cyano-4-(4-methoxy-phenyl)-6-methyl-pyridine-2-carboxylic acid **16b** (1 eq, 0.25 mmol, 0.067 g) was dissolved in acetic acid (0.25 mL) and 10% Pd/C (10% m/m) was added. The mixture was degassed and hydrogenated under 1.0 atm pressure of H_2 for 24 h at 60 ˚C. The catalyst was filtered off and the solvent was removed on vacuum. The residue was taken up in water and extracted with DCM. Aqueous layer was lyophilized to give **17b** as a solid product (0.052 g, 76% yield) that was used in the next step without further purification. $C_{15}H_{16}N_2O_3$, M = 272.31 g/mol, HPLC-ESI-MS: $[M + H]^+ = 273$ *m/z*.



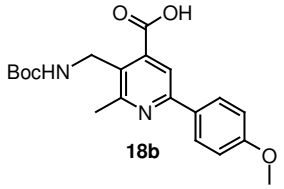
General procedure for the synthesis of 18 - Boc-protection (Scheme S3, conditions b): Boc_2O (1.5 eq, 0.225 mmol, 0.049 g) was added to a solution of **17** (1 eq, 0.15 mmol) in

dioxane (5 mL) and the mixture was stirred for 16 h at 60 ºC. The solvent was removed under reduced pressure and the product was isolated by column chromatography with DCM/MeOH (40:1) as eluent.



18a

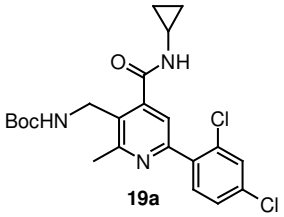
18a; pale solid; 43% yield, $C_{19}H_{20}Cl_2N_2O_4$, M = 411.29 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 411 *m/z*.



18b

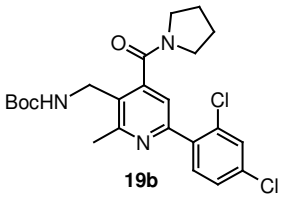
18b; colorless solid; 38% yield, $C_{20}H_{24}N_2O_5$, M = 372.43 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 373 *m/z*.

General procedure for the synthesis of 19 (Scheme S3, conditions c): These compounds were prepared according to the procedure for **11**, using compound **18** as a starting material.



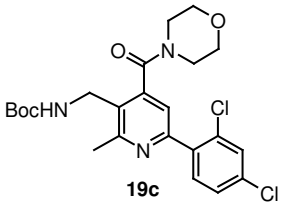
19a

19a; colorless solid; 63% yield, $C_{22}H_{25}Cl_2N_3O_3$, M = 450.37 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 450 *m/z*.



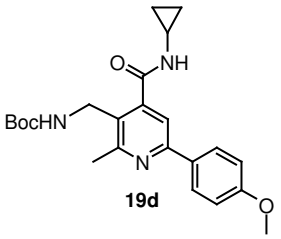
19b

19b; colorless solid; 54% yield, $C_{23}H_{27}Cl_2N_3O_3$, M = 464.40 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 464 *m/z*.



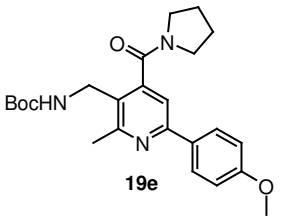
19c

19c; colorless solid; 80% yield, $C_{23}H_{27}Cl_2N_3O_5$, M = 480.40 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 480 *m/z*.



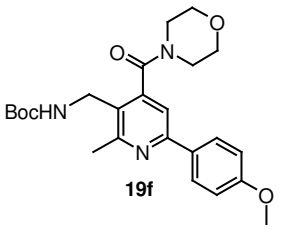
19d

19d; colorless solid; 76% yield, $C_{23}H_{29}N_3O_4$, M = 411.51 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 412 *m/z*.



19e

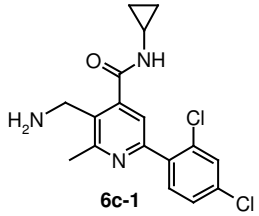
19e; colorless solid; 86% yield, $C_{24}H_{31}N_3O_4$, M = 425.53 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 426 *m/z*.



19f

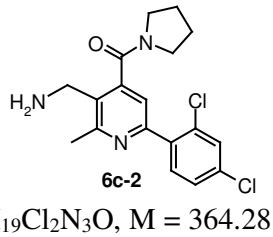
19f; colorless solid; 92% yield, $C_{24}H_{31}N_3O_5$, M = 441.53 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 442 *m/z*.

General procedure for the synthesis of 6 – deprotection (Scheme S3, conditions c): These compounds were prepared according to the procedure for **4**, using compound **19** as a starting material.



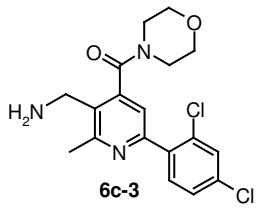
6c-1

6c-1; colorless solid; 65% yield, $C_{17}H_{17}Cl_2N_3O$, M = 350.25 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 350 *m/z*.



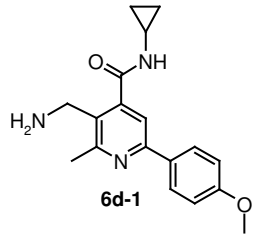
6c-2

6c-2; yellow solid; 57% yield, $C_{18}H_{19}Cl_2N_3O$, M = 364.28 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 364 *m/z*. FT-ICR-MS: calculated for $C_{18}H_{19}Cl_2N_3ONa^+$: 364.0978, found: 364.0978.



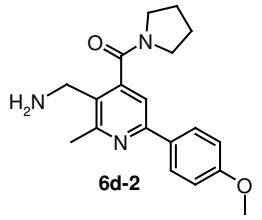
6c-3

6c-3; colorless solid; 63% yield, $C_{18}H_{19}Cl_2N_3O_2$, M = 380.28 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 380 *m/z*.



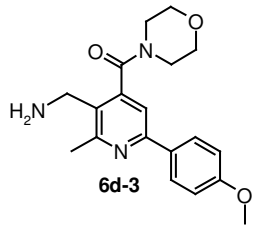
6d-1

6d-1; colorless solid; 75% yield, $C_{18}H_{21}N_3O_2$, M = 311.39 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 312 *m/z*. FT-ICR-MS: calculated for $C_{18}H_{21}N_3O_2H^+$: 312.1707, found: 312.1707.



6d-2

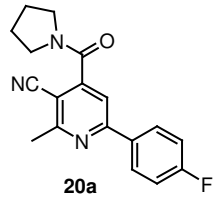
6d-2; yellow solid; 83% yield, $C_{19}H_{23}N_3O_2$, M = 325.41 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 326 *m/z*.



6d-3

6d-3; yellow solid; 70% yield, $C_{19}H_{23}N_3O_3$, M = 341.41 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 442 *m/z*.

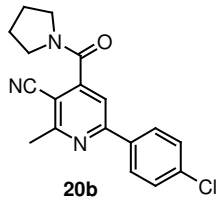
General procedure for the synthesis of 20 (Scheme S3, conditions c): These compounds were prepared according to the procedure for **11**, using compound **16** as a starting material.



20a

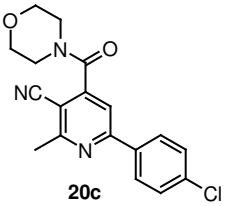
20a; colorless solid; 68% yield, $C_{18}H_{16}FN_3O$, M = 309.35 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 310 *m/z*; m.p. 208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (m, 4 H) 2.84 (s, 3 H) 3.33 (t, *J* = 6.9 Hz, 2 H) 3.70 (t, *J* = 6.9 Hz, 2 H) 7.16 (m, 2 H) 7.58 (s, 1 H) 8.04 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1 (CH_3), 24.3 (CH_2), 26.0 (CH_2), 46.1 (CH_2), 48.3 (CH_2), 103.4 (C), 114.3 (CH), 115.6 (C), 116.1 (d, $^2J_{C\text{-}F}$ = 22.0 Hz, CH), 129.5 (d, $^3J_{C\text{-}F}$ = 8.8 Hz, CH), 133.3 (d,

$^4J_{C\text{-}F}$ = 2.93 Hz, C), 149.81 (C), 158.9 (C), 162.5 (C), 164.3 (C), 164.5 (d, $^1J_{C\text{-}F}$ = 251.76 Hz, C). FT-ICR-MS: calculated for $C_{18}H_{16}FN_3ONa^+$: 332.1170, found: 332.1169.



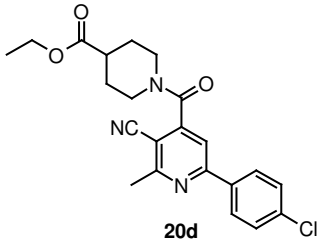
20b

20b; colorless solid; 99% yield, $C_{18}H_{16}ClN_3O$, M = 325.80 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 326 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (m, 4 H) 2.84 (s, 3 H) 3.32 (m, 2 H) 3.70 (m, 2 H) 7.44 (d, *J* = 8.7 Hz, 2 H) 7.60 (s, 1 H) 7.98 (d, *J* = 8.7 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1 (CH_3), 24.2 (CH_2), 26.0 (CH_2), 46.1 (CH_2), 48.3 (CH_2), 103.7 (C), 114.5 (CH), 115.5 (C), 128.7 (CH), 129.2 (CH), 135.4 (C), 137.0 (C), 149.8 (C), 158.7 (C), 162.5 (C), 164.2 (C). FT-ICR-MS: calculated for $C_{18}H_{16}ClN_3ONa^+$: 348.0874, found: 348.0873.



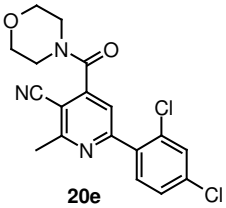
20c

20c; yellow solid; 92% yield, $C_{18}H_{16}ClN_3O_2$, M = 341.80 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 342 *m/z*; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (s, 3 H), 3.34 (m, 2 H), 3.71 (dd, *J* = 5.1, 3.6 Hz, 2 H), 3.83 (m, 4 H), 7.46 (m, 2 H), 7.58 (s, 1 H), 7.99 (m, 2 H). FT-ICR-MS: calculated for $C_{18}H_{16}ClN_3O_2Na^+$: 364.0823, found: 364.0820.



20d

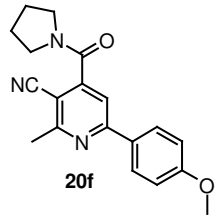
20d; colorless solid; 99% yield, $C_{22}H_{22}ClN_3O_3$, M = 411.89 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 412 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3 H) 1.88 (m, 3 H) 2.09 (m, 1 H) 2.60 (m, 1 H) 2.84 (s, 3 H) 3.20 (m, 2 H) 3.47 (m, 1 H) 4.15 (q, *J* = 7.1 Hz, 2 H) 4.47 (m, 1 H) 7.46 (m, 2 H) 7.55 (s, 1 H) 7.99 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 24.1 (CH_3), 27.5 (CH_2), 28.3 (CH_2), 40.5 (CH), 41.2 (CH_2), 46.3 (CH_2), 60.8 (CH_2), 103.7 (C), 114.4 (CH), 115.3 (C), 128.7 (CH), 129.3 (CH), 135.4 (C), 137.1 (C), 148.9 (C), 158.8 (C), 162.5 (C), 164.5 (C), 173.6 (C). FT-ICR-MS: calculated for $C_{22}H_{22}ClN_3O_3Na^+$: 434.1242, found: 434.1240.



20e

20e; colorless solid; 83% yield, $C_{18}H_{15}Cl_2N_3O_2$, M = 376.25 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 376 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (s, 3 H) 3.36 (m, 2 H) 3.71 (m, 2 H) 3.82 (m, 4 H) 7.38 (dd, *J* = 8.4, 2.0 Hz, 1 H) 7.51 (d, *J* = 2.0 Hz, 1 H) 7.56 (s, 1 H) 7.59 (d, *J* = 8.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0 (CH_3), 42.4 (CH_2), 47.5 (CH_2), 66.5 (CH_2), 66.6 (CH_2), 104.7 (C), 115.0 (C), 119.5 (CH), 127.8 (CH), 130.2 (CH), 132.5 (CH), 132.7 (C),

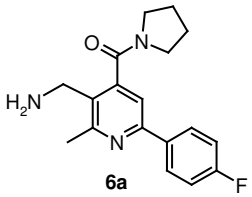
135.4 (C), 136.5 (C), 147.3 (C), 158.5 (C), 162.7 (C), 164.3 (C). FT-ICR-MS: calculated for $C_{18}H_{15}Cl_2N_3O_2Na^+$: 398.0434, found: 398.0436.



20f

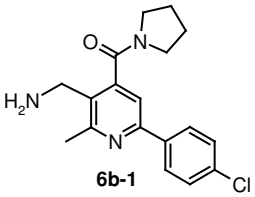
20f; colorless solid; 89% yield, $C_{19}H_{19}N_3O_2$, M = 321.38 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 322 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (m, 4 H), 2.82 (s, 3 H), 3.32 (t, *J* = 6.5 Hz, 2 H), 3.69 (t, *J* = 6.9 Hz, 2 H), 3.85 (s, 3 H), 6.98 (m, 2 H), 7.55 (s, 1 H), 8.00 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1 (CH_3), 24.3 (CH_2), 26.0 (CH_2), 46.0 (CH_2), 48.3 (CH_2), 55.4 (CH_3), 102.4 (C), 113.7 (CH), 114.4 (CH), 115.8 (C), 129.0 (CH), 129.5 (C), 149.5 (C), 159.6 (C), 161.9 (C), 162.3 (C), 164.6 (C). FT-ICR-MS: calculated for $C_{19}H_{19}N_3O_2Na^+$: 344.1370, found: 344.1367.

General procedure for the synthesis of 6 (Scheme S3, conditions e): 51% aqueous solution of hydrazine (20 eq, 3 mmol, 0.20 mL) was added dropwise with in 20 min to a suspension of **20** (1 eq, 0.15 mmol) and Raney Nickel (1 mL, 50% slurry in water) dissolved in THF (60 mL). The catalyst was then filtered off and the solution was acidified with TFA to pH 4. The solvent was removed under reduced pressure and the product **6** was purified by column chromatography with DCM/MeOH (10:1) as eluent.



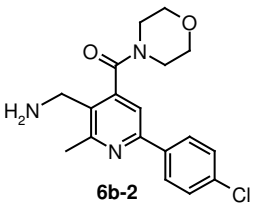
6a

6a; colorless solid; 46% yield, $C_{18}H_{20}FN_3O$, M = 313.38 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 314 *m/z*.



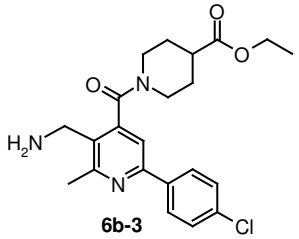
6b-1

6b-1; colorless solid; 53% yield, $C_{18}H_{20}ClN_3O$, M = 329.83 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 330 *m/z*. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.99 (m, 4 H), 2.78 (s, 3 H), 3.43 (t, *J* = 6.6 Hz, 2 H), 3.67 (t, *J* = 7.0 Hz, 2 H), 4.18 (s, 2 H), 7.49 (m, 2 H), 7.87 (s, 1 H), 8.08 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 22.8 (CH_3), 25.2 (CH_2), 27.1 (CH_2), 39.2 (CH_2), 47.4 (CH_2), 30.5 (CH_2), 117.0 (CH), 123.7 (C), 129.7 (CH), 130.0 (CH), 137.1 (C), 137.8 (C), 148.4 (C), 157.7 (C), 161.9 (C), 168.7 (C). FT-ICR-MS: calculated for $C_{18}H_{20}ClN_3OH^+$: 330.1368, found: 330.1369.



6b-2

6b-2; colorless solid; 48% yield, $C_{18}H_{20}ClN_3O_2$, M = 345.83 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 346 *m/z*. FT-ICR-MS: calculated for $C_{18}H_{20}ClN_3O_2H^+$: 346.1317, found: 346.1318.

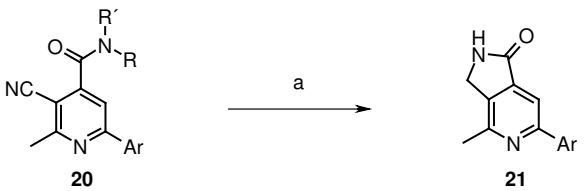


6b-3

6b-3; colorless solid; 52% yield, $C_{22}H_{26}ClN_3O_3$, M = 415.92 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 416 *m/z*.

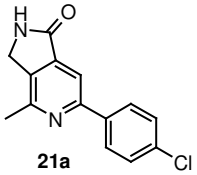
Synthesis of pyrrolopyridines 21:

Scheme S4



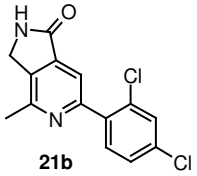
20 **21**

51% aqueous solution of hydrazine (20 eq, 3 mmol) was added dropwise to a suspension of the tertiary amide **20** (1 eq, 0.15 mmol) and Raney Nickel (1 mL, 50% slurry in water) dissolved in MeOH (50 mL). After stirring for 3-16 h at rt (reaction monitored by TLC), the catalyst was filtered off and the solvent was removed under reduced pressure. The residue was taken up in water and extracted with DCM/EA. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated. The product **21** was isolated by column chromatography with DCM/MeOH (40:1) as eluent.



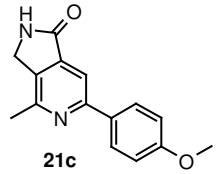
21a

21a; colorless solid; 80% yield, $C_{14}H_{11}ClN_2O$, M = 258.71 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 259 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.56 (s, 3 H), 4.44 (s, 2 H), 7.51 (m, 2 H), 7.97 (s, 1 H), 8.16 (m 2 H), 8.95 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 20.9 (CH_3), 43.8 (CH_2), 110.9 (CH), 128.5 (CH), 128.7 (CH), 133.9 (C), 136.4 (C), 137.2 (C), 141.5 (C), 153.9 (C), 154.0 (C), 168.7 (C).



21b

21b; colorless solid; 66% yield, $C_{14}H_{10}Cl_2N_2O$, M = 293.15 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 293 m/z. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.57 (s, 3 H), 4.49 (s, 2 H), 7.54 (m, 1 H), 7.62 (m, 1 H), 7.69 (s, 1 H), 7.74 (m, 1 H), 9.02 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 20.7 (CH_3), 43.9 (CH_2), 115.4 (CH), 127.6 (CH), 129.4 (CH), 132.2 (C), 133.1 (CH), 133.9 (C), 136.8 (C), 137.5 (C), 140.6 (C), 153.8 (C), 154.2 (C), 168.4 (C).



21c

21c; colorless solid; colorless solid; 69% yield, $C_{15}H_{14}N_2O_2$, M = 254.29 g/mol, HPLC-ESI-MS: $[M + H]^+$ = 255 *m/z*. ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.56 (s, 3 H), 3.81 (s, 3 H), 4.44 (s, 2 H), 7.03 (m, 2 H), 7.88 (s, 1 H), 8.10 (m, 2 H), 8.91 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-D_6) δ 21.0 (CH_3), 43.8 (CH_2), 55.2 (CH_3), 109.9 (CH), 114.1 (CH), 128.1 (CH), 130.9 (C), 135.2 (C), 141.4 (C), 153.5 (C), 160.2 (C), 168.9 (C).