Supporting information

Late-Stage Functionalization of the 4-amino-2-Pyridone Chemotype Using Electrochemical and MCR approaches

Lisa Giannessi, Matteo Longo, Chiara Massera and Marco Radi

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1. General considerations

All solvents and commercially available reagents were purchased from Fisher Scientifics and Fluorochem and used without further purification unless otherwise stated. Solvents used for work-up and purification procedures were of technical grade. TLC was carried out using Sigma-Aldrich TLC plates (silica gel on Al foils, SUPELCO Analytical, Merck 60 F254 silica plates). Visualization was accomplished by irradiation with a UV lamp and/or staining with either KMnO₄ or ninhydrin. Column chromatography was performed over Silica gel 60 Å (40-63µ mesh). Residual solvent was removed using a static oil pump (< 10 mbar).

All reactions were carried out under aerobic conditions unless otherwise stated. Electrolyses were performed using an IKA Electrasyn 2.0, using carbon graphite working electrode and graphite counter electrode, and using a variable stirring rate between 400-1500 rpm. Microwave assisted reaction were performed using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with an operator-selectable power output from 0 to 300 W. The temperature inside the reaction vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. All experiments were performed using a stirring option whereby the reaction mixtures were stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel.

NMR spectra were obtained using a Bruker AV-400 MHz NMR and Jeol 600 MHz ECZ600R NMR spectrometers and are reported in parts per million (ppm) relative to TMS. All heteronuclear NMR spectra were ¹H- decoupled and recorded at room temperature unless otherwise stated. Data for ¹H NMR spectra are reported as follows: chemical shift (δ, ppm), integration, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad), and coupling constant (Hz). Data for ¹³C NMR are reported in terms of chemical shift (δ, ppm). Data for ¹⁹F NMR spectra are reported as follows: chemical shift (δ, ppm), integration, and multiplicity (s, singlet).

Elemental analyses were performed by using a FlashSmart CHNS analyzer (Thermo Fisher) with gas-chromatographic separation. All final compounds were >95% pure as determined by elemental analysis (within 0.4% of the theoretical values). Low resolution mass spectrometry measurements were performed on an Agilent 6100 Series InfinityLab LC/MSD iQ, Single Quadropole analyzer and are reported in the form of (m/z). Melting points were taken using a Gallenkamp melting point apparatus and were uncorrected.
2. Electrochemistry experiments

GENERAL POLISHING PROCEDURE: Graphite and platinum electrodes were washed after each experiment by sonication in acetone (5 minutes x2) and methanol (5 minutes). When the platinum electrode surface resulted passivated, the surface layer was removed by alumina scrub, then washed with water, methanol and acetone. Ag wire electrode was washed using water and acetone.

CYCLIC VOLTAMMETRY EXPERIMENTS:

Figure S1. Electrasyn 2.0 and cyclic voltammetry set of electrodes used for collecting the voltammograms.

1. All CV Experiments were performed with Electrasyn 2.0.
2. Data were elaborated with Excel.
3. Experimental conditions: Methanol as solvent (4.0 mL); TBAClO$_4$ as supporting electrolyte (100 mM), cyclic voltammetry kit as electrodes: 1) Working electrode: 3 mm diameter glassy carbon disc electrode, 2) Counter electrode: platinum plate electrode, 3) Reference electrode: Ag wire (Ag/AgCl); TBAClO$_4$ 0.1 M as supporting electrolyte. Experimental parameters: Segments: 3. Initial voltage: 0.0 V. Upper voltage: 2.0 V. Lower voltage: -1.0 V. Final voltage: 0.0 V. Sweep: 100mV/s.
Figure S2. Voltammograms of 5c in combination with different electrocatalyst (DDQ an TEMPO, 0.2 eq). Graphs: A) In orange: blank (only TBAClO$_4$ 100 mM); In grey: TBAClO$_4$ 100 mM, 5c 10 mM; In blue: TBAClO$_4$ 100 mM, 5c 10 mM and DDQ 2 mM. B) In orange: blank (only TBAClO$_4$ 100 mM); In grey: TBAClO$_4$ 100 mM, 5c 10 mM; In blue: TBAClO$_4$ 100 mM, 5c 10 mM and TEMPO 2 mM.

Figure S3. Voltammograms of 19a-c in the reaction conditions. Graphs: A) In orange: blank (only TBAClO$_4$ 100 mM); In grey: TBAClO$_4$ 100 mM, 19a 10 mM; In blue: TBAClO$_4$ 100 mM, 19a 10 mM and DDQ 2 mM. B) In orange: blank (only TBAClO$_4$ 100 mM); In grey: TBAClO$_4$ 100 mM, 19b 10 mM; In blue: TBAClO$_4$ 100 mM, 19b 10 mM and DDQ 2 mM. C) In orange: blank (only TBAClO$_4$ 100 mM); In grey: TBAClO$_4$ 100 mM, 19c 10 mM; In blue: TBAClO$_4$ 100 mM, 19c 10 mM and DDQ 2 mM.
3. Proposed reaction mechanisms

Scheme S1. Synthesis of compounds of type 6. After the DDQ mediated anodic oxidation of 5c to radical cation 14, this intermediate reacts with the radical X, anodically generated starting from the corresponding supporting electrolyte, giving rise to the tetrameric intermediate of type 27 which, by losing a proton, yields the desired product of type 6.
Scheme S2. Synthesis of compound 8.
After the DDQ mediated anodic oxidation of 5c to radical cation 14, this intermediate is further oxidized to iminium cation 15, which then reacts with methoxide (cathodically generated in situ from the solvent, MeOH). The resulting amine 18 is further oxidized (DDQ catalyzed reaction), giving rise to the corresponding enamine 8.
Scheme S3. MCR using secondary amine as nucleophiles: Mannich reaction.
The iminium cation 28, formed through condensation reaction between amine 23 and formaldehyde, reacts with the 4-amino-2-pyridone 5c or 19a-c, giving rise to the corresponding product 9a-b or 25a-c.

Scheme S4. MCR using primary amine as nucleophiles.
The iminium cation 28, formed through condensation reaction between amine 23 and formaldehyde, reacts with the 4-amino-2-pyridone 5c or 19a-c, giving rise to the corresponding intermediate of type 9. The highly reactive intermediate is not isolable, and reacts with another equivalent of formaldehyde, affording the iminium cation 31, which then gives rise to the corresponding products 10a-d or 26a-c through intramolecular cyclization due to the nucleophilic attack of the N4.
4. Tables for the optimization of reaction conditions

Table S1. Optimization conditions for the synthesis of compound 8.a

<table>
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<th>Entry</th>
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<th>Total charge (F/mol)</th>
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aReaction Conditions: graphite anode (8 x 52.5 x 2 mm), graphite electrode (8 x 52.5 x 2 mm), 5c (0.1 mmol), DDQ (0.02 mmol), electrolyte (0.2 mmol), methanol (4 mL), electrolysis at a constant current for 2-8 F/mol in an undivided cell at room temperature.
bIsolated yields.
cResistance too high.

Table S2. Optimization conditions for the synthesis of 9a.

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<td>2</td>
<td>Microwave, sealed tube</td>
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<td>3</td>
<td>Microwave, open vessel</td>
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<td>72</td>
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### Table S3. Optimization conditions for the synthesis of 10a.

![Chemical structure of 10a](image)

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<th>Yield (%)</th>
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<tr>
<td>2</td>
<td>microwave, sealed tube</td>
<td>40 minutes</td>
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### Table S4. Optimization conditions for the synthesis of 10b.

![Chemical structure of 10b](image)

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<td>microwave, sealed tube</td>
<td>40 minutes</td>
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<td>overnight</td>
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</table>
5. General procedures

GENERAL PROCEDURE 1 (GP1)
In a 10 mL microwave tube, equipped with magnetic stir bar and septum, a mixture 4-hydroxy-6-methyl-2-pyrone (100 mg, 1 equivalent, 0.79 mmol) and the proper amine (2 equivalents) was heated at 100°C for 6 minutes in the microwave apparatus (maximum power input: 300 W; maximum pressure: 250 psi; power max: OFF; stirring: ON). After cooling to room temperature, the solid was solubilized in AcOEt, washed with distilled H₂O, and the organic phase extracted 3 times, then the collected organic layers were washed with BRINE, and finally dried over Na₂SO₄. Once removed the solvent under reduced pressure, the resulting crude was purified by flash chromatography, affording the desired product.

GENERAL PROCEDURE 2 (GP2)
A 10 mL IKA Electrasyn electrochemical vial was charged with compound 5c, 11 or 19a-c (0.10 mmol, 1 eq), DDQ (4.54 mg, 0.02 mmol, 0.2 eq), the appropriate supporting electrolyte (0.2 mmol, 2 eq), TFA (depending on the case, catalytic amount, 1 drop), and MeOH (4 mL). The resulting mixture was then electrolysed at a constant current of 10 mA until complete conversion of the starting material, as monitored by TLC analysis (2-4 F/mol). Upon completion, the crude reaction mixture was poured into water and extracted with ethyl acetate. The combined organic extracts were washed with BRINE, dried over Na₂SO₄, filtered, and the solvent was removed under vacuum. The desired product was then obtained pure after flash chromatography purification.

GENERAL PROCEDURE 3 (GP3)
A 10 mL IKA Electrasyn electrochemical vial was charged with compound 5c (0.10 mmol, 1 eq), DDQ (5.45 mg, 0.02 mmol, 0.2 eq), NaCN (9.8 mg, 0.20 mmol, 2 eq), and MeOH (4.0 mL). The resulting mixture was then electrolysed at a constant current of 1.5 mA until complete conversion of the starting material, as monitored by TLC analysis (8 F/mol). Upon completion, the crude reaction mixture was purified by flash chromatography (DCM/MeOH 98:2), affording the desired product (20%).
A microwave tube was charged with compound 5c or 19a-c (0.1 mmol, 1 eq), the appropriate amine 23 (0.2 mmol, 2 eq), formaldehyde (0.15 mmol, 1.5 eq) acetic acid (20 mol%), and acetonitrile/distilled water (1:1, 2 mL). The resulting mixture was heated at 80°C in the microwave apparatus in sealed tube (maximum power input: 300 W; maximum pressure: 250 psi; power max: OFF; stirring: ON) for 40 minutes, verifying the complete conversion of the starting material by TLC monitoring. Then saturated aqueous NaHCO₃ was added, and the aqueous phase was extracted three times with dichloromethane, the combined organic layers dried over Na₂SO₄, and the solvent evaporated under reduced pressure. The obtained crude of the reaction was purified by flash chromatography, affording the desired product as yellowish solid.

A 10 mL round-bottomed flask was charged with compound 5c or 19a-b (0.1 mmol, 1 eq), the appropriate amine 23 (0.2 mmol, 2 eq), formaldehyde (0.4 mmol, 4 eq), acetic acid (20 mol%), and acetonitrile/distilled water (1:1, 2 mL). The resulting mixture was heated at 80°C in the microwave apparatus (maximum power input: 300 W; maximum pressure: 250 psi; power max: OFF; stirring: ON) for 10-40 minutes, verifying the complete conversion of the starting material by TLC monitoring. Then saturated aqueous NaHCO₃ was added, and the aqueous phase was extracted three times with dichloromethane, the combined organic layers dried over Na₂SO₄, and the solvent evaporated under reduced pressure. The obtained crude of the reaction was purified by flash chromatography, affording the desired product as white solid.
6. Characterization of the compounds

4-Amino-2-pyridones starting materials:

**Compound 5c**

6-methyl-1-(4-(trifluoromethyl)benzyl)-4-((4-(trifluoromethyl)benzyl)amino)pyridin-2(1H)-one

According to GP1, using 4-(trifluoromethyl)benzylamine as proper amine (2 equivalents, 1.58 mmol, 138 µL) the desired product was obtained after flash chromatography purification (CHCl₃/MeOH 99/1-98/2), in 55% yield (180.40 mg). White solid, m.p. 171-173 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.505 (2H, d, J = 7.83 Hz), 7.46 (2H, d, J = 7.83 Hz), 7.33 (2H, d, J = 7.83 Hz), 7.16 (2H, d, J = 7.83 Hz), 5.53 (1H, d, J = 1.89 Hz), 5.46 (1H, d, J = 1.89 Hz), 5.18 (2H, bs), 4.79 (1H, bs), 4.26 (2H, d, J = 4.60 Hz), 2.04 (3H, s). ¹³C NMR (100.6 MHz, CDCl₃) δ 163.5, 153.9, 144.5, 140.7, 140.5, 128.8 (q, J_C-F = 32.51 Hz), 128.5 (q, J_C-F = 32.51 Hz), 126.4, 125.6, 124.7, 124.7, 123.0 (2C, q, J_C-F = 271.69 Hz), 99.0, 89.9, 45.3, 44.9, 19.4. ¹⁹F NMR (564 MHz, CDCl₃) δ - 62.43 (3F, s), - 62.45 (3F, s). MS (ESI) m/z 441.2 [M+H]⁺; 463.3 [M+Na]⁺.

**Compound 11**

N-(6-methyl-1,2-dihydropyridin-4-yl)-N-(4-(trifluoromethyl)benzyl)acetamide

In a 10 mL microwave tube, equipped with magnetic stir bar and septum, a mixture of compound 5c (0.10 mmol, 44-04 mg), acetyl chloride (2.5 eq, 0.25 mmol, 17.77 µL), and pyridine (2.5 eq, 0.25 mmol, 20.14 µL) in anhydrous DCM (1.5 mL) was heated at 45 °C for 30 min in the microwave apparatus (maximum power input: 300 W; maximum pressure: 250 psi; power max: OFF; stirring: ON). After cooling to room temperature, the solution was diluted with Ethyl Acetate and washed with NaHCO₃ sat. sol. The aqueous phase was then extracted with Ethyl Acetate (3 times), and the
collected organic layers washed with BRINE, dried over Na$_2$SO$_4$, filtered, and the solvent removed under reduced pressure. The crude of the reaction was then purified by flash chromatography (DCM/MeOH 98/2), affording in 51% yield (46.00 mg) the desired product as yellowish solids. m.p. 82-84 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52-7.49 (m, 4H), 7.28 (2H, d, $J = 8.37$ Hz), 7.17 (2H, d, $J = 8.37$ Hz), 6.19 (1H, d, $J = 2.30$ Hz), 5.84 (1H, s), 5.26 (2H, s), 4.85 (2H, s), 2.18 (3H, s), 2.09 (3H, s). $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 168.6, 162.7, 151.7, 146.5, 139.6, 138.7, 128.9 (q, $J_{C-F} = 32.83$ Hz), 128.8 (q, $J_{C-F} = 32.51$ Hz), 126.9, 125.7, 124.8, 124.6, 124.5, 122.9 (q, $J_{C-F} = 272.08$ Hz), 121.8 (q, $J_{C-F} = 272.08$ Hz), 113.1, 105.4, 50.3, 45.8, 21.7, 19.7. $^{19}$F NMR (564 MHz, CDCl$_3$) $\delta$ -62.47 (3F, s), -62.57 (3F, s). MS (ESI) $m/z$ 483.1 [M+H]+.

**Compound 19a**

6-methyl-1-(3-(trifluoromethyl)benzyl)-4-(3-(trifluoromethyl)benzyl)amino)pyridin-2(1H)-one

According to GP1, using 3-(trifluoromethyl)benzylamine as proper amine (2 equivalents, 1.58 mmol, 138µL) the desired product was obtained after flash chromatography purification (CHCl$_3$/MeOH 99/1-98/2), in 55% yield (180.40 mg). White solid, m.p. 190-194 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.44-7.28 (6H, m), 7.20 (1H, d, $J = 7.50$ Hz), 5.52 (1H, d, $J = 1.87$ Hz), 5.37 (1H, d, $J = 2.41$ Hz), 5.22 (1H, t, $J = 5.35$ Hz), 5.14 (2H, bs), 4.20 (2H, d, $J = 5.62$ Hz), 2.00 (3H, s). $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 164.7, 155.0, 145.3, 138.9, 138.6, 131.1 (q, $J_{C-F} = 32.21$ Hz), 131.0 (q, $J_{C-F} = 33.28$ Hz), 130.6, 129.6, 129.3, 129.2, 124.4, 124.3, 124.0 (2C), 124.0 (q, $J_{C-F} = 272.26$ Hz), 124.0 (q, $J_{C-F} = 272.97$ Hz), 123.9, 123.8, 123.0, (2C), 100.1, 90.7, 46.3, 45.8, 20.4. $^{19}$F NMR (564 MHz, CDCl$_3$) $\delta$ -62.47 (6F, bs). MS (ESI) $m/z$ 441.2 [M+H]+.

**Compound 19b**

6-methyl-1-phenyl-4-(phenylamino)pyridin-2(1H)-one

According to GP1, using aniline as proper amine (2 equivalents, 1.58 mmol, 156 µL) the desired product was obtained after flash chromatography purification (hexane/ethyl acetate 6/4), in 50% yield (109.2 mg). White solid, m.p. 190-195 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39-7.35 (2H, m), 7.32-7.20 (1H, m), 7.25-7.21 (2H, m), 7.11-7.06 (4H, m), 7.03-7.00 (1H, t, $J = 7.43$ Hz), 6.55 (1H, s), 5.92 (1H, d, $J = 2.48$ Hz), 5.75 (1H, d, $J = 1.73$ Hz), 1.77 (3H, s). $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 165.1, 130.1, 145.9, 139.3, 138.9, 129.5, 129.3, 128.5, 124.2, 122.6, 99.7, 93.6, 21.6. MS (ESI) $m/z$ 277.1 [M+H]+.
Compound 19c
1-(3,5-dimethylphenyl)-4-((3,5-dimethylphenyl)amino)-6-methylpyridin-2(1H)-one
According to GP1, using 3,5-dimethylaniline as proper amine (2 equivalents, 1.58 mmol, 197.2 µL) the desired product was obtained after flash chromatography purification (Dichloromethane/Methanol 98/2), in 40% yield (105.0 mg). White solid, m.p. 210-215 °C. 

\[ ^1H \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta \]:
- 7.01 (1H, s),
- 6.80 (2H, s),
- 6.78 (2H, s),
- 6.74 (1H, s),
- 6.59 (1H, s),
- 6.02 (1H, d, J = 2.34 Hz),
- 5.74 (1H, d, J = 1.69 Hz),
- 2.32 (6H, s),
- 2.29 (6H, s),
- 1.87 (3H, s).

\[ ^{13}C \text{ NMR} (100.6 \text{ MHz, CDCl}_3) \delta \]:
- 165.3,
- 153.0,
- 145.7,
- 139.3,
- 139.2,
- 138.9,
- 138.8,
- 130.1,
- 126.0,
- 125.8,
- 120.1,
- 99.8,
- 93.5,
- 21.5,
- 21.4,
- 21.2.

MS (ESI) m/z 355.2 [M+Na]^+.

e-LSF:

Compound 6a
3-chloro-6-methyl-1-{4-(trifluoromethyl)benzyl}-4-{(4-(trifluoromethyl)benzyl)amino}pyridin-2(1H)-one
According to GP2, with compound 5c as staring material (44.0 mg), using KCl (14.91 mg) as supporting electrolyte, and in the presence of TFA, after electrolyzing the reaction mixture for 4 F/mol, the title compound (19.00 mg) was isolated by flash chromatography (dichloromethane/methanol 98/2) in 40% yield. White solid. m.p. 72-75 °C. 

\[ ^1H \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta \]:
- 7.56 (2H, d, J = 8.55 Hz),
- 7.48 (2H, d, J = 8.55 Hz),
- 7.35 (2H, d, J = 7.60 Hz),
- 7.21 (2H, d, J = 7.60 Hz),
- 5.56 (1H, s),
- 5.33 (1H, t, J = 5.70 Hz),
- 5.27 (2H, s),
- 4.48 (2H, d, J = 5.70 Hz),
- 2.10 (3H, s).

\[ ^{13}C \text{ NMR} (100.6 \text{ MHz, CDCl}_3) \delta \]:
- 158.5,
- 149.3,
- 143.6,
- 140.7,
- 139.8,
- 129.1 (q, \( J_{CF} = 33.88 \text{ Hz} \)),
- 128.8 (q, \( J_{CF} = 31.88 \text{ Hz} \)),
- 126.0,
- 125.9,
- 125.0,
- 124.9,
- 124.8,
- 124.7,
- 123.0 (2C, q, \( J_{CF} = 271.78 \text{ Hz} \)),
- 98.7,
- 94.0,
- 46.3,
- 45.3,
- 19.9.

\[ ^{19}F \text{ NMR} (564 \text{ MHz, CDCl}_3) \delta \]:
- -62.46 (3F, s),
- -62.48 (3F, s).

MS (ESI) m/z 475.3, 477.1 [M+H]^+.
According to GP2, with compound 5c as starting material (44.0 mg), using KBr (23.80 mg) as supporting electrolyte, and in the presence of TFA, after electrolyzing the reaction mixture for 4 F/mol, the title compound (29.60 mg) was isolated by flash chromatography (dichloromethane/methanol 98/2) in 57 % yield. White solid. m.p. 74-76 °C. 1H NMR (400 MHz, CDCl₃) δ 7.55 (2H, d, J = 8.48 Hz), 7.47 (2H, d, J = 8.48 Hz), 7.34 (2H, d, J = 7.63 Hz), 7.19 (2H, d, J = 8.48 Hz), 5.52 (1H, s), 5.37 (1H, t, J = 5.85 Hz), 5.27 (2H, s), 4.47 (2H, d, J = 5.85 Hz), 2.08 (3H, s). 13C NMR (100.6 MHz, CDCl₃) δ 159.8, 151.8, 145.4, 141.8, 141.0, 130.0 (m), 127.0, 126.9, 126.0, 125.9, 125.7, 125.7, 124.0 (2C, q, JCF = 272.1 Hz), 95.2, 91.2, 47.6, 46.5, 20.9. 19F NMR (564 MHz, CDCl₃) δ -62.45 (3F, s), -62.48 (3F, s). MS (ESI) m/z 519.2, 521.2 [M+H]+.

According to GP2, with compound 5c as starting material (44.0 mg), using I₂ (50.76 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 2 F/mol, the title compound (40.80 mg) was isolated by flash chromatography (dichloromethane/methanol 98/2) in 72 % yield. Yellowish solid. m.p. 135-138 °C. 1H NMR (400 MHz, CDCl₃) δ 7.56 (2H, d, J = 8.18 Hz), 7.47 (2H, d, J = 8.18 Hz), 7.34 (2H, d, J = 8.18 Hz), 7.19 (2H, d, J = 8.18 Hz), 5.33 (1H, t, J = 6.00 Hz), 5.29 (2H, s), 4.48 (2H, d, J = 6.00 Hz), 2.09 (3H, s). 13C NMR (100.6 MHz, CDCl₃) δ 169.7, 163.8, 152.8, 147.6, 140.7, 139.8, 129.9 (2C, q, JCF = 33.25 Hz), 128.1, 126.8, 126.0 (2C), 125.7 (2C), 124.0 (2C, q, JCF = 272.15 Hz), 114.3, 106.5, 51.5, 46.9, 22.8, 20.8. 19F NMR (564 MHz, CDCl₃) δ -62.45 (3F, s), -62.48 (3F, s). MS (ESI) m/z 567.2 [M+H]+.
Compound 13

N-(3-bromo-6-methyl-2-oxo-1-(4-(trifluoromethyl)benzyl)-1,2-dihydropyridin-4-yl)-N-(4-(trifluoromethyl)benzyl)acetamide

According to GP2, with compound 11 as starting material (48.2 mg), using KBr (23.80 mg) as supporting electrolyte, and in the presence of TFA, after electrolyzing the reaction mixture for 4 F/mol, the title compound (9.0 mg) was isolated by flash chromatography (dichloromethane 100% – dichloromethane/acetone 95/5) in 16 % yield. White solid. m.p. 73-75 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.53 (2H, d, $J = 8.16$ Hz), 7.48 (2H, d, $J = 7.70$ Hz), 7.33 (2H, d, $J = 8.16$ Hz), 7.20 (2H, d, $J = 7.70$ Hz), 5.62 (1H, s), 5.32 (2H, d, $J = 5.22$ Hz), 5.26 (1H, d, $J = 14.70$ Hz), 4.35 (1H, d, $J = 14.70$ Hz), 2.14 (3H, s), 1.95 (3H, s). $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 167.7, 159.6, 150.0, 144.9, 139.3, 137.9, 129.1 (2C, q, $J_{CF} = 32.51$ Hz), 128.1, 125.9, 124.9, 124.8, 124.2, 122.8 (q, $J_{CF} = 273.5$ Hz), 122.6 (q, $J_{CF} = 270.1$ Hz), 113.5, 107.0, 49.1, 47.6, 21.0, 19.4. $^{19}$F NMR (564 MHz, CDCl$_3$) δ -62.47 (3F, s), -62.63 (3F, s). MS (ESI) m/z 561.3, 563.3 [M+H]$^+$. 

Compound 20a

3-bromo-6-methyl-1-(3-(trifluoromethyl)benzyl)-4-(3-(trifluoromethyl)benzyl)amino)pyridin-2(1H)-one

According to GP2, with compound 19a as starting material (44.0 mg), using KBr (23.80 mg) as supporting electrolyte, and in the presence of TFA, after electrolyzing the reaction mixture for 4 F/mol, the title compound (27.40 mg) was isolated by flash chromatography (dichloromethane/methanol 98/2) in 53 % yield. Yellow solid. m.p. 100-105 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.49-7.48 (2H, m), 7.43-7.41 (3H, m), 7.35-7.31 (2H, m), 7.27-7.25 (1H, m), 5.56 (1H, s), 5.35 (1H, t, $J = 6.00$ Hz), 5.27 (2H, s), 4.46 (2H, d, $J = 6.00$ Hz), 2.09 (3H, s). $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 159.8, 151.8, 146.0, 145.3, 138.7, 137.9, 131.4 (q, $J_{CF} = 31.52$ Hz), 131.0 (q, $J_{CF} = 31.52$ Hz), 130.1
(2C), 129.6, 129.4, 124.7 (2C), 124.3 (2C), 124.0 (2C, q, $J_{CF} = 273.0$ Hz), 123.7, 123.6, 123.3 (2C), 95.3, 91.2, 47.6, 46.6, 20.9. $^{19}$F NMR (564 MHz, CDCl$_3$) $\delta$ -62.47 (3F, s), -62.56 (3F, s). MS (ESI) $m/z$ 519.1, 521.1 [M+H]$^+$, 541.1, 543.1 [M+Na]$^+$.

**Compound 20b**

3-bromo-6-methyl-1-phenyl-4-(phenylamino)pyridin-2(1H)-one

According to GP2, with compound 19b as staring material (27.3 mg), using KBr (23.80 mg) as supporting electrolyte, and in the presence of TFA, after electrolyzing the reaction mixture for 4 F/mol, the title compound (17.10 mg) was isolated by flash chromatography (petroleum ether/ethyl acetate 6/4-5/5) in 48 % yield. Yellow solid. m.p. 186-189 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.43-7.42 (2H, m), 7.37-7.33 (3H, m), 7.20-7.16 (3H, m), 7.13-7.11 (2H, m), 6.63 (1H, s), 5.91 (1H, s), 1.78 (3H, s). $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 160.2, 150.3, 144.9, 138.9, 138.4, 129.6, 129.5, 128.7, 128.3, 125.8, 124.6, 95.8, 92.7, 21.7. MS (ESI) $m/z$ 355.1, 357.1 [M+H]$^+$, 377.0, 379.0 [M+Na]$^+$.

**Compound 20c**

3-bromo-1-(3,5-dimethylphenyl)-4-((3,5-dimethylphenyl)amino)-6-methylpyridin-2(1H)-one

According to GP2, with compound 19c as staring material (33.2 mg), using KBr (23.80 mg) as supporting electrolyte, and in the presence of TFA, after electrolyzing the reaction mixture for 4 F/mol, the title compound (20.2 mg) was isolated by flash chromatography (petroleum ether/ethyl acetate 7/3) in mixture with a second bromination product in 48 % yield (yield of the mixture of product), which cannot by separated.* Yellow solid. m.p. 115-120 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.88 (2H, s), 6.77 (1H, s), 6.72 (2H, s), 6.46 ((1H, s), 5.83 (1H, s), 2.36 (6H, s), 2.26 (6H, s), 1.81 (3H, s). $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 160.3, 150.3, 144.9, 138.9, 138.4, 129.6, 129.5, 128.7, 128.3, 125.8, 125.7, 124.2, 122.3, 95.6, 92.9, 24.0, 21.7, 21.3. MS (ESI) $m/z$ 411.1, 413.1 [M+H]$^+$.

*N.B. Compound 20c could not be isolated as a pure product, but in mixture with a second bromination product. The loss of complete chemoselectivity might be due to a higher reactivity of the more electron-rich starting material 19c, as shown in the voltammograms reported in Figure S3.
Compound 7
2-imino-6-methyl-1,5-bis(4-(trifluoromethyl)benzyl)-1,2-dihydrothiazolo[5,4-c]pyridin-4(5H)-one
According to GP2, with compound 5c as starting material (44.0 mg), using KSCN (19.44 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 4 F/mol, the title compound (13.43 mg) was isolated by flash chromatography (Petroleum ether/AcOEt 9/1-8/2) in 27 % yield. Yellow solid. m.p. 155-160 °C. 1H NMR (400 MHz, CDCl₃) δ 7.54 (2H, d, J = 8.28 Hz), 7.49 (2H, d, J = 8.28 Hz), 7.20 (2H, d, J = 8.28 Hz), 7.57 (1H, s), 5.30 (2H, s), 5.08 (2H, s), 2.18 (3H, s). 13C NMR (100.6 MHz, CDCl₃) δ 163.0, 156.9, 146.7, 146.0, 140.3, 139.5, 130.1 (2C, q, J_C-F = 32.39 Hz), 127.03, 126.9, 126.0 (2C), 125.9, 122.4 (2C, q, J_C-F = 272.1 Hz), 103.9, 94.4, 46.8, 45.8, 21.3. 19F NMR (564 MHz, CDCl₃) δ -62.53 (3F, s), -62.54 (3F, s). MS (ESI) m/z 498.1 [M+H]+.

Compound 21a
2-imino-6-methyl-1,5-bis(3-(trifluoromethyl)benzyl)-1,2-dihydrothiazolo[5,4-c]pyridin-4(5H)-one
According to GP2, with compound 19a as starting material (44.0 mg), using KSCN (19.44 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 4 F/mol, the title compound (14.00 mg) was isolated by flash chromatography (dichloromethane/methanol 98/2) in 28 % yield. White solid. m.p. 155-158 °C. 1H NMR (400 MHz, CDCl₃) δ 7.49-7.35 (7H, m), 7.27-7.25 (1H, m), 5.77 (1H, s), 5.30 (2H, bs), 5.08 (2H, s), 2.20 (3H, s). 13C NMR (100.6 MHz, CDCl₃) δ 163.0, 156.9, 146.7, 146.0, 140.3, 139.5, 130.1 (2C, q, J_C-F = 32.39 Hz), 127.03, 126.9, 126.0 (2C), 124.8 (2C), 123.8 (2C, q, J_C-F = 273.0 Hz), 123.7, 123.6, 123.4 (2C), 104.0, 94.4, 46.8, 45.9, 21.3. 19F NMR (564 MHz, CDCl₃) δ -62.53 (3F, s), -62.54 (3F, s). MS (ESI) m/z 498.2 [M+H]+.
Compound 21b
2-imino-6-methyl-1,5-diphenyl-1,2-dihydrothiazolo[5,4-c]pyridin-4(5H)-one
According to GP2, with compound 19b as staring material (27.3 mg), using KSCN (19.44 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 4 F/mol, the title compound (9.00 mg) was isolated by flash chromatography (petroleum ether/AcOEt/Et$_3$N 40/60/1) in 27 % yield. White solid. m.p. 160-163 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.55-7.51 (2H, m), 7.47-7.38 (4H, m), 7.35-7.32 (2H, m), 7.14-7.12 (2H, m), 5.56 (1H, s), 1.82 (3H, s). $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 164.6, 157.3, 147.5, 145.8, 138.1, 130.3, 129.8, 129.5, 129.0, 128.5, 128.1, 104.3, 94.5, 22.0. MS (ESI) $m/z$ 334.1 [M+H]$^+$. 

Compound 21c
1,5-bis(3,5-dimethylphenyl)-2-imino-6-methyl-1,2-dihydrothiazolo[5,4-c]pyridin-4(5H)-one
According to GP2, with compound 19c as staring material (33.2 mg), using KSCN (19.44 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 4 F/mol, the title compound (8.00 mg) was isolated by flash chromatography (petroleum ether/AcOEt/Et$_3$N 50/50/1) in 21 % yield. Yellow solid. m.p. 103-108 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.06 (1H, s), 6.99 (1H, s), 6.91 (2H, s), 6.73 (2H, s), 5.51 (1H, s), 2.33 (6H, s), 2.27 (6H, s), 1.84, 3H, s). $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 157.4, 147.6, 145.8, 140.3, 139.5, 138.0, 131.3, 130.7, 126.0, 125.6, 104.1, 94.4, 21.9, 21.3 (2C). MS (ESI) $m/z$ 390.2 [M+H]$^+$. 

Compound 17
(2Z,2'E)-2,2'-disulfanediylbis(azaneylylidene)bis(6-methyl-1,5-bis(4-(trifluoromethyl)benzyl)-1,2-dihydrothiazolo[5,4-c]pyridin-4(5H)-one)
According to GP2, with compound 5c as staring material (44.0 mg), using KSCN (19.44 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 4 F/mol, the title compound (14.26 mg) was isolated by flash chromatography (Petroleum ether/Acetone 9/1- 8-2) in 27 % yield. Yellow solid. m.p. 156-159 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49 (4H, d, $J$ = 8.71 Hz), 7.42 (4H, d, $J$ = 8.71 Hz), 7.36-7.31 (8H, 2×2 multiplets), 6.97-6.92 (4H, 2×2 multiplets), 6.90-6.80 (13H, 2×2 multiplets), 5.51-5.50 (1H, s), 1.84 (3H, s). $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 157.4, 147.6, 145.8, 140.3, 139.5, 138.0, 131.3, 130.7, 126.0, 125.6, 104.1, 94.4, 21.9, 21.3 (2C). MS (ESI) $m/z$ 390.2 [M+H]$^+$. 

S19
7.66 Hz), 7.27 (4H, d, J = 7.66 Hz), 7.20 (4H, d, J = 8.71 Hz), 5.82 (2H, s), 5.32 (4H, s), 5.17 (4H, s), 2.20 (6H, s). $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 171.2, 157.3, 146.3 (2C), 140.1, 138.9, 130.1 (2C, q, $J_{C-F}$ = 32.39 Hz), 127.2, 126.8, 125.9 (2C), 125.3-122.5 (2C, q, $J_{C-F}$ = 271.49 Hz), 106.5, 94.2, 47.2, 46.9, 21.4. $^{19}$F NMR (564 MHz, CDCl$_3$) δ -62.56 (6F, s), -62.58 (6F, s). MS (ESI) $m/z$ 1079.0 [M+Na]$^+$. 

**Compound 22a**

(2Z,2'E)-2,2'-disulfanediylbis(azaneylylidene)bis(6-methyl-1,5-bis(3-(trifluoromethyl)benzyl)-1,2-dihydrothiazolo[5,4-c]pyridin-4(5H)-one)

According to GP2, with compound 19a as starting material (44.0 mg), using KSCN (19.44 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 4 F/mol, the title compound (8.9 mg) was isolated by flash chromatography (Petroleum ether/Acetone 9/1-8-2) in 17 % yield. Yellow solid. m.p. 110-115 °C. $^{1}$$H$ NMR (400 MHz, CDCl$_3$) δ 7.46-7.42 (8H, m), 7.39-7.36 (6H, m), 5.84 (2H, s), 5.32 (4H, s), 5.18 (4H, s), 2.21 (6H, s). $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 171.4, 157.3, 146.3, 146.2, 146.1, 137.2, 136.0, 130.3, 129.8, 129.7, 129.6, 125.2, 124.9 (2C), 124.6, 123.8 (2C), 123.4 (2C), 122.5, 106.6, 94.3, 47.9, 46.9, 21.4. $^{19}$F NMR (564 MHz, CDCl$_3$) δ -62.53 (12F, s). MS (ESI) $m/z$ 1079.0 [M+Na]$^+$. 

**Compound 22b**

(2Z,2'Z)-2,2'-disulfanediylbis(azaneylylidene)bis(6-methyl-1,5-diphenyl-1,2-dihydrothiazolo[5,4-c]pyridin-4(5H)-one)

According to GP2, with compound 19b as starting material (27.3 mg), using KSCN (19.44 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 4 F/mol, the title compound (3.5 mg) was isolated by flash chromatography (Petroleum ether/AcOEt 5/5) in 10 % yield. Yellow solid.
Compound 22c

\((E)-2-\left(\left([Z]1,5\text{-bis}(3,5\text{-dimethylphenyl})-6\text{-methyl}-4\text{-oxo}-4,5\text{-dihydrothiazolo}[5,4-c]\text{pyridin}-2(1H)\text{-ylidene})amino\right)\text{disulfaneyl} \text{imino}\right)-5-(3,5\text{-dimethylphenyl})-6\text{-methyl}-1\text{-phenyl}-1,2\text{-dihydrothiazolo}[5,4-c]\text{pyridin}-4(5H)\text{-one}\)

According to GP2, with compound 19c as staring material (33.2 mg), using KSCN (19.44 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 4 F/mol, the title compound (4.0 mg) was isolated by flash chromatography (Petroleum ether/AcOEt 6/4) in 10 % yield. Yellow solid. m.p. 179-183 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.99 (4H, s), 6.74 (4H, s), 6.72 (4H, s), 5.52 (2H, s), 2.28 (12H, s), 2.27 (12H, s), 1.83 (6H, s). \(^13\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) 174.8, 157.6, 147.7, 145.8, 139.9, 139.5, 138.0, 134.9, 131.4, 130.7, 125.9, 125.6, 106.6, 94.5, 29.7, 22.0, 21.3. MS (ESI) \(m/z\) 813.2 \([M+H]^+\).

Compound 8

methyl \((Z)-N-(6\text{-methyl}-2\text{-oxo}-1-(4\text{-trifluoromethyl}benzyl)-1,2\text{-dihydropyridin-4-yl})-4\text{-trifluoromethyl}benzimidate\)

According to GP3, with compound 5c as staring material (44.0 mg), using NaCN (9.80 mg) as supporting electrolyte, after electrolyzing the reaction mixture for 8 F/mol, the title compound (10.0 mg) was isolated by flash chromatography (petroleum ether/ethyl acetate 60/40 – 50/50) in 20 %
yield. Yellowish solid. m.p. 80-90 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.5 (4H, s), 7.48 (2H, $J = 8.00$ Hz, s), 7.13 (2H, $d, J = 8.00$ Hz), 5.71 (1H, $d, J = 2.00$ Hz), 5.62 (1H, s), 5.25 (2H, s), 3.89 (3H, s), 2.11 (3H, s).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 163.0, 156.6, 156.5, 145.1, 139.5, 132.4, 131.5, 128.4 (2C, $q, J_{C-F} = 33.34$ Hz), 128.0, 125.3, 124.49, 124.46, 124.0 (2C, $q, J_{C-F} = 270.1$ Hz), 103.7, 103.3, 53.4, 45.0, 28.4, 19.3. $^{19}$F NMR (564 MHz, CDCl$_3$) $\delta$ -62.53 (3F, s), -62.54 (3F, s). MS (ESI) $m/z$ 469.2 [M+H]$^+$.  

MCR-LSF:

![Chemical Structure](image)

**Compound 9a**

6-methyl-3-((pyrrolidin-1-yl)methyl)-1-(4-(trifluoromethyl)benzyl)-4-((4-(trifluoromethyl)benzyl)amino)pyridin-2(1H)-one

According to GP4, using pyrrolidine (14.22 mg, 16.42 $\mu$L) as amine and 5c as substrate (44.04 mg), the title compound (38.3 mg) was isolated by flash chromatography (dichloromethane/methanol 90/10) in 73% yield after 40 minutes of reaction. White solid. m.p. 120-123 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.19 (1H, s), 7.62 (2H, $d, J = 7.79$ Hz), 7.56 (2H, $d, J = 7.79$ Hz), 7.45 (2H, $d, J = 8.12$ Hz), 7.25 (2H, $d, J = 8.12$ Hz), 5.60 (1H, s), 5.30 (2H, s), 4.52 (2H, $d, J = 5.91$ Hz), 4.03 (2H, s), 2.87 (4H, s), 2.15 (3H, s), 1.88 (4H, s). $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 163.4, 154.6, 146.7, 141.8, 140.0, 128.7, (q, $J_{C-F} = 30.79$ Hz), 128.4 (q, $J_{C-F} = 32.02$ Hz), 126.1, 125.3, 124.8 (2C), 124.6 (2C), 123.11 (q, $J_{C-F} = 272.1$ Hz), 122.9 (q, $J_{C-F} = 272.1$ Hz), 95.5, 92.0, 51.5, 48.8, 45.7, 45.0, 22.1, 20.2. $^{19}$F NMR (564 MHz, CDCl$_3$) $\delta$ -62.33 (3F, s), -62.50 (3F, s). MS (ESI) $m/z$ 524.2 [M+H]$^+$.  

![Chemical Structure](image)

**Compound 9b**

6-methyl-3-((4-methylpiperazin-1-yl)methyl)-1-(4-(trifluoromethyl)benzyl)-4-((4-(trifluoromethyl)benzyl)amino)pyridin-2(1H)-one

According to GP4, using 1-methylpiperazine as amine (20.03 mg, 22.26 $\mu$L) and 5c as substrate (44.04 mg), the title compound (36.0 mg) was isolated by flash chromatography.
(dichloromethane/methanol 90:10) in 65% yield after 40 minutes. White solid. m.p. 134-136 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.97 (1H, t, $J$ = 5.67 Hz), 7.55 (2H, d, $J$ = 8.09 Hz), 7.37 (2H, d, $J$ = 8.09), 7.16 (2H, d, $J$ = 8.09), 5.52 (1H, s), 5.21 (2H, s), 4.39 (2H, d, $J$ = 5.67 Hz), 3.70 (2H, s), 2.49-2.11 (8H, m), 2.15 (3H, s), 2.07 (3H, s). $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 163.2, 154.9, 145.3, 143.1, 141.8, 129.7 (q, $J_C$-$F$ = 32.06 Hz), 129.4 (q, $J_C$-$F$ = 32.06 Hz), 127.2, 126.7, 125.7, 124.1 (2C, q, $J_C$-$F$ = 271.4 Hz), 95.6, 55.1, 54.2, 52.1, 46.5, 46.1, 45.9, 21.1. $^{19}$F NMR (564 MHz, CDCl$_3$) $\delta$ -62.36 (3F, s), -62.42 (3F, s). MS (ESI) $m$/$z$ 553.2 [M+H]$^+$. 

**Compound 25a**

6-methyl-3-(pyrrolidin-1-ylmethyl)-1-(3-(trifluoromethyl)benzyl)-4-((3-(trifluoromethyl)benzyl)amino)pyridin-2(1H)-one

According to GP4, using pyrrolidine (14.22 mg, 16.42 µL) as amine and compound 19a as substrate (44.04 mg), the title compound (29.0 mg) was isolated by flash chromatography (dichloromethane/methanol 95/5) in 55% yield after 40 minutes of reaction. Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.09 (1H, s), 7.48-7.37 (5H, m), 7.33 (1H, t, $J$ = 7.80 Hz), 7.28 (1H, s), 7.21 (1H, d, $J$ = 7.80 Hz), 5.53 (1H, s), 5.22 (2H, s), 4.42 (2H, d, $J$ = 6.32 Hz), 3.93 (2H, s), 2.75 (4H, bs), 2.06 (3H, s), 1.77 (4H, bs). $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 163.3, 155.0, 145.7, 140.1, 138.6, 131.1 (q, $J_C$-$F$ = 31.14 Hz), 130.1, 129.7, 129.3, 129.2, 124.1, 124.1 (q, $J_C$-$F$ = 271.16 Hz), 124.0 (q, $J_C$-$F$ = 271.16 Hz), 123.4, 123.0, 96.0, 53.0, 46.5, 46.0, 29.7, 23.5, 21.1. $^{19}$F NMR (564 MHz, CDCl$_3$) $\delta$ -62.43 (3F, s), -62.50 (3F, s). MS (ESI) $m$/$z$ 524.3 [M+H]$^+$. 

**Compound 25b**

6-methyl-1-phenyl-4-(phenylamino)-3-(pyrrolidin-1-ylmethyl)pyridin-2(1H)-one

According to GP4, using pyrrolidine (14.22 mg, 16.42 µL) as amine and compound 19b as substrate (27.30 mg), the title compound (21.5 mg) was isolated by flash chromatography (dichloromethane/methanol 96/4 – 90/10) in 60% yield after 40 minutes of reaction. Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.96 (1H, bs), 7.42-7.38 (2H, m), 7.33 (1H, t, $J$ = 7.35 Hz), 7.20-7.08 (4H, m), 7.02 (1H, t, $J$ = 7.35 Hz), 6.05 (1H, s), 3.87 (2H, s), 2.72 (4H, bs), 1.81 (4H, bs), 1.78
Compound 25c
1-(3,5-dimethylphenyl)-4-((3,5-dimethylphenyl)amino)-6-methyl-3-(pyrrolidin-1-ylmethyl)pyridin-2(1H)-one
According to GP4, using pyrrolidine (14.22 mg, 16.42 μL) as amine and 19c as substrate (32.24 mg), the title compound (27.8 mg) was isolated by flash chromatography (dichloromethane/methanol 96/4 – 90/10) in 67% yield after 40 minutes of reaction. Yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 9.94 (1H, s), 7.03 (1H, s), 6.83 (2H, s), 6.77 (3H, s), 6.11 (1H, s), 3.90 (2H, s), 2.73 (4H, bs), 2.36 (6H, s), 2.34 (6H, s), 1.89 (3H, s), 1.88 (4H, s). ¹³C NMR (100.6 MHz, CDCl₃) δ 164.0, 152.9, 144.7, 140.5, 139.3, 139.1, 139.0, 129.9, 125.9, 125.2, 120.2, 96.8, 53.1, 51.2, 23.8, 21.8, 21.4, 21.2. MS (ESI) m/z 416.3 [M+H]+.

Compound 10a
3-cyclohexyl-7-methyl-1,6-bis(4-(trifluoromethyl)benzyl)-2,3,4,6-tetrahydropyrido[4,3-d]pyrimidin-5(1H)-one
According to GP5, using cyclohexylamine as amine (19.83 mg, 22.93 μL) and 5c as substrate (44.04 mg, 0.1mmol), the title compound (24.0 mg) was isolated by flash chromatography (ethyl acetate/methanol 98/2 – 95/5) in 63% yield after 40 minutes of reaction. White solid. m.p. 155-158 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.64 (2H, d, J = 7.95 Hz), 7.57 (2H, d, J = 7.95 Hz), 7.40 (2H, d, J = 7.95 Hz), 7.28 (2H, d, J = 7.95 Hz), 5.62 (1H, s), 5.33 (2H, s), 4.53 (2H, s), 4.16 (2H, s), 3.90 (2H, s), 2.55-2.51 (1H, m), 2.15 (3H, s), 1.95 (2H, m), 1.79 (2H, m), 1.63 (1H, m), 1.33-1.13 (5H, m). ¹³C NMR (100.6 MHz, CDCl₃) δ 161.6, 150.7, 143.8, 142.0, 141.7, 129.8 (q, JCF = 39.65 Hz), 129.5 (q, JCF = 39.65 Hz), 129.3, 126.8, 125.9, 125.8, 125.7 (2C), 124.1 (2C, q, JCF = 271.6 Hz), 99.7, 96.2, 66.8, 59.4, 52.3, 46.0, 30.3, 26.0, 25.5, 20.9. ¹⁹F NMR (564 MHz, CDCl₃) δ -62.40 (3F, s), -62.42 (3F, s). MS (ESI) m/z 564.2 [M+H]+.
According to GP5, using isopropylamine as amine (11.82 mg, 17.03 μL) and 5c as substrate (44.04 mg), the title compound (20.5 mg) was isolated by flash chromatography (ethyl acetate/methanol 100/0 – 97/3) in 40% yield after 20 minutes of reaction. White solid. m.p. 83-87 °C. 1H NMR (400 MHz, CDCl3) δ 7.64 (2H, d, J = 8.11 Hz), 7.57 (2H, d, J = 8.11 Hz), 7.41 (2H, d, J = 8.11 Hz) 7.28 (2H, d, J = 8.11 Hz), 5.63 (1H, s), 5.34 (2H, s), 4.57 (2H, s), 4.10 (2H, s), 3.85 (2H, s), 3.00-2.95 (1H, m), 2.15 (3H, s), 1.18 (3H, s), 1.16 (3H, s). 13C NMR (100.6 MHz, CDCl3) δ 161.6, 150.5, 143.8, 141.9, 141.6, 129.8 (q, J_{C,F} = 39.83 Hz), 129.5 (q, J_{C,F} = 40.06 Hz), 126.8, 125.9 (2C), 125.7 (2C), 124.1 (2C, q, J_{C,F} = 277.54 Hz), 99.9, 96.2, 67.1, 52.5, 51.4, 46.1 29.7, 20.9, 19.9. 19F NMR (564 MHz, CDCl3) δ -62.40 (3F, s), -62.41 (3F, s). MS (ESI) m/z 524.2 [M+H]+.

According to GP5, using benzylamine as amine (21.43 mg, 21.85 μL) and 5c as substrate (44.04 mg), the title compound (42.0 mg) was isolated by flash chromatography (ethyl acetate 100%) in 73% yield after 10 minutes of reaction. White solid. m.p. 145-148 °C. 1H NMR (400 MHz, CDCl3) δ 7.62 (2H, d, J = 8.23 Hz), 7.59 (2H, d, J = 8.23 Hz), 7.36 (2H, d, J = 7.99 Hz), 7.31-7.26 (7H, m), 5.67 (1H, s), 5.34 (2H, s), 4.46 (2H, s), 4.03 (2H, s), 3.92 (2H, s), 3.77 (2H, s), 2.18 (3H, s). 13C NMR (100.6 MHz, CDCl3) δ 161.8, 150.3, 144.04, 141.9, 141.7, 137.8, 130.0 (2C, q, J_{C,F} = 32.06 Hz), 129.0, 128.4, 127.7, 127.4, 126.8, 125.8 (3C), 125.7 (2C), 124.2 (q, J_{C,F} = 272.03 Hz), 124.1 (q, J_{C,F} = 271.36 Hz), 98.4, 96.0, 68.1, 57.8, 52.1, 49.7, 46.2, 21.0. 19F NMR (564 MHz, CDCl3) δ -62.39 (3F, s), -62.40 (3F, s). MS (ESI) m/z 572.2 [M+H]+.
Compound 10d
7-methyl-3-phenyl-1,6-bis(4-(trifluoromethyl)benzyl)-2,3,4,6-tetrahydropyrido[4,3-d]pyrimidin-5(1H)-one
According to GP5, using aniline as amine (8.63 mg, 18.26 µL) and 5c as substrate (44.04 mg), the title compound (32.4 mg) was isolated by flash chromatography (petroleum ether/ethyl acetate 40/60) in 58% yield after 10 minutes of reaction. White solid. m.p. 160-165 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.59 (2H, d, $J = 8.09$ Hz), 7.54 (2H, d, $J = 8.09$ Hz), 7.31 (2H, d, $J = 8.09$ Hz), 7.26 (2H, m), 7.22 (2H, d, $J = 8.09$ Hz), 6.98 (2H, d, $J = 8.09$ Hz), 6.94 (2H, t, $J = 7.74$ Hz), 5.58 (1H, s), 5.36 (2H, s), 4.76 (2H, s), 4.54 (2H, s), 4.50 (2H, s), 2.14 (3H, s). $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ 161.5, 151.0, 148.7, 144.3, 141.5, 129.9 (2C, $q, J_{C-F} = 32.09$ Hz), 126.8, 125.8 (3C) 124.1 (2C, $q, J_{C-F} = 272.2$ Hz ), 121.0, 117.8, 99.0, 96.2, 67.8, 51.8, 46.5, 46.2, 29.7, 20.9. $^{19}$F NMR (564 MHz, CDCl$_3$) $\delta$ -62.41 (6F, bs). MS (ESI) $m/z$ 558.2 [M+H]$^+$. 

Compound 26a
3-benzyl-7-methyl-1,6-bis(3-(trifluoromethyl)benzyl)-2,3,4,6-tetrahydropyrido[4,3-d]pyrimidin-5(1H)-one
According to GP5, using benzylamine as amine (21.43 mg, 21.85 µL) and 19a as substrate (44.04 mg), the title compound (45.9 mg) was isolated by flash chromatography (dichloromethane/ethyl acetate 1/1) in 80% yield after 10 minutes of reaction. Yellow oil. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.53 (1H, d, $J = 8.10$ Hz), 7.49 (1H, d, $J = 7.26$ Hz), 7.46 (2H, t, $J = 7.74$ Hz), 7.44-7.40 (3H, m), 7.34 (1H, d, $J = 8.04$ Hz), 7.29-7.25 (4H, m), 7.23-7.20 (1H, m), 5.65 (1H, s), 5.30 (2H, s), 4.43 (2H, s), 4.00 (2H, s), 3.88 (2H, s), 3.74 (2H, s), 2.15 (3H, s). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 161.9, 150.4, 144.1, 139.0, 138.7, 137.9, 131.1 (q, $J_{C-F} = 32.66$ Hz), 131.1 (q, $J_{C-F} = 31.98$ Hz), 130.0, 129.9, 129.5, 129.4, 129.0, 128.5, 127.4, 124.1 (q, $J_{C-F} = 272.03$ Hz), 124.1 (q, $J_{C-F} = 272.23$ Hz), 124.5, 124.2, 123.4, 123.3, 98.6, 96.1, 68.2, 57.8, 52.1, 49.6, 46.2, 21.0. $^{19}$F NMR (564 MHz, CDCl$_3$) $\delta$ -62.55 (6F, s). MS (ESI) $m/z$ 572.3 [M+H]$^+$. 

S26
**Compound 26b**

3-benzyl-7-methyl-1,6-diphenyl-2,3,4,6-tetrahydropyrido[4,3-d]pyrimidin-5(1H)-one

According to GP5, using benzylamine as amine (21.43 mg, 21.85 µL) and 19b as substrate (27.30 mg), the title compound (31.0 mg) was isolated by flash chromatography (dichloromethane/methanol 98/2) in 76% yield after 10 minutes of reaction. White solid. m.p. 110-115 °C. 

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.46 (2H, t, $J = 7.80$ Hz), 7.39 (3H, t, $J = 7.38$ Hz), 7.29 (2H, m), 7.26-7.23 (3H, m), 7.22-7.18 (5H, m), 7.67 (1H, s), 4.36 (2H, s), 3.97 (2H, s), 3.86 (2H, s), 1.80 (3H, s).

$^{13}$C NMR (150 MHz, CDCl$_3$) δ 162.7, 149.7, 144.0, 143.1, 139.1, 138.3, 129.7, 129.5, 129.1, 128.6, 128.4 (2C), 127.3, 126.3, 126.1, 99.6, 97.4, 69.6, 57.2, 49.4, 21.7. MS (ESI) m/z 408.2 [M+H]$^+$.

**Compound 26c**

3-benzyl-1,6-bis(3,5-dimethylphenyl)-7-methyl-2,3,4,6-tetrahydropyrido[4,3-d]pyrimidin-5(1H)-one

According to GP5, using benzylamine as amine (21.43 mg, 21.85 µL) and 19c as substrate (33.24 mg), the title compound (42.4 mg) was isolated by flash chromatography (DCM/Methanol 98/2) in 91% yield after 20 minutes of reaction. White solid. m.p. 115-120 °C. 

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.37-7.34 (2H, m), 7.32-7.28 (2H, m), 7.26-7.24 (1H, m), 7.04 (1H, s), 6.91 (1H, s), 6.85 (2H, s), 6.84 (2H, s), 5.67 (1H, s), 3.90 (2H, s) 2.36 (6H, s), 2.35 (6H, s), 1.86 (3H, s). $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 162.7, 149.7, 143.7, 143.1, 139.3, 139.0, 138.4, 130.0, 129.1, 128.3, 127.8, 127.2, 126.0, 124.1, 98.9, 97.2, 69.7, 57.1, 49.1, 21.6, 21.3 (2C). MS (ESI) m/z 464.3 [M+H]$^+$; 468.3 [M+Na]$^+$. 
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7. NMR Spectra

Starting materials:
Compound 5c

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)

$^{19}$F NMR (564 MHz, CDCl$_3$)
Compound 11

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)

$^{19}$F NMR (564 MHz, CDCl$_3$)
Compound 19b

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)
Compound 19c

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)
e-LSF:
Compound 6a

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)

$^{19}$F NMR (544 MHz, CDCl$_3$)
Compound 6b

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)

$^{19}$F NMR (564 MHz, CDCl$_3$)
Compound 6c

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)

$^{39}$F NMR (564 MHz, CDCl$_3$)
Compound 13

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)

S37
$^{19}$F NMR (564 MHz, CDCl$_3$)
Compound 20a

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)

$^{19}$F NMR (594 MHz, CDCl$_3$)
Compound 20b

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)
Compound 21b

$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (100.6 MHz, CDCl$_3$)
Compound 21c

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)
Compound 22a

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)

$^{19}$F NMR (564 MHz, CDCl$_3$)
Compound 22b

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)
Compound 22c

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)
Compound 8

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)

$^{39}$F NMR (564 MHz, CDCl$_3$)
MCR-LSF:
Compound 9a

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)

$^{19}$F NMR (564 MHz, CDCl$_3$)
Compound 9b
Compound 25c

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)
Compound 10b

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)

$^{19}$F NMR (564 MHz, CDCl$_3$)
Compound 10c

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)

$^{19}$F NMR (564 MHz, CDCl$_3$)
Compound 10d

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100.6 MHz, CDCl$_3$)

$^{31}$P NMR (564 MHz, CDCl$_3$)
Compound 26b

$^1$H NMR (600 MHz, CDCl$_3$)

[Chemical structure image]
Compound 26c

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
8. X-ray diffraction analysis

The crystal structures of compounds 7 and 17 were determined by X-ray diffraction on single crystals grown by slow evaporation of a solution of chloroform and hexane. Crystal data and experimental details for data collection and structure refinement are reported in Table 5. Intensity data and cell parameters were recorded at 200(2) K on a Bruker D8 Venture PhotonII diffractometer (CuKα radiation λ = 1.54178 Å). The raw frame data were processed using SAINT and SADABS to yield the reflection data files. The structures were solved by Direct Methods using the SHELXT program and refined on F₀² by full-matrix least-squares procedures, using SHELXL-2018 in the WinGX suite v.2021.2. All non-hydrogen atoms were refined with anisotropic atomic displacements. The hydrogen atoms were included in the refinement at idealized geometry and refined “riding” on the corresponding parent atoms. In view of the presence of disordered electron density which could not be properly modelled, the structures were subjected to the program SQUEEZE. In both cases, the solvent contribution to the diffraction pattern (water for 7 and chloroform for 17) was removed and modified F₀² written to a new HKL file. The number of electrons corresponding to the solvent molecules were included in the formula, formula weight, calculated density, m and F(000). The weighting schemes used in the last cycle of refinement were \( w = 1/ [\sigma^2 F_0^2 + (0.0538 P)^2 + 2.2826 P] (7) \) and \( w = 1/ [\sigma^2 F_0^2 + 0.3806 P^2] (17) \), where \( P = (F_0^2 + 2F_c^2)/3 \). The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 2351138-2351139 and can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (e-mail deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Table 6. Crystal data and structure refinement information for compounds 7 and 17.

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<td>1.213, -1.000</td>
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</table>

a Goodness-of-fit S = \[\sum w(F_o^2-F_c^2)/ (n-p)\]¹/², where n is the number of reflections and p the number of parameters. b R_1 = \[\sum \left|F_0 \right| - \left|F_c\right| / \Sigma \left|F_0\right| , wR_2 = \left[\sum [w(F_o^2-F_c^2)] / \Sigma[w(F_o^2)]\right]^{1/2}. 
Compound 7 crystallizes in the space group *Fdd2* with one independent molecule in the unit cell (Figure Sx). It consists of a planar bicyclic fragment comprising the atoms C1-C8/C16/N1-N3/S1/O1, and two trifluorotoluene moieties bonded to C8 and C16, that protrude in the same direction from the mean plane of the core, forming an angle of 70.05(3)° and 87.43(2)°, respectively. The molecules form a supramolecular ribbon along the direction of the crystallographic axis c through N-H···O hydrogen bonds [N3-H3N···O1(-x+3/2, -y+1, z+1/2). N3···O1=2.9876(2) Å; N3-H3N···O1=166.9(3)°].

**Figure S4.** Top: ortep view of 7 with labelling scheme and ellipsoids at the 20% probability level. Bottom: supramolecular ribbon along the c-axis direction of the unit cell. H bonds are represented as cyan dotted lines.

Compound 17 crystallizes in the space group *P*-1 with one independent molecule in the unit cell (Figure Sy and Figure 2 in the main text). It can be described as a dimeric form of 7, in which the -C=NH fragment (-C7=N3-H3N) is replaced by a -C=N-S- moiety that generates a dimer through a -C=N-S-S-N=C- bridge. Also in this case, the bicyclic moieties are planar and the trifluorotoluene fragments protrude from the main planes passing through the planar core forming angles of...
83.04(3)°, 80.77(3)°, 82.63(2)° and 80.99(4)°. Since the -C=NH fragment is not present in the molecule, no classic N-H···O hydrogen bonds are formed, and the crystal packing is mainly consolidated by dispersion interactions.

Figure S5. Top: ortep view of 17 with partial labelling scheme and ellipsoids at the 20% probability level. Solvent molecules have been omitted for clarity. The fluorine atoms in the trifluorotoluene rings are disordered over two geometrical positions, but only the major component is shown in the figure.