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Chemistry & Drug Discovery

Supporting Information

Identification and Optimization of the First Highly Selective GLUT1 Inhibitor BAY-876

Holger Siebeneicher,[a] Arwed Cleve,[a] Hartmut Rehwinkel,[a] Roland Neuhaus,[a] Iring Heisler,[b] Thomas Müller,[b] Marcus Bauser,[a] and Bernd Buchmann*[a]

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Supplementary Material

Materials and methods. All commercially available starting materials and solvents were purchased and used without further purification. Microwave irradiation was applied with a Biotage Initiator 60. Flash column chromatography was performed on prepacked flash chromatography columns PF-15-SIHP purchased from Interchim or KP-Sil purchased from Biotage using a Biotage Isolera separation system. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on Bruker Avance spectrometers operating at 300 or 400 MHz for ^{1}H NMR and at 75 or 100 MHz for ^{13}C NMR acquisitions. NMR signal multiplicities are reported as they appear, without considering higher-order effects. Chemical shifts (δ) are given in ppm with the residual solvent signal used as reference ($CDCl_3$: s, 7.26 ppm (^{1}H) and t, 77.1 ppm (^{13}C); [D_6]DMSO: quint, 2.50 ppm (^{1}H) and quint, 40.1 ppm (^{13}C)). LC-MS spectra were recorded on a Waters Acquity UPLC-MS SQD 3001 spectrometer, using an Acquity UPLC BEH C18 1.7 50x2.1mm column, with acetonitrile and water + 0.1% formic acid as eluents for the acidic method (method 1), or with acetonitrile and water + 0.2% ammonia (32 vol%) as eluents for the basic method (method 2), gradient: 0-1.6 min 1-99% acetonitrile; 1.6-2.0 min 99% acetonitrile both at 60°C, a flow of 0.8 mL/min, an injection volume of 2 µL, with DAD scan at 210–400 nm, ELSD. All tested compounds were at least 95% pure as determined by ^{1}H NMR spectroscopy.

General procedure 1 for the nitration of pyrazoles: To a solution of the corresponding pyrazoles (1.0 equiv) in conc. sulfuric acid (0.44 mL/ mmol) was carefully added dropwise at 0°C 65% nitric acid (2.5 equiv). After stirring for 10 min the reaction mixture was heated to 115°C, and stirring was continued for 4 h at this temperature. After cooling to room temperature, the mixture was poured into ice-water and extracted three times with ethyl acetate. The combined organic layer was washed with conc. aq. sodium bicarbonate and brine, dried over sodium sulfate, filtered and evaporated to obtain the desired 4-nitro-1*H*-pyrazoles that were purified by flash column chromatography.

General procedure 2A for the *N*-alkylation of pyrazoles: The corresponding pyrazoles (1.0 equiv) were dissolved in acetonitrile (2.9 mL/ mmol), and the corresponding haloalkyl compounds (1.2 equiv) and cesium carbonate (1.2 equiv) were added. The suspension was stirred at 60°C for 2 h. After cooling to room temperature, the reaction mixture was filtered, the filtrate was evaporated and the residue partitioned between ethyl acetate and water. The layers were separated and the aqueous layer was extracted two further times with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate, filtered and evaporated to obtain the desired 1-alkyl-1*H*-pyrazoles that were purified by flash column chromatography.

General procedure 2B for the *N*-alkylation of pyrazoles: The corresponding pyrazoles (1.0 equiv) and the corresponding haloalkyl compounds (1.2 equiv) were dissolved in dimethylsufoxide (3.5 mL/ mmol), and 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine (DBU; 1.5 equiv) was added. The reaction was stirred at room temperature for 18 h. The mixture was then diluted with ethyl acetate. The organic phase was washed with water and half-concentrated brine, dried over sodium sulfate, filtered and evaporated to obtain the desired 1-alkyl-1*H*-pyrazoles that were purified by flash column chromatography.

General procedure 3A for the reduction of 4-nitro-1*H*-pyrazoles: The corresponding 4-nitro-1*H*-pyrazoles (1.0 equiv) were dissolved in methanol (6.7 mL/mmol), and palladium on carbon (10 wt. %; 0.05 equiv) and ammonium formiate (10 equiv) were added. The reaction mixture was heated to 80°C for 1 h. After cooling to room temperature, the suspension was filtered through Celite, and the filtrate was evaporated. The residue was partitioned between water and ethyl acetate. The layers were separated and the organic layer was washed with brine, dried over sodium sulfate, filtered and evaporated to obtain the the desired 1*H*-pyrazol-4-amines that were directly used in the next step without further purification.

General procedure 3B for the reduction of 4-nitro-1*H*-pyrazoles: To a solution of the corresponding 4-nitro-1*H*-pyrazoles (1.0 equiv) in ethanol (11 mL/mmol) were added water (5.7 mL/mmol), acetic acid (1.1 mL/ mmol), and zinc dust (3.5 equiv). This reaction mixture was stirred at 60°C for 2 h. After cooling to 25°C, the suspension was filtered through Celite, washed with ethyl acetate and the complete filtrate was evaporated. To the residue water and conc. aq. sodium carbonate were added. This aqueous phase was extracted three times with ethyl acetate.The combined organic layer was washed with brine, dried over sodium sulfate, filtered and evaporated. The crude product was purified by flash column chromatography to obtain the desired 1*H*-pyrazol-4-amines that were directly used in the next step.

General procedure 3C for the reduction of 4-nitro-1*H*-pyrazoles: To a solution of the corresponding 4-nitro-1*H*-pyrazoles (1.0 equiv) in ethanol (5.1 mL/mmol) was added tin(II) chloride (5.0 equiv). This reaction mixture was stirred at 78°C for 8 h. After cooling to room temperature, the reaction mixture was adjusted to pH 8 by addition of 2 M sodium hydroxide solution. The resulting precipitate was isolated by filtration and the filtrate extracted with dichloromethane. The combined organic layer was washed with brine, dried over sodium sulfate, filtered and evaporated to obtain the desired 1*H*-pyrazol-4-amines that were directly used in the next step without further purification.

General procedure 4 for the Pfitzinger conversion of isatins into quinoline-4-carboxylic acids: The corresponding isatins (1.0 equiv) were suspended in water (2.3 mL/mmol) in a microwave vial. Potassium hydroxide (1.1 equiv), acetic acid (2.0 equiv) and sodium acetate (1.4 equiv) were added so that the pH was close to 5. The solution was cooled to 10°C and the corresponding carbonyl compounds (2.0 equiv) were added rapidly. The microwave vial was sealed and heated at 120°C for 2 h by microwave irradiation. The reaction was stopped by addition of 10% aqueous hydrochloric acid solution and the resulting precipitate was isolated by filtration, washed with water and dried in a vacuum drying cabinet at 50°C overnight to obtain the target compounds.

General procedure 5 for the Pfitzinger conversion of isatins into quinoline-2,4-dicarboxylic acids: To a slurry of the corresponding isatins (1.0 equiv) in 33% aq. potassium hydroxide solution (2.3 mL/ mmol) at 40°C pyruvic acid (2.0 equiv) was added, and heating at 40°C was continued for 16 h. To the viscous paste 33% aq. potassium hydroxide solution (7.5 mL/mmol) was added and stirred. The solid was isolated by filtration and washed

with 33% aq. potassium hydroxide solution and ethanol. The solid then was diluted in water and 10% aq. sulfuric acid was added until the pH went below 7. The precipitate was isolated by filtration and dried for 8 h in vacuo. The thus obtained target compounds were used without further purification.

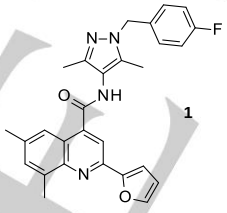
General procedure 6 for the esterification of quinoline-2,4-dicarboxylic acids: A mixture of the corresponding quinoline-2,4-dicarboxylic acids (1.0 equiv) and thionyl chloride (10 equiv) was heated at 80°C for 16 h. After cooling to 25°C, the resulting suspension was evaporated to dryness in vacuo. This crude product was suspended in methanol (2.0 mL/mmol) and heated to reflux for 3 h. After cooling to 25°C, the precipitate was isolated by filtration. Water was added to the filtrate and the additional precipitate was isolated by filtration. The combined solids were purified by flash column chromatography to yield the desired dimethyl quinoline-2,4-dicarboxylates.

General procedure 7 for the selective aminolysis of dimethyl quinoline-2,4-dicarboxylates: To a solution of the corresponding dimethyl quinoline-2,4-dicarboxylates (1.0 equiv) in methanol (3.5 mL/mmol) was added a 7 M solution of ammonia in methanol (25 equiv) or the corresponding primary or secondary amine (2 equiv). The mixture was stirred for 2 h at 50°C. After cooling to 25°C, the precipitate was isolated by filtration and dried yielding the desired methyl 2-carbamoylquinoline-4-carboxylates.

General procedure 8 for the selective hydrolysis of methyl 2-carbamoylquinoline-4-carboxylates: To a solution of the corresponding methyl 2-carbamoylquinoline-4-carboxylates (1.0 equiv) in methanol (4.6 mL/mmol) and THF (1.7 mL/mmol) was added a solution of sodium hydroxide (9.0 equiv) in water (9.2 mL/mmol). This mixture was stirred for 2 h at 25°C and then concentrated in vacuo. The residue was diluted with water, and 10% aq. sulfuric acid was added until pH reached 5. After stirring for additional 15 min the precipitate was filtered and dried yielding the desired 2-carbamoylquinoline-4-carboxylic acids.

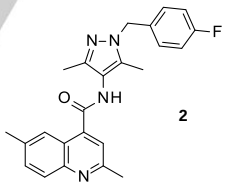
General procedure 9A for the formation of quinoline-4-carboxamides: The corresponding 1*H*-pyrazol-4-amines (1.0 equiv) were dissolved in THF (22 mL/mmol). To this solution, the corresponding quinoline-4-carboxylic acids (1.2 equiv), *N*,*N*-diisopropylethylamine (1.5 equiv), and TBTU (1.5 equiv) were added. The reaction mixture was stirred at room temperature overnight and then concentrated in vacuo. Purification of the residue by preparative HPLC yielded the desired target compounds.

General procedure 9B for the formation of quinoline-4-carboxamides: The corresponding 1*H*-pyrazol-4-amines (1.0 equiv) were dissolved in DMSO (8 mL/mmol). To this solution, the corresponding quinoline-4-carboxylic acids (1.2 equiv), *N*,*N*-diisopropylethylamine (1.2 equiv), and HATU (1.2 equiv) were added. The reaction mixture was stirred at room temperature overnight and then concentrated in vacuo. Purification of the residue by preparative HPLC yielded the desired target compounds.



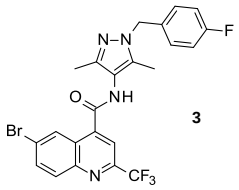
1

***N*-[1-(4-Fluorobenzyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]-2-(2-furyl)-6,8-dimethylquinoline-4-carboxamide (1)**: Prepared according to general procedure 9A from 1-(4-fluorobenzyl)-3,5-dimethyl-1*H*-pyrazol-4-amine (26.7 mg, 100 µmol, CAS-RN 514800-78-3) and 2-(2-furyl)-6,8-dimethyl-quinoline-4-carboxylic acid (21.9 mg, 100 µmol, CAS-RN 351357-33-0). Yield: 11.2 mg (24%): ^{1}H NMR (400 MHz, [D6]DMSO): δ=2.16 (s, 3H), 2.20 (s, 3H), 2.46 (s, 3H), 2.75 (s, 3H), 5.25 (s, 2H), 6.75 (dd, *J*=3.3, 1.8 Hz, 1H), 7.20 (dd, *J*=8.9, 8.9 Hz, 2H), 7.25 (dd, *J*=8.9, 5.4 Hz, 2H), 7.41 (dd, *J*=3.3, 0.8 Hz, 1H), 7.55 (s, 1H), 7.73 (s, 1H), 7.97 (dd, *J*=1.8, 0.8 Hz, 1H), 8.01 (s, 1H), 9.95 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.38 min, m/z 469.2 $[M+H]^+$.



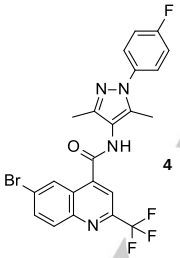
2

***N*-[1-(4-Fluorobenzyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]-2,6-dimethylquinoline-4-carboxamide (2)**: Prepared according to general procedure 9A from 1-(4-fluorobenzyl)-3,5-dimethyl-1*H*-pyrazol-4-amine (80 mg, 365 µmol, CAS-RN 514800-78-3) and 2,6-dimethylquinoline-4-carboxylic acid (88.1 mg, 438 µmol, CAS-RN 104175-33-9). Yield: 119 mg (81%): ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.21 (s, 3H), 2.29 (s, 3H), 2.51 (s, 3H), 2.71 (s, 3H), 5.21 (s, 2H), 7.02 (t, *J*=8.7 Hz, 2H), 7.14 (dd, *J*=8.7, 5.4 Hz, 2H), 7.36 (s, 1H), 7.43 (s, 1H), 7.55 (dd, *J*=8.5, 1.8 Hz, 1H), 7.92 (d, *J*=8.8 Hz, 1H), 7.98 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=9.9 (s, CH_3), 11.6 (s, CH_3), 21.8 (s, CH_3), 25.1 (s, CH_3), 52.8 (s, CH_2), 114.6 (s, C), 115.7 (d, $J_{C\text{-}F}$=21.5 Hz, CH), 119.5 (s, CH), 122.6 (s, C), 123.7 (s, CH), 128.5 (d, $J_{C\text{-}F}$=8.1 Hz, CH), 128.8 (s, CH), 132.3 (s, CH), 132.5 (d, $J_{C\text{-}F}$=3.1 Hz, C), 135.2 (s, C) 137.0 (s, C), 141.1 (s, C), 143.9 (s, C), 146.9 (s, C), 157.4 (s, C), 162.3 (d, $J_{C\text{-}F}$=246.2 Hz, C), 166.7 (s, C); LC-MS (ESI+, method 1): R_t=0.97 min, m/z 403.3 $[M+H]^+$.



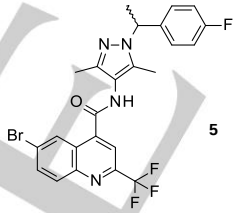
3

6-Bromo-*N*-[1-(4-fluorobenzyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]-2-(trifluoromethyl)quinoline-4-carboxamide (3): Prepared according to general procedure 9A from 1-(4-fluorobenzyl)-3,5-dimethyl-1*H*-pyrazol-4-amine (150 mg, 684 µmol, CAS-RN 514800-78-3) and 6-bromo-2-(trifluoromethyl)quinoline-4-carboxylic acid (263 mg, 820 µmol, CAS-RN 1023815-61-3). Yield: 286 mg (80%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=2.15 (s, 3H), 2.19 (s, 3H), 5.25 (s, 2H), 7.13-7.29 (m, 4H), 8.15 (dd, *J*=9.0, 2.3 Hz, 1H), 8.23 (d, *J*=9.0 Hz, 1H), 8.29 (s, 1H), 8.50 (d, *J*=2.1 Hz, 1H), 10.17 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.39 min, m/z 521.0 [M+H]$^+$.



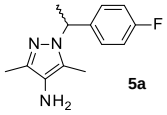
4

6-Bromo-*N*-[1-(4-fluorophenyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]-2-(trifluoromethyl)quinoline-4-carboxamide (4): Prepared according to general procedure 9B from 6-bromo-2-(trifluoromethyl)quinoline-4-carboxylic acid (80 mg, 250 µmol, CAS-RN 1023815-61-3) and 1-(4-fluorophenyl)-3,5-dimethyl-1*H*-pyrazol-4-amine (77 mg, 300 µmol, CAS-RN 956706-42-6). Yield: 73 mg (57%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.23 (s, 3H), 2.29 (s, 3H), 7.31-7.41 (m, 2H), 7.55-7.64 (m, 2H), 8.15 (d, *J*=9.1, 2.3 Hz, 1H), 8.24 (d, *J*=9.1 Hz, 1H), 8.33 (s, 1H), 8.52 (d, *J*=2.0 Hz, 1H), 10.32 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.39 min, m/z 507.0 [M+H]$^+$.



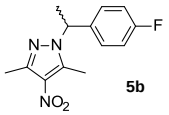
5

(±)-6-Bromo-*N*-{1-[1-(4-fluorophenyl)ethyl]-3,5-dimethyl-1*H*-pyrazol-4-yl}-2-(trifluoromethyl)quinoline-4-carboxamide (5): Prepared according to general procedure 9B from 6-bromo-2-(trifluoromethyl)quinoline-4-carboxylic acid (100 mg, 312 µmol, CAS-RN 1023815-61-3) and (±)-1-[1-(4-fluorophenyl)ethyl]-3,5-dimethyl-1*H*-pyrazol-4-amine (87 mg, 375 µmol, **5a**). Yield: 125 mg (75%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.77 (d, *J*=7.0 Hz, 3H), 2.14 (s, 3H), 2.17 (s, 3H), 5.57 (q, *J*=6.9 Hz, 1H), 7.11-7.21 (m, 2H), 7.24-7.32 (m, 2H), 8.14 (dd, *J*=9.0, 2.1 Hz, 1H), 8.22 (d, *J*=9.0 Hz, 1H), 8.27 (s, 1H), 8.48 (d, *J*=2.1 Hz, 1H), 10.13 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.47 min, m/z 535.1 [M+H]$^+$.



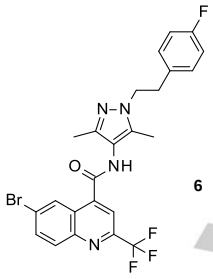
5a

(±)-1-[1-(4-Fluorophenyl)ethyl]-3,5-dimethyl-1*H*-pyrazol-4-amine (5a): Prepared according to general procedure 3C from (±)-1-[1-(4-fluorophenyl)ethyl]-3,5-dimethyl-4-nitro-1*H*-pyrazole (1.44 g, 5.47 mmol, **5b**). Yield: 883 mg (69%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.66 (d, *J*=6.9 Hz, 3H), 1.94 (s, 3H), 2.01 (s, 3H), 5.34 (q, *J*=6.9 Hz, 1H), 7.05-7.17 ppm (m, 4H); LC-MS (ESI+, method 1): R_t=0.69 min, m/z 234.1 [M+H]$^+$.



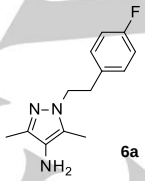
5b

(±)-1-[1-(4-Fluorophenyl)ethyl]-3,5-dimethyl-4-nitro-1*H*-pyrazole (5b): Prepared according to general procedure 2A from 3,5-dimethyl-4-nitro-1*H*-pyrazole (935 mg, 6.63 mmol, CAS-RN 14531-55-6) and (±)-1-(1-bromoethyl)-4-fluorobenzene (1.48 g, 7.29 mmol, CAS-RN 65130-46-3). Yield: 1.45 g (83%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.75 (d, *J*=6.8 Hz, 3H), 2.41 (s, 3H), 2.56 (s, 3H), 5.77 (q, *J*=6.8 Hz, 1H), 7.11-7.21 (m, 2H), 7.28-7.36 ppm (m, 2H); LC-MS (ESI+, method 1): R_t=1.27 min, m/z 264.1 [M+H]$^+$.



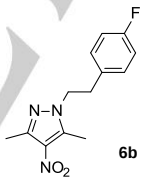
6

6-Bromo-*N*-{1-[2-(4-fluorophenyl)ethyl]-3,5-dimethyl-1*H*-pyrazol-4-yl}-2-(trifluoromethyl)quinoline-4-carboxamide (6): Prepared according to general procedure 9B from 6-bromo-2-(trifluoromethyl)quinoline-4-carboxylic acid (100 mg, 312 µmol, CAS-RN 1023815-61-3) and 1-[2-(4-fluorophenyl)ethyl]-3,5-dimethyl-1*H*-pyrazol-4-amine (87 mg, 375 µmol, **6a**). Yield: 91.1 mg (54%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.97 (s, 3H), 2.14 (s, 3H), 3.03 (t, *J*=7.2 Hz, 2H), 4.16 (t, *J*=7.2 Hz, 2H), 7.04-7.13 (m, 2H), 7.15-7.24 (m, 2H), 8.14 (dd, *J*=9.0, 2.1 Hz, 1H), 8.22 (d, *J*=9.0 Hz, 1H), 8.27 (s, 1H), 8.46 (d, *J*=2.1 Hz, 1H), 10.10 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.38 min, m/z 535.0 [M+H]$^+$.



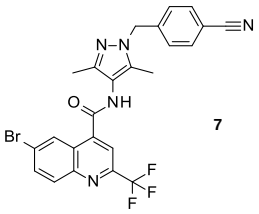
6a

1-[2-(4-Fluorophenyl)ethyl]-3,5-dimethyl-1*H*-pyrazol-4-amine (6a): Prepared according to general procedure 3C from 1-[2-(4-fluorophenyl)ethyl]-3,5-dimethyl-4-nitro-1*H*-pyrazole (500 mg, 1.90 mmol, **6b**). Yield: 427 mg (96%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.86 (s, 3H), 2.00 (s, 3H), 2.92 (t, *J*=7.3 Hz, 2H), 4.00 (t, *J*=7.3 Hz, 2H), 7.04-7.12 (m, 2H), 7.12-7.19 ppm (m, 2H); LC-MS (ESI+, method 1): R_t=0.64 min, m/z 234.0 [M+H]$^+$.



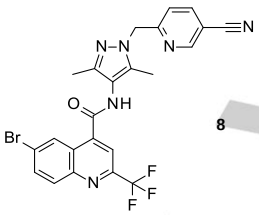
6b

1-[2-(4-Fluorophenyl)ethyl]-3,5-dimethyl-4-nitro-1*H*-pyrazole (6b): Prepared according to general procedure 2A from 3,5-dimethyl-4-nitro-1*H*-pyrazole (2.0 g, 14.2 mmol, CAS-RN 14531-55-6) and 1-(2-bromoethyl)-4-fluorobenzene (3.5 g, 17.0 mmol, CAS-RN 332-42-3). Yield: 3.08 g (83%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.27 (s, 3H), 2.40 (s, 3H), 3.02 (t, *J*=7.0 Hz, 2H), 4.27 (t, *J*=7.0 Hz, 2H), 7.04-7.12 (m, 2H), 7.12-7.19 ppm (m, 2H); LC-MS (ESI+, method 1): R_t=1.20 min, m/z 264.1 [M+H]$^+$.



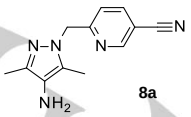
7

6-Bromo-*N*-[1-(4-cyanobenzyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]-2-(trifluoromethyl)quinoline-4-carboxamide (7): Prepared according to general procedure 9A from 4-[(4-amino-3,5-dimethyl-1*H*-pyrazol-1-yl)methyl]benzonitrile (50 mg, 221 µmol, CAS-RN 1152951-06-8) and 6-bromo-2-(trifluoromethyl)quinoline-4-carboxylic acid (85 mg, 265 µmol, CAS-RN 1023815-61-3). Yield: 26 mg (22%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=2.16 (s, 3H), 2.19 (s, 3H), 5.39 (s, 2H), 7.32 (d, *J*=8.5 Hz, 2H), 7.85 (d, *J*=8.5 Hz, 2H), 8.11 - 8.19 (m, 1H), 8.23 (d, *J*=9.0 Hz, 1H), 8.30 (s, 1H), 8.51 (d, *J*=1.9 Hz, 1H), 10.19 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.32 min, m/z 528.2 [M+H]$^+$.



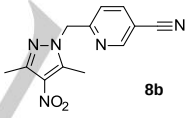
8

6-Bromo-*N*-{1-[(5-cyanopyridin-2-yl)methyl]-3,5-dimethyl-1*H*-pyrazol-4-yl}-2-(trifluoromethyl)quinoline-4-carboxamide (8): Prepared according to general procedure 9B from 6-bromo-2-(trifluoromethyl)quinoline-4-carboxylic acid (127 mg, 396 µmol, CAS-RN 1023815-61-3) and 6-[(4-amino-3,5-dimethyl-1*H*-pyrazol-1-yl)methyl]nicotinonitrile (108 mg, 475 µmol, **8a**). Yield: 75.6 mg (36%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.15 (s, 3H), 2.24 (s, 3H), 5.48 (s, 2H), 7.24 (d, *J*=8.1 Hz, 1H), 8.16 (dd, *J*=9.0, 2.1 Hz, 1H), 8.24 (d, *J*=9.0 Hz, 1H), 8.30-8.37 (m, 2H), 8.52 (d, *J*=2.0 Hz, 1H), 9.01 (d, *J*=1.3 Hz, 1H), 10.23 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.23 min, m/z 529.1 [M+H]$^+$.



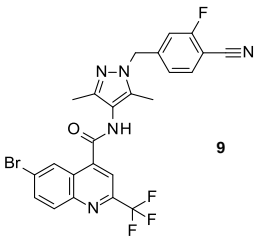
8a

6-[(4-Amino-3,5-dimethyl-1*H*-pyrazol-1-yl)methyl]nicotinonitrile (8a): Prepared according to general procedure 3B from 6-[(3,5-dimethyl-4-nitro-1*H*-pyrazol-1-yl)methyl]nicotinonitrile (2.11 g, 8.20 mmol, **8b**). Yield: 920 mg (49%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.00 (s, 3H), 2.03 (s, 3H), 3.46 (s, 2H), 5.26 (s, 2H), 6.88 (dd, *J*=8.2, 0.7 Hz, 1H), 8.24 (dd, *J*=8.1, 2.0 Hz, 1H), 8.97 ppm (dd, *J*=2.0, 0.8 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.44 min, m/z 228.1 [M+H]$^+$.



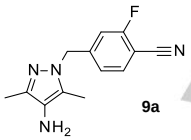
8b

6-[(3,5-Dimethyl-4-nitro-1*H*-pyrazol-1-yl)methyl]nicotinonitrile (8b): Prepared according to general procedure 2A from 3,5-dimethyl-4-nitro-1*H*-pyrazole (1.19 g, 8.46 mmol, CAS-RN 14531-55-6) and 6-(bromomethyl)nicotinonitrile (2.0 g, 10.2 mmol, CAS-RN 158626-15-4). Yield: 2.11 g (97%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.39 (s, 3H), 2.60 (s, 3H), 5.62 (s, 2H), 7.47-7.54 (m, 1H), 8.34 (dd, *J*=8.2, 2.1 Hz, 1H), 8.97 ppm (dd, *J*=2.1, 0.8 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.91 min, m/z 258.1 [M+H]$^+$.



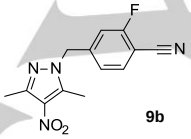
9

6-Bromo-*N*-[1-(4-cyano-3-fluorobenzyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]-2-(trifluoromethyl)quinoline-4-carboxamide (9): Prepared according to general procedure 9B from 6-bromo-2-(trifluoromethyl)quinoline-4-carboxylic acid (100 mg, 312 µmol, CAS-RN 1023815-61-3) and 4-[(4-amino-3,5-dimethyl-1*H*-pyrazol-1-yl)methyl]-2-fluorobenzonitrile (91.6 mg, 375 µmol, **9a**). Yield: 73.9 mg (43%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=2.13 (s, 3H), 2.23 (s, 3H), 5.39 (s, 2H), 7.15 (t, *J*=7.7 Hz, 1H), 7.72 (dd, *J*=7.8, 1.4 Hz, 1H), 7.90 (dd, *J*=10.0, 1.5 Hz, 1H), 8.09-8.18 (m, 1H), 8.19-8.25 (m, 1H), 8.29 (s, 1H), 8.50 (d, *J*=2.1 Hz, 1H), 10.19 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.33 min, m/z 546.2 $[M+H]^+$.



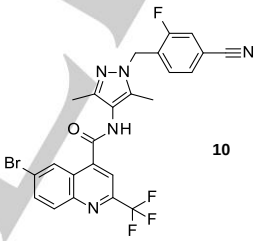
9a

4-[(4-Amino-3,5-dimethyl-1*H*-pyrazol-1-yl)methyl]-2-fluorobenzonitrile (9a): Prepared according to general procedure 3B from 4-[(3,5-dimethyl-4-nitro-1*H*-pyrazol-1-yl)methyl]-2-fluorobenzonitrile (1.14 g, 4.16 mmol, **9b**). Yield: 1.02 g (100%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.98 (s, 3H), 2.02 (s, 3H), 3.62 (br s, 2H), 5.19 (s, 2H), 6.85 (t, *J*=7.7 Hz, 1H), 7.63 (dd, *J*=7.9, 1.5 Hz, 1H), 7.85 ppm (dd, *J*=9.9, 1.4 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.57 min, m/z 245.1 $[M+H]^+$.



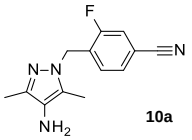
9b

4-[(3,5-Dimethyl-4-nitro-1*H*-pyrazol-1-yl)methyl]-2-fluorobenzonitrile (9b): Prepared according to general procedure 2A from 3,5-dimethyl-4-nitro-1*H*-pyrazole (659 mg, 4.67 mmol, CAS-RN 14531-55-6) and 4-(bromomethyl)-2-fluorobenzonitrile (1.0 g, 4.67 mmol, CAS-RN 222978-03-2). Yield: 1.14 g (89%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=2.37 (s, 3H), 2.61 (s, 3H), 5.49 (s, 2H), 7.30 (t, *J*=7.7 Hz, 1H), 7.68 (dd, *J*=8.0, 1.4 Hz, 1H), 7.91 ppm (dd, *J*=10.0, 1.5 Hz, 1H); LC-MS (ESI+, method 1): R_t=1.10 min, m/z 275.1 $[M+H]^+$.



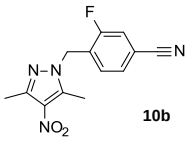
10

6-Bromo-*N*-[1-(4-cyano-2-fluorobenzyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]-2-(trifluoromethyl)quinoline-4-carboxamide (10): Prepared according to general procedure 9B from 6-bromo-2-(trifluoromethyl)quinoline-4-carboxylic acid (142 mg, 445 µmol, CAS-RN 1023815-61-3) and 4-[(4-amino-3,5-dimethyl-1*H*-pyrazol-1-yl)methyl]-3-fluorobenzonitrile (137 mg, 534 µmol, **10a**). Yield: 179 mg (73%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.14 (s, 3H), 2.24 (s, 3H), 5.40 (s, 2H), 7.16 (t, *J*=7.7 Hz, 1H), 7.73 (dd, *J*=8.0, 1.4 Hz, 1H), 7.92 (dd, *J*=9.9, 1.5 Hz, 1H), 8.16 (dd, *J*=9.0, 2.1 Hz, 1H), 8.24 (d, *J*=9.1 Hz, 1H), 8.32 (s, 1H), 8.52 (d, *J*=2.0 Hz, 1H), 10.22 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.32 min, m/z 546.1 $[M+H]^+$.



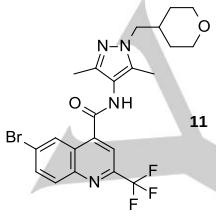
10a

4-[(4-Amino-3,5-dimethyl-1H-pyrazol-1-yl)methyl]-3-fluorobenzonitrile (10a): Prepared according to general procedure 3B from 4-[(3,5-dimethyl-4-nitro-1*H*-pyrazol-1-yl)methyl]-3-fluorobenzonitrile (1.84 g, 6.71 mmol, **10b**). Yield: 1.24 g (76%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.98 (s, 3H), 2.02 (s, 3H), 3.47 (br s, 2H), 5.19 (s, 2H), 6.86 (t, *J*=7.7 Hz, 1H), 7.62 (dd, *J*=7.8, 1.5 Hz, 1H), 7.84 ppm (dd, *J*=9.9, 1.5 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.60 min, m/z 245.1 [M+H]$^+$.



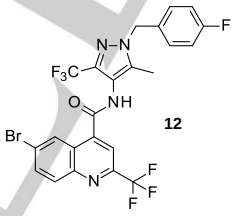
10b

4-[(3,5-Dimethyl-4-nitro-1*H*-pyrazol-1-yl)methyl]-3-fluorobenzonitrile (10b): Prepared according to general procedure 2A from 3,5-dimethyl-4-nitro-1*H*-pyrazole (934 mg, 6.62 mmol, CAS-RN 14531-55-6) and 4-(bromomethyl)-3-fluorobenzonitrile (1.7 g, 7.94 mmol, CAS-RN 105942-09-4). Yield: 1.84 g (100%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.38 (s, 3H), 2.63 (s, 3H), 5.50 (s, 2H), 7.31 (t, *J*=7.7 Hz, 1H), 7.70 (dd, *J*=7.9, 1.5 Hz, 1H), 7.92 ppm (dd, *J*=10.0, 1.4 Hz, 1H); LC-MS (ESI+, method 1): R_t=1.19 min, m/z 275.2 [M+H]$^+$.



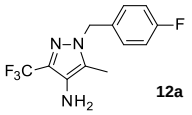
11

6-Bromo-*N*-[3,5-dimethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-pyrazol-4-yl]-2-(trifluoromethyl)quinoline-4-carboxamide (11): Prepared according to general procedure 9B from 6-bromo-2-(trifluoromethyl)quinoline-4-carboxylic acid (100 mg, 312 µmol, CAS-RN 1023815-61-3) and 3,5-dimethyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-pyrazol-4-amine (78.5 mg, 375 µmol, CAS-RN 1250928-53-0). Yield: 99.8 mg (62%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.17-1.36 (m, 2H), 1.37-1.48 (m, 2H), 2.05 (br s, 1H), 2.11 (s, 3H), 2.21 (s, 3H), 3.19-3.30 (m, 2H), 3.78-3.90 (m, 4H), 8.10-8.18 (m, 1H), 8.20-8.25 (m, 1H), 8.28 (s, 1H), 8.49 (s, 1H), 10.13 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.22 min, m/z 511.2 [M+H]$^+$.



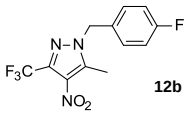
12

6-Bromo-*N*-[1-(4-fluorobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-2-(trifluoromethyl)quinoline-4-carboxamide (12): Prepared according to general procedure 9B from 6-bromo-2-(trifluoromethyl)quinoline-4-carboxylic acid (300 mg, 937 µmol, CAS-RN 1023815-61-3) and 1-(4-fluorobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (307 mg, 1.13 mmol, **12a**). Yield: 439 mg (81%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=2.30 (s, 3H), 5.46 (s, 2H), 7.18-7.36 (m, 4H), 8.15 (dd, *J*=9.0, 2.1 Hz, 1H), 8.20-8.27 (m, 2H), 8.41 (d, *J*=1.9 Hz, 1H), 10.50 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.49 min, m/z 575.1 [M+H]$^+$.



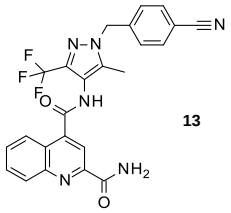
12a

1-(4-Fluorobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (12a): Prepared according to general procedure 3A from 1-(4-fluorobenzyl)-5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (4.21 g, 13.9 mmol, **12b**). Yield: 3.37 g (89%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.07 (s, 3H), 3.99 (s, 2H), 5.24 (s, 2H), 7.05-7.21 ppm (m, 4H); LC-MS (ESI+, method 1): R_t=1.08 min, m/z 274.0 [M+H]$^+$.



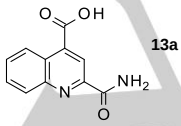
12b

1-(4-Fluorobenzyl)-5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (12b): Prepared according to general procedure 2A from 3-methyl-4-nitro-5-(trifluoromethyl)-1*H*-pyrazole (3.51 g, 937 µmol, CAS-RN 27116-80-9) and 1-(bromomethyl)-4-fluorobenzene (3.51 g, 18.0 mmol, CAS-RN 459-46-1). Yield: 4.21 g (88%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ= 2.65 (s, 3H), 5.52 (s, 2H), 7.17-7.26 (m, 2H), 7.29-7.36 ppm (m, 2H); LC-MS (ESI+, method 1): R_t=1.32 min, m/z 304.1 $[M+H]^+$.



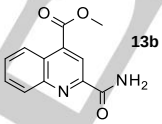
13

***N*^{4}-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]quinoline-2,4-dicarboxamide (13)**: Prepared according to general procedure 9B from 2-carbamoylquinoline-4-carboxylic acid (800 mg, 3.70 mmol, **13a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (1.24 g, 4.44 mmol, **65)**. Yield: 1.12 g (63%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=2.27 (s, 3H), 5.61 (s, 2H), 7.38 (d, *J*=8.3 Hz, 2H), 7.78-7.99 (m, 5H), 8.17-8.24 (m, 2H), 8.26 (s, 1H), 8.41 (br s, 1H), 10.43 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.11 min, m/z 479.2 $[M+H]^+$.



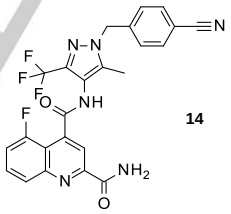
13a

2-Carbamoylquinoline-4-carboxylic acid (13a): Prepared according to general procedure 8 from methyl 2-carbamoylquinoline-4-carboxylate (2.88 g, 12.5 mmol, **13b**). Yield: 2.27 g (84%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=7.78-7.98 (m, 3H), 8.18-8.27 (m, 1H), 8.37 (br s, 1H), 8.43-8.54 (m, 1H), 8.79 (br d, *J*=8.6 Hz, 1H), 13.83 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=0.66 min, m/z 217.1 $[M+H]^+$.



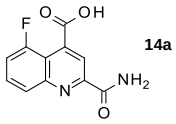
13b

Methyl 2-carbamoylquinoline-4-carboxylate (13b): Prepared according to general procedure 7 from dimethyl quinoline-2,4-dicarboxylate (10.0 g, 40.8 mmol, CAS-RN 7170-24-3). Yield: 8.21 g (87%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=4.01 (s, 3H), 7.80-7.98 (m, 3H), 8.21 (dd, *J*=8.3, 0.8 Hz, 1H), 8.39 (br s, 1H), 8.53 (s, 1H), 8.70 ppm (dd, *J*=8.5, 0.9 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.90 min, m/z 231.1 $[M+H]^+$.



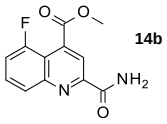
14

***N*^{4}-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-5-fluoroquinoline-2,4-dicarboxamide (14)**: Prepared according to general procedure 9B from 2-carbamoyl-5-fluoroquinoline-4-carboxylic acid (100 mg, 427 µmol, **14a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (144 mg, 512 µmol, **65)**. Yield: 108 mg (51%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.29 (s, 3H), 5.61 (s, 2H), 7.39 (d, *J*=8.6 Hz, 2H), 7.68 (ddd, *J*=11.4, 7.9, 1.0 Hz, 1H), 7.87-7.92 (m, 2H), 7.93-8.03 (m, 2H), 8.07-8.12 (m, 2H), 8.46 (d, *J*=1.5 Hz, 1H), 10.29 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.03 min, m/z 497.1 $[M+H]^+$.



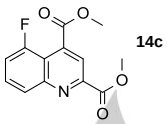
14a

2-Carbamoyl-5-fluoroquinoline-4-carboxylic acid (14a): Prepared according to general procedure 8 from methyl 2-carbamoyl-5-fluoroquinoline-4-carboxylate (1.84 g, 7.41 mmol, **14b**). Yield: 1.24 g (71%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=7.65 (ddd, *J*=11.4, 7.9, 1.0 Hz, 1H), 7.90-7.99 (m, 2H), 8.07 (dd, *J*=8.6, 0.8 Hz, 1H), 8.13 (s, 1H), 8.41 (br s, 1H), 14.06 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=0.55 min, m/z 235.0 [M+H]$^+$.



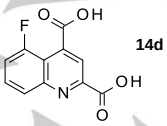
14b

Methyl 2-carbamoyl-5-fluoroquinoline-4-carboxylate (14b): Prepared according to general procedure 7 from dimethyl 5-fluoroquinoline-2,4-dicarboxylate (9.40 g, 35.7 mmol, **14c**). Yield: 1.84 g (21%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=3.98 (s, 3H), 7.68 (ddd, *J*=11.4, 7.9, 1.0 Hz, 1H), 7.93-8.01 (m, 2H), 8.09 (dd, *J*=8.5, 0.9 Hz, 1H), 8.25 (s, 1H), 8.43 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=0.87 min, m/z 249.1 [M+H]$^+$.



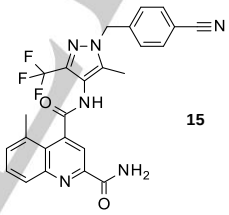
14c

Dimethyl 5-fluoroquinoline-2,4-dicarboxylate (14c): Prepared according to general procedure 6 from 5-fluoroquinoline-2,4-dicarboxylic acid (6.63 g, 28.2 mmol, **14d**). Crude yield: 9.40 g: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=3.97 (s, 3H), 3.98 (s, 3H), 7.71 (ddd, *J*=11.4, 7.9, 1.0 Hz, 1H), 7.98 (ddd, *J*=8.1, 7.9, 6.1 Hz, 1H), 8.13 (s, 1H), 8.14 (m, 1H), 8.26 (s, 1H); LC-MS (ESI+, method 1): R_t=0.96 min, m/z 264.1 [M+H]$^+$.



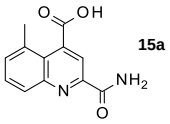
14d

5-Fluoroquinoline-2,4-dicarboxylic acid (14d): Prepared according to general procedure 5 from 4-fluoro-1*H*-indole-2,3-dione (10.0 g, 60.56 mmol, CAS-RN 346-34-9) and 2-oxopropanoic acid (9.3 g, 106 mmol, CAS-RN 127-17-3). Yield: 6.63 g (47%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=7.63-7.70 (m, 1H), 7.95 (td, *J*=8.2, 5.8 Hz, 1H), 8.08-8.13 (m, 2H), 13.96 ppm (br s, 2H); LC-MS (ESI+, method 1): R_t=0.44 min, m/z 236.0 [M+H]$^+$.



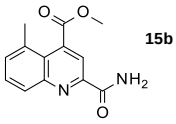
15

***N*^{4}-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-5-methylquinoline-2,4-dicarboxamide (15)**: Prepared according to general procedure 9B from 2-carbamoyl-5-methylquinoline-4-carboxylic acid (60 mg, 261 µmol, **15a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (58 mg, 208 µmol, **65)**. Yield: 15.7 mg (12%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.30 (s, 3H), 2.71 (s, 3H), 5.62 (s, 2H), 7.41 (d, *J*=8.4 Hz, 2H), 7.64 (d, *J*=6.8 Hz, 1H), 7.83 (dd, *J*=8.4, 7.1 Hz, 1H), 7.87-7.94 (m, 3H), 8.06-8.11 (m, 2H), 8.39 (d, *J*=1.8 Hz, 1H), 10.47 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.09 min, m/z 493.4 [M+H]$^+$.



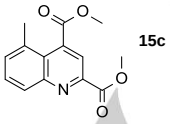
15a

2-Carbamoyl-5-methylquinoline-4-carboxylic acid (15a): Prepared according to general procedure 8 from methyl 2-carbamoyl-5-methylquinoline-4-carboxylate (1.90 g, 7.78 mmol, **15b**). Yield: 0.18 g (10%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.67 (s, 3H), 7.56-7.60 (m, 1H), 7.75-7.84 (m, 2H), 7.98 (s, 1H), 8.03 (d, *J*=8.1 Hz, 1H), 8.30 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=0.64 min, m/z 231.1 [M+H]$^+$.



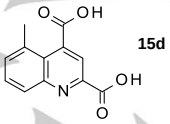
15b

Methyl 2-carbamoyl-5-methylquinoline-4-carboxylate (15b): Prepared according to general procedure 7 from dimethyl 5-methylquinoline-2,4-dicarboxylate (2.10 g, 8.10 mmol, **15c**). Yield: 1.90 g (96%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.55 (s, 3H), 3.99 (s, 3H), 7.64 (dt, *J*=7.1, 1.1 Hz, 1H), 7.78-7.89 (m, 2H), 8.04-8.08 (m, 1H), 8.12 (s, 1H), 8.33 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=0.93 min, m/z 245.1 [M+H]$^+$.



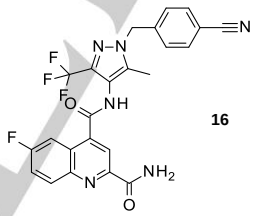
15c

Dimethyl 5-methylquinoline-2,4-dicarboxylate (15c): Prepared according to general procedure 6 from 5-methylquinoline-2,4-dicarboxylic acid (1.64 g, 7.09 mmol, **15d**). Crude yield: 2.10 g: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.57 (s, 3H), 3.98 (s, 3H), 4.01 (s, 3H), 7.70 (d, *J*=6.8 Hz, 1H), 7.82-7.89 (m, 1H), 8.12 (d, *J*=8.8 Hz, 1H), 8.16 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.03 min, m/z 260.1 [M+H]$^+$.



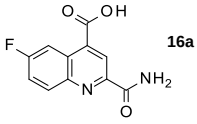
15d

5-Methylquinoline-2,4-dicarboxylic acid (15d): Prepared according to general procedure 5 from 4-methyl-1*H*-indole-2,3-dione (2.0 g, 12.4 mmol, CAS-RN 1128-44-5) and 2-oxopropanoic acid (1.91 g, 21.7 mmol, CAS-RN 127-17-3). Yield: 1.64 g (57%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.70 (s, 3H), 7.63-7.68 (m, 1H), 7.82 (dd, *J*=8.4, 7.1 Hz, 1H), 8.02 (s, 1H), 8.09 ppm (d, *J*=7.9 Hz, 1H); LC-MS (ESI-, method 1): R_t=0.44 min, m/z 232.0 [M+H]$^+$.



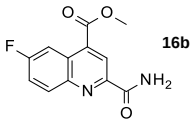
16

***N*^{4}-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-6-fluoroquinoline-2,4-dicarboxamide (16)**: Prepared according to general procedure 9B from 2-carbamoyl-6-fluoroquinoline-4-carboxylic acid (125 mg, 432 µmol, **16a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (145 mg, 519 µmol, **65)**. Yield: 97.2 mg (45%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.26 (s, 3H), 5.60 (s, 2H), 7.39 (d, *J*=8.3 Hz, 2H), 7.84-7.96 (m, 5H), 8.23-8.33 (m, 1H), 8.34-8.43 (m, 2H), 10.47 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.12 min, m/z 497.0 [M+H]$^+$.



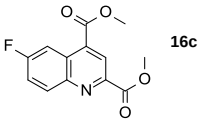
16a

2-Carbamoyl-6-fluoroquinoline-4-carboxylic acid (16a): Prepared according to general procedure 8 from methyl 2-carbamoyl-6-fluoroquinoline-4-carboxylate (210 mg, 846 µmol, **16b**). Yield: 156 mg (79%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=7.83-7.93 (m, 2H), 8.27 (m, 1H), 8.35 (br s, 1H), 8.53-8.63 (m, 2H), 13.76 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=0.71 min, m/z 235.0 [M+H]$^+$.



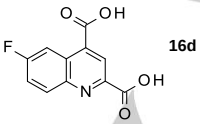
16b

Methyl 2-carbamoyl-6-fluoroquinoline-4-carboxylate (16b): Prepared according to general procedure 7 from dimethyl 6-fluoroquinoline-2,4-dicarboxylate (310 mg, 1.78 mmol, **16c**). Yield: 210 mg (70%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=4.01 (s, 3H), 7.83-7.96 (m, 2H), 8.28 (dd, *J*=9.4, 5.8 Hz, 1H), 8.38 (br s, 1H), 8.48 (dd, *J*=10.9, 2.8 Hz, 1H), 8.59 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=0.96 min, m/z 249.1 [M+H]$^+$.



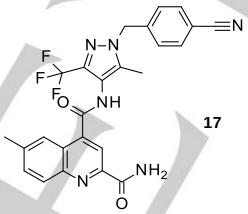
16c

Dimethyl 6-fluoroquinoline-2,4-dicarboxylate (16c): Prepared according to general procedure 6 from 6-fluoroquinoline-2,4-dicarboxylic acid (2.15 g, 7.90 mmol, **16d**). Yield: 1.82 g (87%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=3.98 (s, 3H), 4.01 (s, 3H), 7.91 (ddd, *J*=9.2, 8.2, 2.9 Hz, 1H), 8.36 (dd, *J*=9.3, 5.8 Hz, 1H), 8.48 (dd, *J*=10.8, 2.9 Hz, 1H), 8.54 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.08 min, m/z 264.1 [M+H]$^+$.



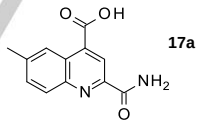
16d

6-Fluoroquinoline-2,4-dicarboxylic acid (16d): Prepared according to general procedure 5 from 5-fluoro-1*H*-indole-2,3-dione (2.0 g, 12.1 mmol, CAS-RN 443-69-6) and 2-oxopropanoic acid (1.87 g, 21.2 mmol, CAS-RN 127-17-3). Yield: 1.86 g (65%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=7.81-7.93 (m, 1H), 8.33 (dd, *J*=9.3, 5.8 Hz, 1H), 8.52-8.62 (m, 2H), 13.82 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=0.42 min, m/z 236.0 [M+H]$^+$.



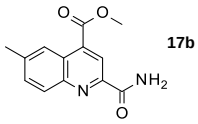
17

***N*^{4}-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-6-methylquinoline-2,4-dicarboxamide (17)**: Prepared according to general procedure 9B from 2-carbamoyl-6-methylquinoline-4-carboxylic acid (100 mg, 434 µmol, **17a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (122 mg, 434 µmol, **65)**. Yield: 18.4 mg (9%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.26 (s, 3H), 2.54 (s, 3H), 5.60 (s, 2H), 7.39 (d, *J*=8.3 Hz, 2H), 7.78 (dd, *J*=8.7, 1.9 Hz, 1H), 7.85-7.93 (m, 3H), 7.95 (s, 1H), 8.10 (d, *J*=8.7 Hz, 1H), 8.22 (s, 1H), 8.36 (br s, 1H), 8.46 (s, 1H), 10.39 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.01 min, m/z 493.2 [M+H]$^+$.



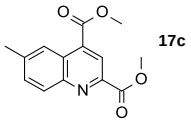
17a

2-Carbamoyl-6-methylquinoline-4-carboxylic acid (17a): Prepared according to general procedure 8 from methyl 2-carbamoyl-6-methylquinoline-4-carboxylate (500 mg, 2.05 mmol, **17b**). Crude yield: 480 mg: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=2.56 (s, 3H), 7.76 (dd, *J*=8.8, 1.8 Hz, 1H), 7.84 (br s, 1H), 8.09 (d, *J*=8.7 Hz, 1H), 8.32 (br s, 1H), 8.46 (s, 1H), 8.55 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=0.76 min, m/z 230.9 [M+H]$^+$.



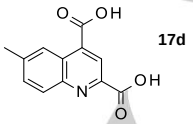
17b

Methyl 2-carbamoyl-6-methylquinoline-4-carboxylate (17b): Prepared according to general procedure 7 from dimethyl 6-methylquinoline-2,4-dicarboxylate (3.17 g, 12.23 mmol, **17c**). Yield: 2.72 g (91%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=2.57 (s, 3H), 4.00 (s, 3H), 7.78 (dd, *J*=8.7, 1.7 Hz, 1H), 7.86 (br s, 1H), 8.10 (d, *J*=8.7 Hz, 1H), 8.34 (br s, 1H), 8.42-8.51 ppm (m, 2H); LC-MS (ESI+, method 1): R_t=0.99 min, m/z 244.9 [M+H]$^+$.



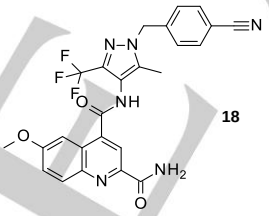
17c

Dimethyl 6-methylquinoline-2,4-dicarboxylate (17c): Prepared according to general procedure 6 from 6-methylquinoline-2,4-dicarboxylic acid (5.50 g, 23.79 mmol, **17d**). Yield: 6.16 g (95%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.59 (s, 3H), 3.98 (s, 3H), 4.02 (s, 3H), 7.82 (dd, *J*=8.7, 1.9 Hz, 1H), 8.17 (d, *J*=8.6 Hz, 1H), 8.45 (s, 1H), 8.48 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=0.99 min, m/z 260.1 [M+H]$^+$.



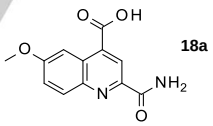
17d

6-Methylquinoline-2,4-dicarboxylic acid (17d): Prepared according to general procedure 5 from 5-methyl-1*H*-indole-2,3-dione (5.50 g, 23.79 mmol, CAS-RN 608-05-09) and 2-oxopropanoic acid (5.50 g, 23.79 mmol, CAS-RN 127-17-3). Yield: 20.60 g (96%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.58 (s, 3H), 7.78 (dd, *J*=8.7, 1.9 Hz, 1H), 8.13 (d, *J*=8.8 Hz, 1H), 8.42 (s, 1H), 8.57 (s, 1H), 13.84 ppm (br s, 2H); LC-MS (ESI+, method 1): R_t=0.55 min, m/z 232.1 [M+H]$^+$.



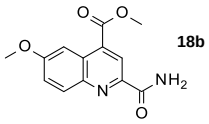
18

***N*^{4}-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-6-methoxyquinoline-2,4-dicarboxamide (18)**: Prepared according to general procedure 9B from 2-carbamoyl-6-methoxyquinoline-4-carboxylic acid (1.50 g, 5.79 mmol, **18a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (1.95 g, 6.95 mmol, **65)**. Yield: 1.46 g (50%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.29 (s, 3H), 3.90 (s, 3H), 5.62 (s, 2H), 7.41 (d, *J*=8.4 Hz, 2H), 7.53 (d, *J*=2.8 Hz, 1H), 7.61 (dd, *J*=9.1, 2.7 Hz, 1H), 7.84 (br d, *J*=2.0 Hz, 1H), 7.91 (d, *J*=8.1 Hz, 2H), 8.13 (d, *J*=9.4 Hz, 1H), 8.24 (s, 1H), 8.32 (br d, *J*=1.8 Hz, 1H), 10.40 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.10 min, m/z 509.3 [M+H]$^+$.



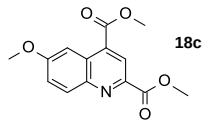
18a

Methyl 2-carbamoyl-6-methylquinoline-4-carboxylate (18a): Prepared according to general procedure 8 from methyl 2-carbamoyl-6-methoxyquinoline-4-carboxylate (1.45 g, 5.57 mmol, **18b**). Yield: 1.33 g (97%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=3.93 (s, 3H), 7.57 (dd, *J*=9.2, 2.9 Hz, 1H), 7.79 (br d, *J*=1.5 Hz, 1H), 8.09 (d, *J*=9.1 Hz, 1H), 8.23-8.30 (m, 2H), 8.51 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=0.74 min, m/z 247.1 [M+H]$^+$.



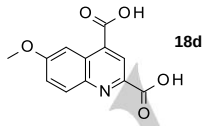
18b

Methyl 2-carbamoyl-6-methoxyquinoline-4-carboxylate (18b): Prepared according to general procedure 7 from dimethyl 6-methoxyquinoline-2,4-dicarboxylate (2.65 g, 9.63 mmol, **18c**). Yield: 1.45 g, (58%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=3.97 (s, 3H), 4.03 (s, 3H), 7.62 (dd, *J*=9.3, 2.8 Hz, 1H), 7.82 (br s, 1H), 8.14 (d, *J*=9.3 Hz, 1H), 8.18 (d, *J*=2.8 Hz, 1H), 8.30 (br s, 1H), 8.56 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=0.97 min, m/z 261.1 [M+H]$^+$.



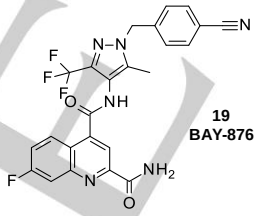
18c

Dimethyl 6-methoxyquinoline-2,4-dicarboxylate (18c): Prepared according to general procedure 6 from 6-methoxyquinoline-2,4-dicarboxylic acid (3.00 g, 12.14 mmol, **18d**). Yield: 2.65 g (79%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=3.95 (s, 3H), 3.95 (s, 3H), 4.00 (s, 3H), 7.60 (dd, *J*=9.2, 2.8 Hz, 1H), 8.12-8.19 (m, 2H), 8.48 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.07 min, m/z 276.1 [M+H]$^+$.



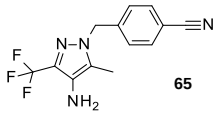
18d

6-Methoxyquinoline-2,4-dicarboxylic acid (18d): Prepared according to general procedure 5 from 5-methoxy-1*H*-indole-2,3-dione (5.00 g, 28.22 mmol, CAS-RN 39755-95-8). and 2-oxopropanoic acid (4.35 g, 49.40 mmol, CAS-RN 127-17-3). Yield: 3.01 g (43%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=3.94 (s, 3H), 7.57 (dd, *J*=9.4, 2.8 Hz, 1H), 8.14 (d, *J*=9.1 Hz, 1H), 8.25 (d, *J*=2.8 Hz, 1H), 8.48 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=0.42 min, m/z 248.0 [M+H]$^+$.



19
BAY-876

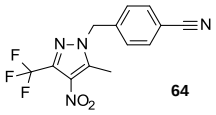
***N*^{4}-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-7-fluoroquinoline-2,4-dicarboxamide (19, BAY-876)**: To a solution of 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (144 mg, 0.51 mmol, **65**) in DMSO (2.3 mL) was added HATU (195 mg, 0.51 mmol), *N*,*N*-diisopropylethylamine (112 µL, 0.64 mmol) and 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (100 mg, 0.43 mmol, **70**). The reaction mixture was stirred for 1 h at 25°C. This mixture was directly purified by preparative HPLC to obtain the desired compound **19** (98 mg, 46%): ^{1}H NMR (300 MHz, [D$_6$]DMSO) δ=2.27 (s, 3H), 5.61 (s, 2 H), 7.38 (d, *J*=8.3 Hz, 2 H), 7.74-7.84 (m, 1H), 7.86 - 7.95 (m, 3H), 7.97 (br s, 1H), 8.24 - 8.33 (m, 2H), 8.40 (br s, 1H), 10.48 ppm (s, 1H); ^{13}C NMR (101 MHz, [D$_6$]DMSO) δ=9.3 (s, CH$_3$), 53.1 (s, CH$_2$), 111.0 (s, C), 113.3 (d, J_{C-F}= 20.3 Hz, CH), 114.8 (s, C), 116.4 (s, CH), 118.6 (s, C), 119.7 (d, J_{C-F}= 25.7 Hz, CH), 121.4 (q, J_{C-F}= 269.1 Hz, C), 122.4(s, C), 128.1 (d, J_{C-F}= 10.3 Hz, CH), 128.2 (s, 2CH), 132.9 (s, 2CH), 136.2 (q, J_{C-F}= 35.6 Hz, C), 138.7 (s, C), 141.7 (s, C), 142.6 (s, C), 147.9 (d, J_{C-F}= 13.0 Hz, C), 151.4 (s, C), 163.0 (d, J_{C-F}= 250.4 Hz, C), 165.5 (s, C), 166.1 ppm (s, C); LC-MS (ESI+, method 1): R_t=1.11 min, m/z 497.1 [M+H]$^+$.



65

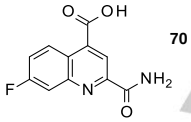
4-{[4-Amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (65): To a solution of 4-{[5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (3.20 g, 10.3 mmol, **64**) in ethanol (160 mL) was added water (80 mL), acetic acid (16 mL), and zinc dust (3.20 g, 49.0 mmol). This reaction mixture was stirred at 60°C for 1.5 h. After cooling to 25°C the suspension was filtered through Celite, washed with ethyl acetate, and the complete filtrate was evaporated. To the residue was added water (100 mL) and conc. aq. sodium carbonate (50 mL). This aqueous phase was extracted three times with ethyl acetate (150 mL). The combined organic layer was washed with brine, dried over sodium sulfate, filtered and evaporated to obtain a crude product that was purified by flash chromatography to obtain compound **65** (2.66 g, 92%): ^{1}H NMR (300 MHz,

[D6]DMSO) δ=2.05 (s, 3H), 4.06 (s, 2H), 5.38 (s, 2H), 7.22 (d, *J*=8.5 Hz, 2H), 7.79-7.85 ppm (m, 2 H); LC-MS (ESI+, method 1): R_t=0.96 min, m/z 281.1 $[M+H]^+$.



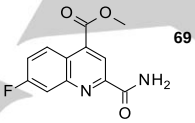
64

4-{[5-Methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (64): 3-Methyl-4-nitro-5-(trifluoromethyl)-1*H*-pyrazole (4.30 g, 22.0 mmol, **62**, CAS-RN 27116-80-9) was dissolved in acetonitrile (65 mL), and 4-(bromomethyl)benzonitrile (5.19 g, 26.5 mmol, **63**, CAS-RN 17201-43-3) and cesium carbonate (8.62 g, 26.5 mmol) were added. The suspension was stirred at 60°C for 2 h. Then, the reaction mixture was filtered, the filtrate was evaporated, and the crude product was purified by flash chromatography to obtain the desired compound **64** (6.30 g, 92%): ^{1}H NMR (300 MHz, [D6]DMSO) δ=2.63 (s, 3H), 5.67 (s, 2H), 7.41 (d, *J*=8.5 Hz, 2H), 7.86 ppm (d, *J*=8.5 Hz, 2H); LC-MS (ESI+, method 1): R_t=1.21 min, m/z 311.1 $[M+H]^+$.



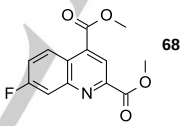
70

2-Carbamoyl-7-fluoroquinoline-4-carboxylic acid (70): To a solution of methyl 2-carbamoyl-7-fluoroquinoline-4-carboxylate (3.00 g, 12.1 mmol, **69**) in methanol (56 mL) and tetrahydrofuran (20 mL) was added a solution of sodium hydroxide (4.35 g, 109 mmol) in water (111 mL). This mixture was stirred for 1 h at 25°C and then concentrated in vacuo. The residue was diluted with water. 10% aq. sulfuric acid was added until pH 5 was reached. After stirring for additional 15 min the solid was isolated by filtration and dried in vacuo to obtain the desired compound **69** (2.38 g, 84%), which was used without further purification: ^{1}H NMR (300 MHz, [D6]DMSO) δ=7.76 (ddd, *J*=9.4, 8.4, 2.8 Hz, 1H), 7.89 (dd, *J*=9.9, 2.7 Hz, 1H), 7.92 (br s, 1H), 8.35 (br s, 1H), 8.46 (s, 1H), 8.89 ppm (dd, *J*=9.4, 6.2 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.70 min, m/z 235.1 $[M+H]^+$.



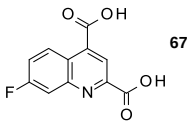
69

Methyl 2-carbamoyl-7-fluoroquinoline-4-carboxylate (69): To a solution of dimethyl 7-fluoroquinoline-2,4-dicarboxylate (3.05 g, 11.6 mmol, **68**) in methanol (42 mL) was added a 7 M solution of ammonia in methanol (41 mL; 290 mmol) and stirred for 3.5 h at 50°C. After cooling to 25°C, the precipitate was isolated by filtration and dried to give the desired compound **69** (2.33 g, 81%), which was used without further purification: ^{1}H NMR (400 MHz, [D6]DMSO) δ=4.03 (s, 3H), 7.83 (ddd, *J*=9.4, 8.4, 2.8 Hz, 1H), 7.94 (dd, *J*=9.9, 2.8 Hz, 1H), 7.97 (br s, 1H), 8.39 (br s, 1H), 8.52 (s, 1H), 8.83 ppm (dd, *J*=9.4, 6.1 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.95 min, m/z 249.1 $[M+H]^+$.



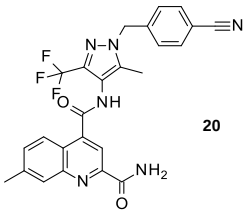
68

Dimethyl 7-fluoroquinoline-2,4-dicarboxylate (68): A mixture of 7-fluoroquinoline-2,4-dicarboxylic acid (6.0 g, 25.5 mmol, **67**) and thionyl chloride (28 mL, 383 mmol) was heated at 80°C for 2 d. After cooling to 25°C the resulting suspension was evaporated to dryness in vacuo. This crude product was suspended in methanol (47 mL) and refluxed for 3 hours. After cooling to 25°C the solid was isolated by filtration to give compound **68** (3.06 g, 46%), which was used without further purification: ^{1}H NMR (300 MHz, [D6]DMSO) δ=3.99 (s, 3H), 4.01 (s, 3H), 7.85 (ddd, *J*=9.2, 8.4, 2.6 Hz, 1H), 8.07 (dd, *J*=9.8, 2.6 Hz, 1H), 8.45 (s, 1H), 8.80 ppm (dd, *J*=9.5, 6.1 Hz, 1H); LC-MS (ESI+, method 1): R_t=1.07 min, m/z 264.0 $[M+H]^+$.



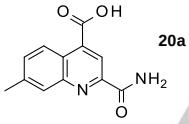
67

7-Fluoroquinoline-2,4-dicarboxylic acid (67): To a mixture of 6-fluoro-1*H*-indole-2,3-dione (5.0 g, 30.3 mmol, **66**, CAS-RN 324-03-8) in 33% aq. potassium hydroxide solution (75 mL) was added pyruvic acid (4.67 g, 53.0 mmol) and this mixture was heated at 40°C for 18 h. After cooling to room temperature 10% aq. sulfuric acid was added until pH reached about 1. The precipitate was isolated by filtration and dried in vacuo to give the desired compound **67** (6.02 g, 85%), which was used without further purification: ^{1}H NMR (300 MHz, [D6]DMSO) δ=7.78 (ddd, *J*=9.4, 8.5, 2.8 Hz, 1H), 7.99 (dd, *J*=10.0, 2.6 Hz, 1H), 8.42 (s, 1H), 8.89 ppm (dd, *J*=9.5, 6.3 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.56 min, m/z 236.1 $[M+H]^+$.



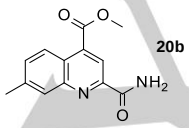
20

***N*⁴-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-7-methylquinoline-2,4-dicarboxamide (20)**: Prepared according to general procedure 9B from 2-carbamoyl-7-methylquinoline-4-carboxylic acid (97.0 mg, 421 µmol, **20a**) and -{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (98.4 mg, 351 µmol, **65)**. Yield: 20.2 mg (12%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.27 (s, 3H), 2.59 (s, 3H), 5.62 (s, 2H), 7.40 (d, *J*=8.6 Hz, 2H), 7.67 (dd, *J*=8.6, 1.8 Hz, 1H), 7.88-7.94 (m, 3H), 8.00 (s, 1H), 8.11 (d, *J*=8.6 Hz, 1H), 8.21 (s, 1H), 8.35 (br d, *J*=2.0 Hz, 1H), 10.40 ppm (s, 1H); LC-MS (ESI+, method 1): *R*$_t$=1.14 min, m/z 493.3 [M+H]$^+$.



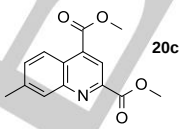
20a

2-Carbamoyl-7-methylquinoline-4-carboxylic acid (20a): Prepared according to general procedure 8 from methyl 2-carbamoyl-7-methylquinoline-4-carboxylate (166.0 mg, 680 µmol, **20b**). Yield: 97.0 mg (62%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.58 (s, 3H), 7.64-7.72 (m, 1H), 7.86 (br s, 1H), 7.97-8.04 (m, 1H), 8.30 (br s, 1H), 8.36-8.46 (m, 1H), 8.66-8.73 (m, 1H); LC-MS (ESI+, method 1): *R*$_t$=0.65 min, m/z 231.1 [M+H]$^-$.



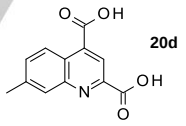
20b

Methyl 2-carbamoyl-7-methylquinoline-4-carboxylate (20b): Prepared according to general procedure 7 from dimethyl 7-methylquinoline-2,4-dicarboxylate (270.0 mg, 1.04 mmol, **20c**). Yield: 166 mg (65%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.59 (s, 3H), 4.02 (s, 2H), 7.71 (dd, *J*=8.6, 1.8 Hz, 1H), 7.90 (br s, 1H), 8.01 (s, 1H), 8.33 (br s, 1H), 8.48 (s, 1H), 8.62 ppm (d, *J*=8.9 Hz, 1H); LC-MS (ESI+, method 1): *R*$_t$=1.00 min, m/z 245.1 [M+H]$^+$.



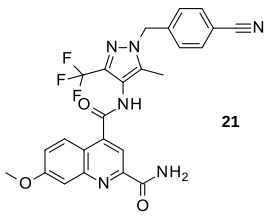
20c

Dimethyl 7-methylquinoline-2,4-dicarboxylate (20c): Prepared according to general procedure 6 from 7-methylquinoline-2,4-dicarboxylic acid (1.16 g, 5.02 mmol, **20d**). Yield: 0.27 g (28%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.57 (s, 3H), 3.97 (s, 3H), 4.00 (s, 3H), 7.73 (dd, *J*=8.8, 7.8 Hz, 1H), 8.06 (br s, 1H), 8.41 (s, 1H), 8.61 ppm (d, *J*=8.8 Hz, 1H); LC-MS (ESI+, method 1): *R*$_t$=1.12 min, m/z 260.1 [M+H]$^+$.



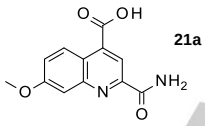
20d

7-Methylquinoline-2,4-dicarboxylic acid (20d): Prepared according to general procedure 5 from 6-methyl-1*H*-indole-2,3-dione (2.00 g, 12.41 mmol, CAS-RN 1128-47-8) and 2-oxopropanoic acid (1.91 g, 21.72 mmol, CAS-RN 127-17-3). Yield: 1.15 g (58%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.58 (s, 3H), 7.71 (dd, *J*=8.7, 1.9 Hz, 1H), 8.04 (s, 1H), 8.41 (s, 1H), 8.70 ppm (d, *J*=8.6 Hz, 1H); LC-MS (ESI+, method 1): *R*$_t$=0.55 min, m/z 232.0 [M+H]$^+$.



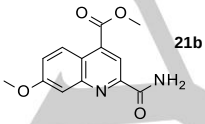
21

***N*⁴-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-7-methoxyquinoline-2,4-dicarboxamide (21)**: Prepared according to general procedure 9B from 2-carbamoyl-7-methoxyquinoline-4-carboxylic acid (150.0 mg, 609 µmol, **21a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (204.9 mg, 731 µmol, **65)**. Yield: 35.7 mg (12%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.25 (s, 3H), 3.97 (s, 3H), 5.60 (s, 2H), 7.38 (d, *J*=8.6 Hz, 2H), 7.47 (dd, *J*=9.2, 2.7 Hz, 1H), 7.55 (d, *J*=2.5 Hz, 1H), 7.84-7.91 (m, 3H), 8.07-8.13 (m, 2H), 8.29-8.35 (m, 1H), 10.37 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.10 min, m/z 509.2 [M+H]$^+$.



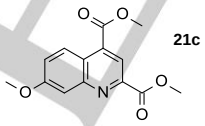
21a

2-Carbamoyl-7-methoxyquinoline-4-carboxylic acid (21a): Prepared according to general procedure 8 from methyl 2-carbamoyl-7-methoxyquinoline-4-carboxylate (400.0 mg, 1.54 mmol, **21b**). Yield: 349 mg (92%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=3.95 (s, 3H), 7.38-7.46 (m, 1H), 7.48-7.58 (m, 1H), 7.77-7.85 (m, 1H), 8.20-8.32 (m, 2H), 8.67 ppm (dd, *J*=9.3, 2.2 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.75 min, m/z 247.0 [M+H]$^+$.



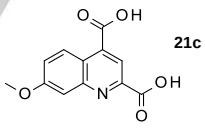
21b

Methyl 2-carbamoyl-7-methoxyquinoline-4-carboxylate (21b): Prepared according to general procedure 7 from dimethyl 7-methoxyquinoline-2,4-dicarboxylate (545.0 mg, 1.98 mmol, **21c**). Yield: 408 mg (79%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=3.98 (s, 3H), 4.01 (s, 3H), 7.51 (dd, *J*=9.4, 2.8 Hz, 1H), 7.58 (d, *J*=2.8 Hz, 1H), 7.88 (br s, 1H), 8.34 (br s, 1H), 8.39 (s, 1H), 8.63 ppm (d, *J*=9.4 Hz, 1H); LC-MS (ESI+, method 2): R_t=0.94 min, m/z 261.1 [M+H]$^+$.



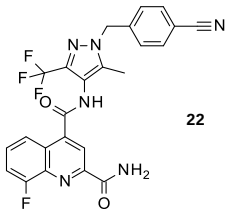
21c

Dimethyl 7-methoxyquinoline-2,4-dicarboxylate (21c): Prepared according to general procedure 6 from 7-methoxyquinoline-2,4-dicarboxylic acid (1.50 g, 6.07 mmol, **21d**). Yield: 549 mg (33%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=3.98 (s, 3H), 3.99 (s, 3H), 4.01 (s, 3H), 7.54 (dd, *J*=9.4, 2.8 Hz, 1H), 7.67 (d, *J*=2.8 Hz, 1H), 8.34 (s, 1H), 8.63 (d, *J*=9.4 Hz, 1H); LC-MS (ESI+, method 1): R_t=1.07 min, m/z 276.0 [M+H]$^+$.



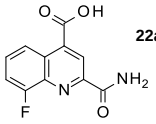
21c

7-Methoxyquinoline-2,4-dicarboxylic acid (21d): Prepared according to general procedure 5 from 6-methoxy-1*H*-indole-2,3-dione (5.00 g, 28.22 mmol, CAS-RN 52351-75-4) and 2-oxopropanoic acid (4.35 g, 49.40 mmol, CAS-RN 127-17-3). Yield: 2.71 g (39%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=3.96 (s, 3H), 7.49 (dd, *J*=9.4, 2.6 Hz, 1H), 7.60 (d, *J*=2.5 Hz, 1H), 8.31 (s, 1H), 8.69 (d, *J*=9.4 Hz, 1H), 13.83 (br s, 2H); LC-MS (ESI+, method 1): R_t=0.32 min, m/z 248.0 [M+H]$^+$.



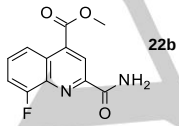
22

***N*⁴-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-8-fluoroquinoline-2,4-dicarboxamide (22)**: Prepared according to general procedure 9B from 2-carbamoyl-8-fluoroquinoline-4-carboxylic acid (90.0 mg, 384 µmol, **22a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (107.7 mg, 384 µmol, **65)**. Yield: 63.9 mg (33%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.27 (s, 3H), 5.60 (s, 2H), 7.38 (d, *J*=8.3 Hz, 2H), 7.75-7.85 (m, 2H), 7.87-7.92 (m, 2H), 7.98-8.02 (m, 2H), 8.26 (br d, *J*=1.5 Hz, 1H), 8.33 (s, 1H), 10.49 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.07 min, m/z 497.2 [M+H]$^+$.



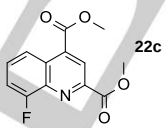
22a

2-Carbamoyl-8-fluoroquinoline-4-carboxylic acid (22a): Prepared according to general procedure 8 from methyl 2-carbamoyl-8-fluoroquinoline-4-carboxylate (500.0 mg, 2.01 µmol, **22b**). Yield: 190 mg (40%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=7.70-7.87 (m, 2H), 7.96 (br s, 1H), 8.20 (s, 1H), 8.53-8.62 (m, 2H),14.17 (br s, 1H); LC-MS (ESI+, method 1): R_t=0.66 min, m/z 235.1 [M+H]$^+$.



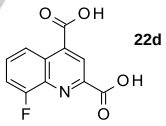
22b

Methyl 2-carbamoyl-8-fluoroquinoline-4-carboxylate (22b): Prepared according to general procedure 7 from dimethyl 8-fluoroquinoline-2,4-dicarboxylate (4.40 g, 16.72 µmol, **22c**). Yield: 3.90 g, (94%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=4.03 (s, 3H), 7.73-7.90 (m, 2H), 8.00 (br s, 1H), 8.24 (br s, 1H), 8.53 (d, *J*=8.1 Hz, 1H), 8.61 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=0.78 min, m/z 249.1 [M+H]$^+$.



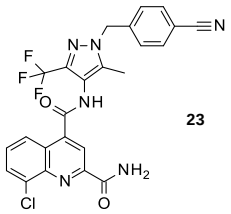
22c

Dimethyl 8-fluoroquinoline-2,4-dicarboxylate (22c): Prepared according to general procedure 6 from 8-fluoroquinoline-2,4-dicarboxylic acid (4.70 g, 19.99 µmol, **22d**). Yield: 4.40 g (84%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=3.99 (s, 3H), 4.02 (s, 3H), 7.76-7.93 (m, 2H), 8.48-8.55 ppm (m, 2H); LC-MS (ESI+, method 1): R_t=1.04 min, m/z 264.0 [M+H]$^+$.



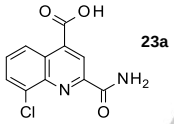
22d

8-Fluoroquinoline-2,4-dicarboxylic acid (22d): Prepared according to general procedure 5 from 7-fluoro-1*H*-indole-2,3-dione (5.36 g, 32.46 mmol, CAS-RN 317-20-4) and 2-oxopropanoic acid (5.00 g, 56.81 mmol, CAS-RN 127-17-3). Yield: 4.75 g, (62%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=7.70-7.90 (m, 2H), 8.51 (s, 1H), 8.59 (d, *J*=8.3 Hz, 1H), 14.00 (br s, 2H; LC-MS (ESI+, method 1): R_t=0.71 min, m/z 236.1 [M+H]$^+$.



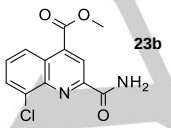
23

8-Chloro-N^4-[1-(4-cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]quinoline-2,4-dicarboxamide (23): Prepared according to general procedure 9B from 2-carbamoyl-8-chloroquinoline-4-carboxylic acid (100.0 mg, 399 µmol, **23a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (134.2 mg, 479 µmol, **65)**. Yield: 28.5 mg (14%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.27 (s, 3H), 5.60 (s, 2H), 7.38 (d, *J*=8.3 Hz, 2H), 7.79 (dd, *J*=8.3, 7.8 Hz, 1H), 7.87-7.91 (m, 2H), 8.03-8.18 (m, 4H), 8.34 (s, 1H), 10.48 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.15 min, m/z 513.1 [M+H]$^+$.



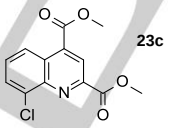
23a

2-Carbamoyl-8-chloroquinoline-4-carboxylic acid (23a): Prepared according to general procedure 8 from methyl 2-carbamoyl-8-chloroquinoline-4-carboxylate (1.68 g, 6.35 mmol, **23b**). Yield: 1.60 g (100%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=7.81 (dd, *J*=8.6, 7.6 Hz, 1H), 8.06 (br s, 1H), 8.08 (br s, 1H), 8.15 (d, *J*=7.6 Hz, 1H), 8.57 (s, 1H), 8.76 (d, *J*=8.6 Hz, 1H), 14.13 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=0.76 min, m/z 251.0 [M+H]$^+$.



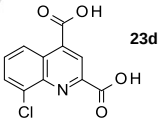
23b

Methyl 2-carbamoyl-8-chloroquinoline-4-carboxylate (23b): Prepared according to general procedure 7 from dimethyl 8-chloroquinoline-2,4-dicarboxylate (2.24 g, 8.01 mmol, **23c**). Yield: 1.69 g (80%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=4.02 (s, 3H), 7.81 (dd, *J*=8.7, 7.7 Hz, 1H), 8.07 (br d, *J*=4.0 Hz, 2H), 8.14 (dd, *J*=7.5, 1.0 Hz, 1H), 8.58 (s, 1H), 8.66 ppm (dd, *J*=8.7, 1.1 Hz, 1H); LC-MS (ESI+, method 1): R_t=1.00 min, m/z 265.0 [M+H]$^+$.



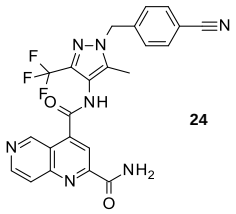
23c

Dimethyl 8-chloroquinoline-2,4-dicarboxylate (23c): Prepared according to general procedure 6 from 8-chloroquinoline-2,4-dicarboxylic acid (3.34 g, 13.27 mmol, **23d**). Yield: 2.20 g (60%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=3.99 (s, 3H), 4.01 (s, 3H), 7.84 (dd, *J*=8.6, 7.6 Hz, 1H), 8.16 (dd, *J*=7.5, 0.9 Hz, 1H), 8.53 (s, 1H), 8.66 ppm (dd, *J*=8.7, 1.1 Hz, 1H); LC-MS (ESI+, method 2): R_t=1.15 min, m/z 280.0 [M+H]$^+$.



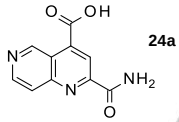
23d

8-chloroquinoline-2,4-dicarboxylic acid (23d): Prepared according to general procedure 5 from 7-chloro-1*H*-indole-2,3-dione (5.00 g, 27.53 mmol, CAS-RN 7477-63-6) and 2-oxopropanoic acid (4.24 g, 48.19 mmol, CAS-RN 127-17-3). Yield: 3.34 g (48%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=7.70-7.79 (m, 1H), 8.05-8.11 (m, 1H), 8.41 (s, 1H), 8.72 ppm (dd, *J*=8.7, 0.9 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.58 min, m/z 252.0 [M+H]$^+$.



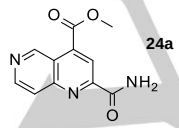
24

***N*⁴-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-1,6-naphthyridine-2,4-dicarboxamide (24)**: Prepared according to general procedure 9B from 2-carbamoyl-1,6-naphthyridine-4-carboxylic acid (130.0 mg, 464 µmol, **24a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (134.2 mg, 479 µmol, **65)**. Yield: 44.7 mg (24%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.30 (s, 3H), 5.62 (s, 2H), 7.41 (d, *J*=8.6 Hz, 2H), 7.88-7.93 (m, 2H), 8.07-8.13 (m, 2H), 8.42 (s, 1H), 8.53 (s, 1H), 8.93 (d, *J*=5.8 Hz, 1H), 9.63 (s, 1H), 10.62 ppm (s, 1H); LC-MS (ESI+, method 2): R_t=0.94 min, m/z 480.2 [M+H]$^+$.



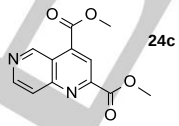
24a

2-Carbamoyl-1,6-naphthyridine-4-carboxylic acid (24a): Prepared according to general procedure 8 from methyl 2-carbamoyl-1,6-naphthyridine-4-carboxylate (144 mg, 623 µmol, **24b**). Yield: 84.0 mg (60%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=7.96-8.10 (m, 2H), 8.46 (s, 1H), 8.54 (s, 1H), 8.87 (d, *J*=5.8 Hz, 1H), 10.16 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=0.28 min, m/z 218.0 [M+H]$^+$.



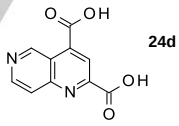
24a

Methyl 2-carbamoyl-1,6-naphthyridine-4-carboxylate (24b): Prepared according to general procedure 7 from dimethyl 1,6-naphthyridine-2,4-dicarboxylate (2.88 g, 11.70 mmol, **24c**). Yield: 1.77 g (60%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=4.04 (s, 3H), 8.02-8.11 (m, 2H), 8.50 (br s, 1H), 8.60 (s, 1H), 8.91 (d, *J*=5.8 Hz, 1H), 10.09 ppm (d, *J*=0.8 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.62 min, m/z 232.1 [M+H]$^+$.



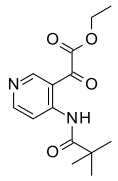
24c

Dimethyl 1,6-naphthyridine-2,4-dicarboxylate (24c): Prepared according to general procedure 6 from 1,6-naphthyridine-2,4-dicarboxylic acid (3.46 g, 15.86 mmol, **24d**). Yield: 2.88 g (74%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=4.00 (s, 3H), 4.05 (s, 3H), 8.27 (dd, *J*=5.9, 0.9 Hz, 1H), 8.56 (s, 1H), 8.95 (d, *J*=6.0 Hz, 1H), 10.13 ppm (d, *J*=0.8 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.86 min, m/z 247.1 [M+H]$^+$.



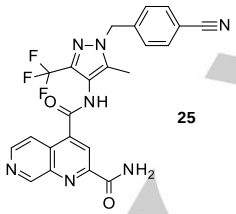
24d

1,6-Naphthyridine-2,4-dicarboxylic acid (24d): Prepared according to general procedure 5 from ethyl {4-[(2,2-dimethylpropanoyl)amino]pyridin-3-yl}(oxo)acetate (4.86 g, 17.46 mmol, **24e**) and 2-oxopropanoic acid (2.69 g, 30.56 mmol, CAS-RN 127-17-3). Yield: 2.62 g, (69%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=8.13 (dd, *J*=5.8, 0.8 Hz, 1H), 8.53 (s, 1H), 8.90 (d, *J*=5.8 Hz, 1H), 10.19 (s, 1H), 14.12 ppm (br s, 2H); LC-MS (ESI+, method 1): R_t=0.18 min, m/z 219.0 [M+H]$^+$.



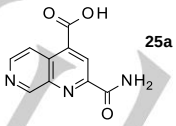
24e

Ethyl {4-[(2,2-dimethylpropanoyl)amino]pyridin-3-yl}(oxo)acetate (24e): 2,2-dimethyl-*N*-(pyridin-4-yl)propanamide (9.00 g, 50.50 mmol, CAS-RN 70298-89-4) was dissolved in THF (135 mL) and cooled to -78°C. *n*-Butyllithium (79 mL, 126.24 mmol) was added dropwise and strrring was continued for 3 h at -10°C. The solution was recooled to -78°C before addition of diethyl oxalate (17.56 mL, 129.77 mmol) in THF (5 mL). After 15 min at -78°C stirring was continued for 1 h at 25°C. The reaction mixture was poured cautiously into ice water and extracted for 2 times with 55 mL of ethyl acetate. After drying over sodium sulfate, filtration and evaporation the crude product was purified by flash column chromatography to yield 6.16 g (42%) of the desired ethyl {4-[(2,2-dimethylpropanoyl)amino]pyridin-3-yl}(oxo)acetate: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.22 (s, 9H), 1.29 (t, *J*=7.2 Hz, 3H), 4.34 (q, *J*=7.2 Hz, 2H), 8.04 (d, *J*=5.6 Hz, 1H), 8.67 (d, *J*=5.6 Hz, 1H), 8.80 (s, 1H), 10.70 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=0.95 min, m/z 279.0 $[M+H]^+$.



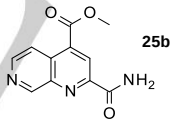
25

***N*^{4}-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-1,7-naphthyridine-2,4-dicarboxamide (25)**: Prepared according to general procedure 9B from 2-carbamoyl-1,7-naphthyridine-4-carboxylic acid (250.0 mg, 1.15 mmol, **25a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (387.1 mg, 1.38 mmol, **65)**. Yield: 15.0 mg (2.7%): ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.30 (s, 3H), 5.47 (s, 2H), 5.80 (br d, *J*=3.3 Hz, 1H), 7.31 (d, *J*=8.4 Hz, 2H), 7.68-7.75 (m, 3H), 8.01 (br d, *J*=3.0 Hz, 1H), 8.29 (dd, *J*=5.8, 0.8 Hz, 1H), 8.75 (s, 1H), 8.83 (d, *J*=5.8 Hz, 1H), 9.64 ppm (d, *J*=1.0 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.95 min, m/z 480.1 $[M+H]^+$.



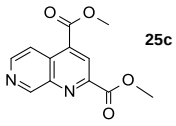
25a

2-Carbamoyl-1,7-naphthyridine-4-carboxylic acid (25a): Prepared according to general procedure 8 from methyl 2-carbamoyl-1,7-naphthyridine-4-carboxylate (390 mg, 1.69 mmol, **25b**). Yield: 0.25 g, (68%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=7.99 (br s, 1H), 8.47 (br s, 1H), 8.65-8.74 (m, 2H), 8.78 (dd, *J*=6.0, 3.0 Hz, 1H), 9.56 (dd, *J*=13.4, 0.8 Hz, 1H), 13.95 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=0.42 min, m/z 218.0 $[M+H]^+$.



25b

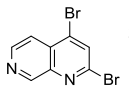
Methyl 2-carbamoyl-1,7-naphthyridine-4-carboxylate (25b): Prepared according to general procedure 7 from dimethyl 1,7-naphthyridine-2,4-dicarboxylate (500 mg, 2.03 mmol, **25c**). Yield: 0.39 g (83%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=4.02 (s, 3H), 8.03 (br s, 1H), 8.50 (br s, 1H), 8.61 (dd, *J*=5.9, 0.9 Hz, 1H), 8.75 (s, 1H), 8.81 (d, *J*=6.0 Hz, 1H), 9.55 ppm (d, *J*=0.8 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.67 min, m/z 232.1 $[M+H]^+$.



25c

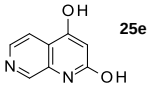
Dimethyl 1,7-naphthyridine-2,4-dicarboxylate (25c): 2,4-dibromo-1,7-naphthyridine (693 mg, 2.41 mmol, **25d**) was suspended in methanol (20 mL) in an autoclave and di(1-adamantyl)-*n*-butylphosphine (43.1 mg, 120 µmol), palladium(II) acetate (27.0 mg, 120 µmol) and triethylamine (1.01 mL, 7.22 mmol) were added. The autoclave was purged 3 times with carbon monoxide and put to a carbon monoxide pressure of 215 psi. After stirring for 30 min at 25°C the autoclave was evaporated and filled again with carbon monoxide to a pressure of 194 psi. Under this pressure the reaction mixture was stirred at 80°C for 16 h and afterwards filtrated and evaporated. The crude product was purified by flash column chromatography to yield 500 mg

(84%) of the desired dimethyl 1,7-naphthyridine-2,4-dicarboxylate: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=4.02 (s, 3H), 4.04 (s, 3H), 8.63 (dd, *J*=5.8, 1.0 Hz, 1H), 8.70 (s, 1H), 8.86 (d, *J*=5.8 Hz, 1H), 9.64 ppm (d, *J*=1.0 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.82 min, m/z 246.9 [M+H]$^+$.



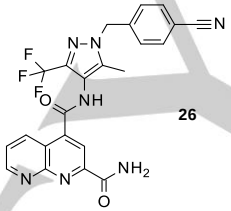
25d

2,4-Dibromo-1,7-naphthyridine (25d): 1,7-naphthyridine-2,4-diol (1.22 g, 7.52 mmol, **25e**) was suspended in 1-butyl-1-methylpyrrolidinium trifluoromethansulfonate (15.8 mL) and phosphorus oxybromide (7.11 g, 24.81 mmol) was added. The reaction mixture was stirred at 85°C for 16 h and poured into ice cold 50% sodium hydroxide solution. The precipitate was filtered off and dried. The crude product was resuspended in methanol and after stirring for 1 h again filtrated and dried to yield 690 mg (30%) of the desired 2,4-dibromo-1,7-naphthyridine: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=7.98 (dd, *J*=5.8, 0.6 Hz, 1H), 8.50 (s, 1H), 8.80 (d, *J*=5.7 Hz, 1H), 9.38 (d, *J*=0.6 1H); LC-MS (ESI+, method 1): R_t=1.07 min, m/z 286.9 [M+H]$^+$.



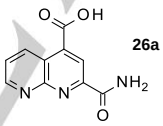
25e

1,7-Naphthyridine-2,4-diol (25e): methyl 3-aminoisonicotinate (2.50 g, 16.43 mmol, CAS-RN 55279-30-6) was dissolved in ethyl acetate (16 mL) and potassium *tert*-butoxide (3.69 g, 32.86 mmol) was added slowly. The reaction mixture was stirred for 18 h at 75°C. Afterwards water (50 mL) was poured into the reaction mixture and after phase separation the aqueous layer was extracted with ethyl acetate. The aqueous layer was acidified to pH = 6 with 2 N HCl solution. The resulting precipitate was filtered off and dried to yield 550 mg (21%) of the desired 1,7-naphthyridine-2,4-diol: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=5.89 (s, 1H), 7.65 dd, *J*=5.2, 0.5 Hz,1H), 8.29 (d, *J*=5.3 Hz, 1H), 8.61 (d, *J*=0.5 Hz, 1H), 11.43 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=0.42 min, m/z 163.0 [M+H]$^+$.



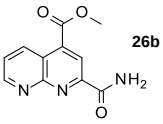
26

***N*^{4}-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-1,8-naphthyridine-2,4-dicarboxamide (26)**: Prepared according to general procedure 9B from 2-carbamoyl-1,8-naphthyridine-4-carboxylic acid (100.0 mg, 460 µmol, **26a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (154.8 mg, 553 µmol, **65)**. Yield: 17.3 mg (6.5%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.26 (s, 3H), 5.60 (s, 2H), 7.38 (d, *J*=8.6 Hz, 2H), 7.83 (dd, *J*=8.5, 4.2 Hz, 1H), 7.86-7.91 (m, 2H), 7.99 (m, 1H), 8.41 (s, 1H), 8.46 (m, 1H), 8.66 (dd, *J*=8.6, 2.0 Hz, 1H), 9.26 (dd, *J*=4.2, 1.9 Hz, 1H), 10.52 ppm (s, 1H); LC-MS (ESI+, method 2): R_t=0.93 min, m/z 480.2 [M+H]$^+$.



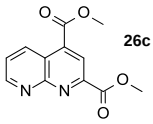
26a

2-Carbamoyl-1,8-naphthyridine-4-carboxylic acid (26a): Prepared according to general procedure 8 from methyl 2-carbamoyl-1,8-naphthyridine-4-carboxylate (1.71 g, 5.92 mmol, **26b**). Crude yield: 1.72 g: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=7.81 (dd, *J*=8.6, 4.3 Hz, 1H), 7.94 (br s, 1H), 8.40 (br s, 1H), 8.60 (s, 1H), 9.21-9.28 (m, 2H), 14.08 ppm (br s, 1H); LC-MS (ESI-, method 1): R_t=0.70 min, m/z 215.9 [M-H]$^-$.

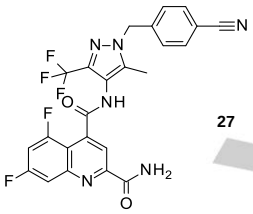


26b

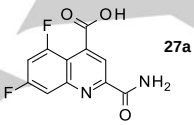
Methyl 2-carbamoyl-1,8-naphthyridine-4-carboxylate (26b): Prepared according to general procedure 7 from dimethyl 1,8-naphthyridine-2,4-dicarboxylate (810 mg, 3.29 mmol, **26c**). Yield: 320 mg (42%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=4.02 (s, 3H), 7.85 (dd, *J*=8.7, 4.1 Hz, 1H), 7.99 (br s, 1H), 8.46 (br s, 1H), 8.63 (s, 1H), 9.18 (dd, *J*=8.7, 1.9 Hz, 1H), 9.26 ppm (dd, *J*=4.1, 1.9 Hz, 1H); LC-MS (ESI+, method 2): R_t=0.67 min, m/z 232.1 [M+H]$^+$.



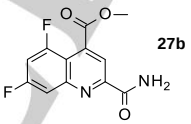
Dimethyl 1,8-naphthyridine-2,4-dicarboxylate (26c): 2,4-Dibromo-1,8-naphthyridine (4.05 g, 13.50 mmol, CAS-RN 54569-27-6) was suspended in a 10:1 mixture of methanol and THF (170 mL) in an autoclave, and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (2.21 g, 2.70 mmol) and triethylamine (2.07 mL, 14.85 mmol) were added. The autoclave was purged 3 times with carbon monoxide and put to a carbon monoxide pressure of 203 psi. After stirring for 30 min at 25°C the autoclave was evaporated and filled again with carbon monoxide to a pressure of 187 psi. Under this pressure the reaction mixture was stirred at 100°C for 22 h and afterwards evaporated. The crude product was purified by flash column chromatography to yield 810 mg (12%) of dimethyl 1,8-naphthyridine-2,4-dicarboxylate: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=4.02 (s, 3H), 4.04 (s, 3H), 7.89 (dd, *J*=8.6, 4.1 Hz, 1H), 8.58 (s, 1H), 9.18 (dd, *J*=8.5, 1.7 Hz, 1H), 9.31 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=0.76 min, m/z 247.0 [M+H]$^+$.



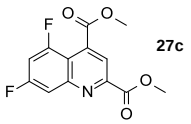
***N*^{4}-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-5,7-difluoroquinoline-2,4-dicarboxamide (27)**: Prepared according to general procedure 9B from 2-carbamoyl-5,7-difluoroquinoline-4-carboxylic acid (130.0 mg, 314 µmol, **27a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (154.8 mg, 553 µmol, **65)**. Yield: 18.3 mg (6.9%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.26 (s, 3H), 5.59 (s, 2H), 7.37 (d, *J*=8.5 Hz, 2H), 7.80-7.91 (m, 4H), 8.01 (br s, 1H), 8.04 (s, 1H), 8.40 (br s, 1H), 10.29 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.06 min, m/z 515.2 [M+H]$^+$.



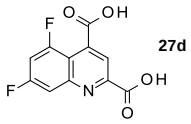
2-Carbamoyl-5,7-difluoroquinoline-4-carboxylic acid (27a): Prepared according to general procedure 8 from methyl 2-carbamoyl-5,7-difluoroquinoline-4-carboxylate (230 mg, 864 µmol, **27b**). Yield: 150 mg (68%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=7.76-7.85 (m, 2H), 7.96 (br s, 1H), 8.07 (s, 1H), 8.34 (br s, 1H), 14.01 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=0.60 min, m/z 253.0 [M+H]$^+$.



Methyl 2-carbamoyl-5,7-difluoroquinoline-4-carboxylate (27b): Prepared according to general procedure 7 from dimethyl 5,7-difluoroquinoline-2,4-dicarboxylate (910 mg, 3.24 mmol, **27c**). Yield: 0.85 g (99%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=3.96 (s, 3H), 7.79-7.91 (m, 2H), 8.00 (br s, 1H), 8.21 (s, 1H), 8.38 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=0.92 min, m/z 267.0 [M+H]$^+$.

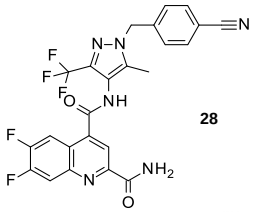


Dimethyl 5,7-difluoroquinoline-2,4-dicarboxylate (27c): Prepared according to general procedure 6 from 5,7-difluoroquinoline-2,4-dicarboxylic acid (850 mg, 3.36 mmol, **27d**). Yield: 0.91 g (96%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=3.96 (s, 3H), 3.97 (s, 3H), 7.91 (ddd, *J*=11.6, 9.3, 2.5 Hz, 1H), 8.00 (ddd, *J*=9.6, 2.4, 1.4 Hz, 1H), 8.24 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.04 min, m/z 282.1 [M+H]$^+$.



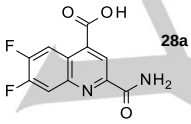
27d

5,7-Difluoroquinoline-2,4-dicarboxylic acid (27d): Prepared according to general procedure 5 from 4,6-difluoro-1*H*-indole-2,3-dione (1.85 g, 10.10 mmol, CAS-RN 126674-93-9) and 2-oxopropanoic acid (1.56 g, 17.68 mmol, CAS-RN 127-17-3). Yield: 0.85 g (33%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=7.74 (ddd, *J*=11.1, 9.4, 2.5 Hz, 1H), 7.85 (ddd, *J*=9.8, 2.3, 1.3 Hz, 1H), 7.91 ppm (s, 1H), 14.25 (br s, 2H); LC-MS (ESI+, method 1): *R*$_t$=0.54 min, m/z 254.0 [M+H]$^+$.



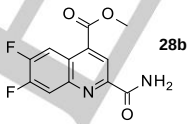
28

***N*^{4}-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-6,7-difluoroquinoline-2,4-dicarboxamide (28)**: Prepared according to general procedure 9B from 2-carbamoyl-6,7-difluoroquinoline-4-carboxylic acid (100.0 mg, 397 µmol, **28a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (133.4 mg, 476 µmol, **65)**. Yield: 20.2 mg (10%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.26 (s, 3H), 5.60 (s, 2H), 7.38 (d, *J*=8.3 Hz, 2H), 7.86-792 (m, 2H), 7.96-8.02 (m, 1H), 8.16 (dt, *J*=11.5, 8.6 Hz, 2H), 8.35-8.41 (m, 2H), 10.54 ppm (s, 1H); LC-MS (ESI+, method 1): *R*$_t$=1.16 min, m/z 515.3 [M+H]$^+$.



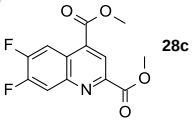
28a

2-Carbamoyl-6,7-difluoroquinoline-4-carboxylic acid (28a): Prepared according to general procedure 8 from methyl 2-carbamoyl-6,7-difluoroquinoline-4-carboxylate (720.0 mg, 2.71 mmol, **28b**). Yield: 570 mg (84%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=7.94 (br s, 1H), 8.13 (dd, *J*=11.2, 8.2 Hz, 1H), 8.32 (br s, 1H), 8.56 (s, 1H), 8.80 ppm (dd, *J*=12.7, 9.1 Hz, 1H); LC-MS (ESI+, method 1): *R*$_t$=0.82 min, m/z 253.0 [M+H]$^+$.



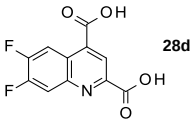
28b

Methyl 2-carbamoyl-6,7-difluoroquinoline-4-carboxylate (28b): Prepared according to general procedure 7 from dimethyl 6,7-difluoroquinoline-2,4-dicarboxylate (1.00 g, 3.56 mmol, **28c**). Yield: 720 mg (76%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=4.01 (s, 3H), 7.95 (br s, 1H), 8.15 (dd, *J*=11.0, 8.2 Hz, 1H), 8.33 (br s, 1H), 8.56 (s, 1H), 8.69 ppm (dd, *J*=12.6, 8.8 Hz, 1H); LC-MS (ESI+, method 1): *R*$_t$=1.01 min, m/z 267.1 [M+H]$^+$.



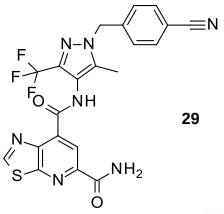
28c

Dimethyl 6,7-difluoroquinoline-2,4-dicarboxylate (28c): Prepared according to general procedure 6 from 6,7-difluoroquinoline-2,4-dicarboxylic acid (6.12 g, 24.17 mmol, **28d**). Yield: 6.12 g (90%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=3.98 (s, 3H), 4.01 (s, 3H), 8.35 (dd, *J*=11.2, 8.2 Hz, 1H), 8.49 (s, 1H), 8.67 ppm (dd, *J*=12.4, 8.8 Hz, 1H); LC-MS (ESI+, method 1): *R*$_t$=1.11 min, m/z 282.1 [M+H]$^+$.



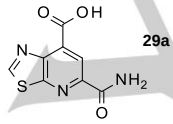
28d

6,7-Difluoroquinoline-2,4-dicarboxylic acid (28d): Prepared according to general procedure 5 from 5,6-difluoro-1*H*-indole-2,3-dione (10.00 g, 54.61 mmol, CAS-RN 774-47-0) and 2-oxopropanoic acid (8.42 g, 95.57 mmol, CAS-RN 127-17-3). Yield: 6.12 g (44%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=8.29 (dd, *J*=11.2, 8.2 Hz, 1H), 8.52 (s, 1H), 8.80 (dd, *J*=12.6, 9.0 Hz, 1H), 13.99 (br s, 2H); LC-MS (ESI+, method 1): *R*$_t$=0.66 min, m/z 254.0 [M+H]$^+$.



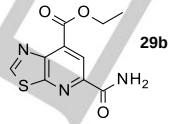
29

***N*^{7}-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl][1,3]thiazolo[5,4-*b*]pyridine-5,7-dicarboxamide (29)**: Prepared according to general procedure 9B from 5-carbamoyl[1,3]thiazolo[5,4-*b*]pyridine-7-carboxylic acid (70 mg, 314 µmol, **29a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (105.5 mg, 376 µmol, **65)**. Yield: 20.7 mg (14%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.23 (s, 3H), 5.62 (s, 2H), 7.38 (d, *J*=8.4 Hz, 2H), 7.87-7.94 (m, 3H), 8.47 (s, 1H), 8.59 (s, 1H), 9.96 (s, 1H), 10.74 ppm (s, 1H); LC-MS (ESI+, method 1): *R*$_t$=1.05 min, m/z 486.1 [M+H]$^+$.



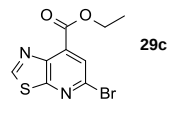
29a

5-Carbamoyl[1,3]thiazolo[5,4-*b*]pyridine-7-carboxylic acid (29a): Prepared according to general procedure 8 from ethyl 5-carbamoyl[1,3]thiazolo[5,4-*b*]pyridine-7-carboxylate (186 mg, 739 µmol, **29b**). Yield: 140 mg (85%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=7.88 (s, 1H), 8.43 (s, 1H), 8.45 (s, 1H), 9.82 (s, 1H), 14.01 (br s, 1H); LC-MS (ESI+, method 1): *R*$_t$=0.45 min, m/z 224.1 [M+H]$^+$.



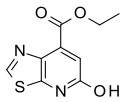
29b

Ethyl 5-carbamoyl[1,3]thiazolo[5,4-*b*]pyridine-7-carboxylate (29b): Ethyl 5-bromo[1,3]thiazolo[5,4-*b*]pyridine-7-carboxylate (740 mg, 2.58 mmol, **29c**) was suspended in THF (2 mL) and a solution of ammonia in dioxane (0.5 M, 20.6 mL, 10.3 mmol) in an autoclave, and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (105 mg, 129 µmol) was added. The autoclave was purged 3 times with carbon monoxide and put to a carbon monoxide pressure of 159 psi. After stirring for 30 min at 25°C the autoclave was evaporated and filled again with carbon monoxide to a pressure of 214 psi. Under this pressure the reaction mixture was stirred at 100°C for 22 h and afterwards evaporated. The crude product was filtered over Celite, concentrated in vacuo, and purified by flash column chromatography to yield 186 mg (29%) of ethyl 5-carbamoyl[1,3]thiazolo[5,4-*b*]pyridine-7-carboxylate: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.39 (t, *J*=7.1 Hz, 3H), 4.47 (q, *J*=7.1 Hz, 2H), 7.90 (br s, 1H), 8.45 (br s, 1H), 8.49 (s, 1H), 9.85 ppm (s, 1H); LC-MS (ESI+, method 1): *R*$_t$=0.68 min, m/z 252.1 [M+H]$^+$.



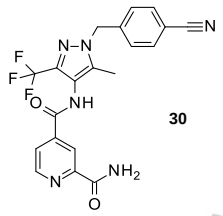
29c

Ethyl 5-bromo[1,3]thiazolo[5,4-*b*]pyridine-7-carboxylate (29c): Ethyl 5-hydroxy[1,3]thiazolo[5,4-*b*]pyridine-7-carboxylate (2.18 g, 8.07 mmol, **29d**) was suspended in acetonitrile (20 mL), and phosphorus oxybromide (4.23 g, 16.14 mmol) was added. The reaction mixture was stirred at reflux for 3 h and then poured cautiously into saturated sodium bicarbonate solution. The aqueous phase was extracted with ethyl acetate. The combined organic layer was extracted with brine, dried over sodium sulfate, filtered and evaporated to obtain a crude product that was purified by flash chromatography to yield 740 mg (27%) of the desired ethyl 5-bromo[1,3]thiazolo[5,4-*b*]pyridine-7-carboxylate: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.37 (t, *J*=7.1 Hz, 3H), 4.44 (q, *J*=7.1 Hz, 2H), 8.08 (s, 1H), 9.70 ppm (s, 1H); LC-MS (ESI+, method 1): *R*$_t$=0.98 min, m/z 287.0 [M+H]$^+$.



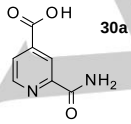
29d

Ethyl 5-hydroxy[1,3]thiazolo[5,4-*b*]pyridine-7-carboxylate (29d): To a solution of 1,3-thiazol-5-amine (5 g, 49.9 mmol, CAS-RN 17721-00-5) in water (18.9 mL), a suspension of sodium 1,4-diethoxy-1,4-dioxobut-2-en-2-olate (10.5 g, 49.9 mmol, CAS-RN 52980-17-3) in water (24.5 mL) was added. The mixture was stirred at 85°C overnight. Then, it was concentrated in vacuo and purified by flash chromatography to yield 4.26 g (38%) of the desired ethyl 5-hydroxy[1,3]thiazolo[5,4-*b*]pyridine-7-carboxylate: ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ=1.36 (t, *J*=7.2 Hz, 3H), 4.41 (q, *J*=7.2 Hz, 2H), 7.06 (s, 1H), 9.25 (s, 1H), 12.05 ppm (br s, 1H); LC-MS (ESI+, method 1): *R*$_t$=0.63 min, m/z 225.2 [M+H]$^+$.



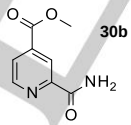
30

***N*^{4}-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]pyridine-2,4-dicarboxamide (30)**: Prepared according to general procedure 9B from 2-carbamoylpyridine-4-carboxylic acid (71.1 mg, 428 µmol, **30a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (100.0 mg, 357 µmol, **65)**. Yield: 6.7 mg (4.4%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.16 (s, 3H), 5.59 (s, 2H), 7.36 (d, *J*=8.4 Hz, 2H), 7.81 (br s, 1H), 7.90 (d, *J*=8.4 Hz, 2H), 8.03 (dd, *J*=5.1, 1.8 Hz, 1H), 8.25 (br s, 1H), 8.54 (s, 1H), 8.85 (d, *J*=5.1 Hz, 1H), 10.39 ppm (s, 1H); LC-MS (ESI+, method 1): *R*$_t$=0.95 min, m/z 429.2 [M+H]$^+$.



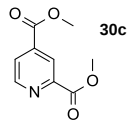
30a

2-Carbamoylpyridine-4-carboxylic acid (30a): Prepared according to general procedure 8 from methyl 2-carbamoylpyridine-4-carboxylate (780.0 mg, 4.33 mmol, **30b**). Yield: 327 mg (46%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=7.52 (br s, 1H), 7.81 (dd, *J*=4.8, 1.5 Hz, 1H), 8.03 (br s, 1H), 8.34 (dd, *J*=1.5, 0.8 Hz, 1H), 8.52 ppm (dd, *J*=4.8, 0.8 Hz, 1H); LC-MS (ESI+, method 1): *R*$_t$=0.45 min, m/z 166.9 [M+H]$^+$.



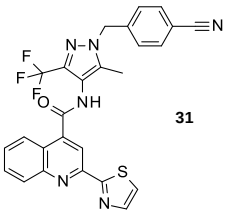
30b

Methyl 2-carbamoylpyridine-4-carboxylate (30b): Prepared according to general procedure 7 from dimethyl pyridine-2,4-dicarboxylate (300 mg, 1.54 mmol, **30c**). Yield: 273 mg (99%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=3.92 (s, 3H), 7.79 (br s, 1H), 8.01 (dd, *J*=4.9, 1.6 Hz, 1H), 8.22 (br s, 1H), 8.40-8.44 (m, 1H), 8.84 ppm (dd, *J*=5.1, 0.8 Hz, 1H); LC-MS (ESI+, method 1): *R*$_t$=0.62 min, m/z 181.0 [M+H]$^+$.



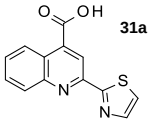
30c

Dimethyl pyridine-2,4-dicarboxylate (30c): Prepared according to general procedure 6 from pyridine-2,4-dicarboxylic acid (5.00 g, 29.92 mmol, CAS-RN 499-80-9). The intermediate dimethyl pyridine-2,4-dicarboxylate hydrochloride (3.65 g, 15.76 mmol) was triturated with satured sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with brine. After drying over sodium sulfate, filtration and evaporation the crude product was dried to yield 3.50 g of the desired dimethyl pyridine-2,4-dicarboxylate as crude product: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=3.93 (s, 3H), 3.94 (s, 3H), 8.09 (dd, *J*=4.9, 1.7 Hz, 1H), 8.40 (dd, *J*=1.7, 0.9 Hz, 1H), 8.95 ppm (dd, *J*=4.8, 0.8 Hz, 1H); LC-MS (ESI+, method 1): *R*$_t$=0.62 min, m/z 196.0 [M+H]$^+$.



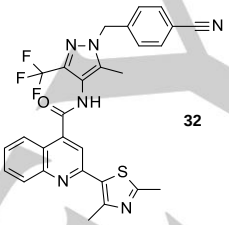
31

***N*-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-2-(1,3-thiazol-2-yl)quinoline-4-carboxamide (31)**: Prepared according to general procedure 9B from 2-(1,3-thiazol-2-yl)quinoline-4-carboxylic acid (236.0 mg, 460 µmol, **31a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (154.9 mg, 553 µmol, **65)**. Yield: 43 mg (15%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.28 (s, 3H), 5.61 (s, 2H), 7.39 (d, *J*=8.6 Hz, 2H), 7.76 (ddd, *J*=8.3, 7.0, 1.1 Hz, 1H), 7.87-7.93 (m, 3H), 8.03 (d, *J*=3.3 Hz, 1H), 8.13 (d, *J*=3.3 Hz, 1H), 8.14-8.19 (m, 2H), 8.41 (s, 1H), 10.47 ppm (s, 1H); LC-MS (ESI+, method 2): R_t=1.29 min, m/z 519.1 [M+H]$^+$.



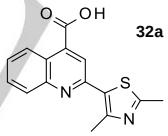
31a

2-(1,3-Thiazol-2-yl)quinoline-4-carboxylic acid (31a): Prepared according to general procedure 5 from 1*H*-indole-2,3-dione (590 mg, 3.93 mmol, CAS-RN 91-56-5) and 1-(1,3-thiazol-2-yl)ethanone (815 µL, 7.86 mmol, CAS-RN 24295-03-2). Crude yield: 1.12 g: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=7.76 (ddd, *J*=8.5, 7.0, 1.3 Hz, 1H), 7.89 (ddd, *J*=8.5, 7.0, 1.3 Hz, 1H), 8.01 (d, *J*=3.3 Hz, 1H), 8.10 (d, *J*=3.0 Hz, 1H), 8.16 (ddd, *J*=8.6, 1.3, 0.5 Hz, 1H), 8.67 (s, 1H), 8.75 ppm (dd, *J*=8.6, 0.8 Hz, 1H); LC-MS (ESI+, method 2): R_t=0.52 min, m/z 257.0 [M+H]$^+$.



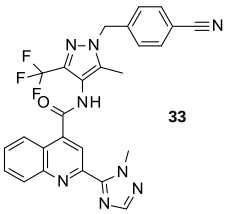
32

***N*-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-2-(2,4-dimethyl-1,3-thiazol-5-yl)quinoline-4-carboxamide (32)**: Prepared according to general procedure 9B from 2-(2,4-dimethyl-1,3-thiazol-5-yl)quinoline-4-carboxylic acid (126.8 mg, 446 µmol, **32a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (150.0 mg, 535 µmol, **65)**. Yield: 67.2 mg (23%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.30 (s, 3H), 2.69 (s, 3H), 2.76 (s, 3H), 5.63 (s, 2H), 7.39 (d, *J*=8.6 Hz, 2H), 7.70 (ddd, *J*=8.4, 7.1, 1.3 Hz, 1H), 7.86 (ddd, *J*=8.4, 6.9, 1.4 Hz, 1H), 7.89-7.93 (m, 2H), 7.95 (s, 1H), 8.05-8.09 (m, 1H), 8.11-8.15 (m, 1H), 10.40 ppm (s, 1H); LC-MS (ESI+, method 2): R_t=1.27 min, m/z 547.1 [M+H]$^+$.



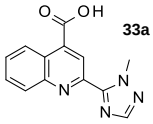
32a

2-(2,4-Dimethyl-1,3-thiazol-5-yl)quinoline-4-carboxylic acid (32a): Prepared according to general procedure 5 from 1*H*-indole-2,3-dione (484 mg, 3.22 mmol, CAS-RN 91-56-5) and 1-(2,4-dimethyl-1,3-thiazol-5-yl)ethanone (870 µL, 6.44 mmol, CAS-RN 38205-60-6). Yield: 0.91 g (99%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.66 (s, 3H), 2.71 (s, 3H), 7.69 (ddd, *J*=8.5, 7.0, 1.3 Hz, 1H), 7.83 (ddd, *J*=8.5, 7.0, 1.5 Hz, 1H), 8.04 (d, *J*=7.8 Hz, 1H), 8.16 (s, 1H), 8.65 (dd, *J*=8.5, 0.9 Hz, 1H), 13.97 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=0.99 min, m/z 285.0 [M+H]$^+$.



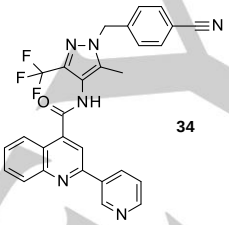
33

***N*-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-2-(1-methyl-1*H*-1,2,4-triazol-5-yl)quinoline-4-carboxamide (33)**: Prepared according to general procedure 9B from 2-(1-methyl-1*H*-1,2,4-triazol-5-yl)quinoline-4-carboxylic acid (86.8 mg, 253 µmol, **33a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (100.0 mg, 303 µmol, **65)**. Yield: 13.0 mg (7.1%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=2.28 (s, 3H), 4.47 (s, 3H), 5.61 (s, 2H), 7.38 (d, *J*=8.5 Hz, 2H), 7.81 (ddd, *J*=8.2, 7.1, 1,1 Hz, 1H), 7.87-7.98 (m, 3H), 8.15-8.21 (m, 2H), 8.25 (d, *J*=8.7 Hz, 1H), 8.37 (s, 1H), 10.49 ppm (s, 1H); LC-MS (ESI+, method 1): *R*$_t$=1.19 min, m/z 517.2 [M+H]$^+$.



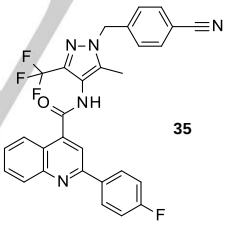
33a

2-(1-Methyl-1*H*-1,2,4-triazol-5-yl)quinoline-4-carboxylic acid (33a): Prepared according to general procedure 5 from 1*H*-indole-2,3-dione (800 mg, 5.33 mmol, CAS-RN 91-56-5) and 1-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethanone (1.00 g, 7.99 mmol, CAS-RN 106535-28-8). Crude yield: 1.81 g: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=4.45 (s, 3H), 7.79 (td, *J*=7.7, 1.3 Hz, 1H), 7.91 (td, *J*=7.6, 1.4 Hz, 1H), 8.14 (s, 1H), 8.22 (d, *J*=8.3 Hz, 1H), 8.61 (s, 1H), 8.77 ppm (dd, *J*=8.6, 1.0 Hz, 1H); LC-MS (ESI+, method 1): *R*$_t$=0.85 min, m/z 255.1 [M+H]$^+$.



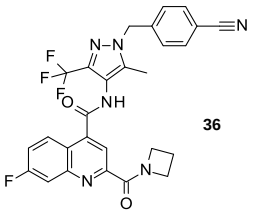
34

***N*-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-2-(pyridin-3-yl)quinoline-4-carboxamide (34)**: Prepared according to general procedure 9B from 2-(pyridin-3-yl)quinoline-4-carboxylic acid (89 mg, 357 µmol, CAS-RN 7482-91-9) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (100.0 mg, 357 µmol, **65)**. Yield: 43.5 mg (24%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.31 (s, 3H), 5.62 (s, 2H), 7.37 (d, *J*=8.6 Hz, 2H), 7.64 (dd, *J*=7.8, 4.8 Hz, 1H), 7.73 (ddd, *J*=8.3, 7.1, 1.3 Hz, 1H), 7.86-7.92 (m, 3H), 8.17 (d, *J*=8.1 Hz, 1H), 8.20 (d, *J*=8.6 Hz, 1H), 8.38 (s, 1H), 8.69 (dt, *J*=8.0, 1.9 Hz, 1H), 8.74 (dd, *J*=4.7, 1.6 Hz, 1H), 9.51 (d, *J*=1.5 Hz, 1H), 10.37 ppm (s, 1H); LC-MS (ESI+, method 1): *R*$_t$=1.13 min, m/z 513.2 [M+H]$^+$.



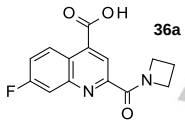
35

***N*-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-2-(4-fluorophenyl)quinoline-4-carboxamide (35)**: Prepared according to general procedure 9B from 2-(4-fluorophenyl)quinoline-4-carboxylic acid (95 mg, 357 µmol, CAS-RN 441-28-1) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (100.0 mg, 357 µmol, **65)**. Yield: 84 mg (44%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=2.30 (s, 3H), 5.62 (s, 2H), 7.34-7.48 (m, 4H), 7.69 (td, *J*=7.7, 1.0 Hz, 1H), 7.82-7.92 (m, 3H), 8.13-8.15 (m, 1H), 8.16-8.18 (m, 1H), 8.27 (s, 1H), 8.35-8.44 (m, 2H), 10.36 ppm (s, 1H); LC-MS (ESI+, method 1): *R*$_t$=1.40 min, m/z 530.2 [M+H]$^+$.



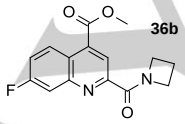
36

2-(Azetidin-1-ylcarbonyl)-*N*-[1-(4-cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-7-fluoroquinoline-4-carboxamide (36): Prepared according to general procedure 9B from 2-(azetidin-1-ylcarbonyl)-7-fluoroquinoline-4-carboxylic acid (96.6 mg, 345 µmol, **36a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (105.0 mg, 287 µmol, **65)**. Yield: 38.2 mg (19%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.25 (s, 3H), 2.29-2.39 (m, 2H), 4.16 (t, *J*=7.7 Hz, 2H), 4.74 (t, *J*=7.7 Hz, 2H), 5.60 (s, 2H), 7.38 (d, *J*=8.3 Hz, 2H), 7.77 (td, *J*=8.9, 2.8 Hz, 1H), 7.86-7.91 (m, 2H), 7.95 (dd, *J*=9.9, 2.6 Hz, 1H), 8.12 (s, 1H), 8.25 (dd, *J*=9.3, 6.0 Hz, 1H), 10.44 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.23 min, m/z 537.2 [M+H]$^+$.



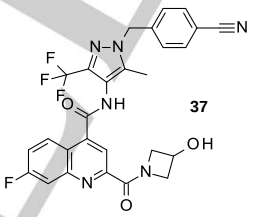
36a

2-(Azetidin-1-ylcarbonyl)-7-fluoroquinoline-4-carboxylic acid (36a): Prepared according to general procedure 8 from methyl 2-(azetidin-1-ylcarbonyl)-7-fluoroquinoline-4-carboxylate (390.0 mg, 1.35 mmol, **36b**). Yield: 0.21 g (57%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.34 (quin, *J*=7.7 Hz, 2H), 4.16 (t, *J*=7.7 Hz, 2H), 4.76 (t, *J*=7.7 Hz, 2H), 7.76 (ddd, J=9.3, 8.4, 2.8 Hz, 1H), 7.93 (dd, *J*=9.9, 2.8 Hz, 1H), 8.35 (s, 1H), 8.87 ppm (dd, *J*=9.5, 6.2 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.91 min, m/z 275.1 [M+H]$^+$.



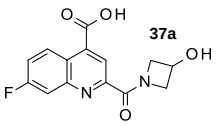
36b

Methyl 2-(azetidin-1-ylcarbonyl)-7-fluoroquinoline-4-carboxylate (36b): Prepared according to general procedure 7 from dimethyl 7-fluoroquinoline-2,4-dicarboxylate (217.0 mg, 3.80 mmol, **68**) and azetidine. Yield: 0.39 g (71%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.35 (quin, *J*=7.7 Hz, 2H), 4.02 (s, 3H), 4.16 (dd, *J*=8.1, 7.4 Hz, 2H), 4.77 (t, *J*=7.7 Hz, 2H), 7.81 (ddd, *J*=9.4, 8.6, 2.8 Hz, 1H), 7.97 (dd, *J*=9.8, 2.7 Hz, 1H), 8.40 (s, 1H), 8.79 ppm (dd, *J*=9.5, 6.2 Hz, 1H); LC-MS (ESI+, method 1): R_t=1.13 min, m/z 289.1 [M+H]$^+$.



37

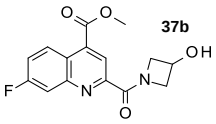
***N*-[1-(4-cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-7-fluoro-2-[(3-hydroxyazetidin-1-yl)carbonyl]quinoline-4-carboxamide (37)**: Prepared according to general procedure 9B from 7-fluoro-2-[(3-hydroxyazetidin-1-yl)carbonyl]quinoline-4-carboxylic acid (220.0 mg, 493 µmol, **37a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (166.0 mg, 591 µmol, **65)**. Yield: 35.8 mg (8.5%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.27 (s, 3H), 3.90 (ddd, *J*=10.8, 4.3, 1.4 Hz, 1H), 4.37 (ddd, *J*=10.7, 6.8, 1.5 Hz, 1H), 4.48 (ddd, *J*=10.8, 4.5, 1.1 Hz, 1H), 4.54-4.62 (m, 1H), 4.92 (ddd, *J*=10.7, 6.5, 1.5 Hz, 1H), 5.62 (s, 2H), 5.82 (d, *J*=6.3 Hz, 1H), 7.39 (d, *J*=8.6 Hz, 2H), 7.79 (ddd, *J*=9.3, 8.5, 2.8 Hz, 1H), 7.87-7.93 (m, 2H), 8.01 (dd, *J*=9.9, 2.8 Hz, 1H), 8.15 (s, 1H), 8.27 (dd, *J*=9.4, 6.1 Hz, 1H), 10.48 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.09 min, m/z 553.2 [M+H]$^+$.



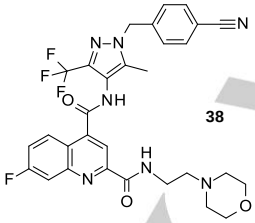
37a

7-Fluoro-2-[(3-hydroxyazetidin-1-yl)carbonyl]quinoline-4-carboxylic acid (37a): Prepared according to general procedure 8 from methyl 7-fluoro-2-[(3-hydroxyazetidin-1-yl)carbonyl]quinoline-4-carboxylate (150.0 mg, 493 µmol, **37b**) using lithium hydroxide as base. Crude yield: 0.22 g: ^{1}H NMR (400

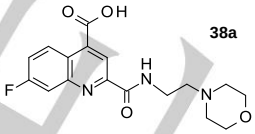
MHz, [D$_6$]DMSO): δ=3.87 (dd, *J*=10.8, 4.2 Hz, 1H), 4.34 (dd, *J*=10.7, 6.8 Hz, 1H), 4.46 (dd, *J*=10.7, 4.1 Hz, 1H), 4.51-4.60 (m, 1H), 4.85-4.94 (m, 1H), 5.80 (br s, 1H), 7.5-7.73 (m, 1H), 7.80-7.91 (m, 1H), 8.13-8.26 m, 1H), 8.87 ppm (dd, *J*=9.0, 6.7 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.71 min, m/z 291.0 [M+H]$^+$.



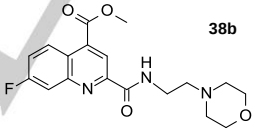
Methyl 7-fluoro-2-[(3-hydroxyazetidin-1-yl)carbonyl]quinoline-4-carboxylate (37b): Prepared according to general procedure 7 from dimethyl 7-fluoroquinoline-2,4-dicarboxylate (750.0 mg, 2.85 mmol, **68**) and azetidin-3-ol hydrochloride (1:1). Yield: 150 mg (17%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=3.89 (ddd, *J*=10.9, 4.3, 1.5 Hz, 1H), 4.01 (s, 3H), 4.36 (ddd, *J*=10.8, 6.8, 1.7 Hz, 1H), 4.49 (ddd, *J*=10.9, 4.6, 1.3 Hz, 1H), 4.53-4.62 (m, 1H), 4.93 (ddd, *J*=10.8, 6.5, 1.7 Hz, 1H), 5.81 (d, *J*=6.3 Hz, 1H), 7.81 (ddd, *J*=9.4, 8.4, 2.8 Hz, 1H), 8.00 (dd, *J*=9.9, 2.5 Hz, 1H), 8.40 (s, 1H), 8.78 ppm (dd, *J*=9.4, 6.1 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.93 min, m/z 305.1 [M+H]$^+$.



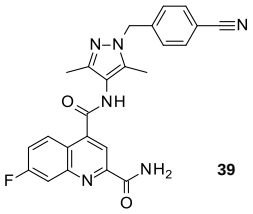
***N*^{4}-[1-(4-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-7-fluoro-*N*^{2}-[2-(morpholin-4-yl)ethyl]quinoline-2,4-dicarboxamide (38)**: Prepared according to general procedure 9B from 7-fluoro-2-{[2-(morpholin-4-yl)ethyl]carbamoyl}quinoline-4-carboxylic acid (125.0 mg, 360 µmol, **38a**) and 4-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (121.0 mg, 432 µmol, **65)**. Yield: 42.6 mg (19%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.28 (s, 3H), 2.43-2.49 (m, 4H), 2.55 (t, *J*=6.8 Hz, 2H), 3.52 (q, *J*=6.6 Hz, 2H), 3.57-3.63 (m, 4H), 5.62 (s, 2H), 7.40 (d, *J*=8.6 Hz, 2H), 7.81 (ddd, *J*=9.4, 8.4, 2.5 Hz, 1H), 7.88-7.93 (m, 2H), 7.95 (dd, *J*=9.9, 2.5 Hz, 1H), 8.28 (s, 1H), 8.30 (dd, *J*=9.4, 6.1 Hz, 1H), 9.00 (t, *J*=6.0 Hz, 1H), 10.50 ppm (s, 1H); LC-MS (ESI+, method 2): R_t=1.20 min, m/z 610.3 [M+H]$^+$.



7-Fluoro-2-{[2-(morpholin-4-yl)ethyl]carbamoyl}quinoline-4-carboxylic acid (38a): Prepared according to general procedure 8 from methyl 7-fluoro-2-{[2-(morpholin-4-yl)ethyl]carbamoyl}quinoline-4-carboxylate (690.0 mg, 1.91 mmol, **38b**). Yield: 0.25 g (38%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.75-2.90 (m, 6H), 3.57-3.62 (m, 2H), 77 3.72 (br t, *J*=4.4 Hz, 4H), 7.65-7.78 (m, 2H), 8.38 (s, 1H), 8.91 (dd, *J*=9.4, 6.3 Hz, 1H), 8.99 ppm (br t, *J*=5.8 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.54 min, m/z 348.0 [M+H]$^+$.

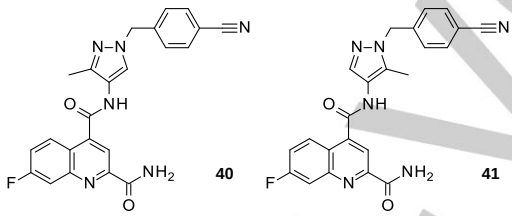


Methyl 7-fluoro-2-{[2-(morpholin-4-yl)ethyl]carbamoyl}quinoline-4-carboxylate (38b): Prepared according to general procedure 7 from dimethyl 7-fluoroquinoline-2,4-dicarboxylate (750.0 mg, 2.85 mmol, **68**) and 2-(morpholin-4-yl)ethanamine. Crude Yield: 0.80 g: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.16-2.23 (m, 8H), 2.42-2.47 (m, 2H), 3.47 (q, *J*=6.5 Hz, 2H), 4.01 (s, 3H), 7.81 (ddd, *J*=9.4, 8.4, 2.8 Hz, 1H), 7.93 (dd, *J*=9.8, 2.5 Hz, 1H), 8.50 (s, 1H), 8.80 (dd, *J*=9.5, 6.0 Hz, 1H), 8.86 ppm (br t, *J*=5.8 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.74 min, m/z 362.0 [M+H]$^+$.



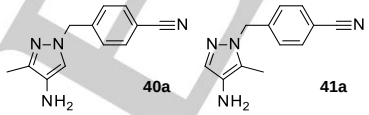
39

***N*⁴-[1-(4-Cyanobenzyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]-7-fluoroquinoline-2,4-dicarboxamide (39)**: Prepared according to general procedure 9B from methyl 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (100.0 mg, 427 µmol, **70**) and 4-[(4-amino-3,5-dimethyl-1*H*-pyrazol-1-yl)methyl]benzonitrile (116 mg, 512 µmol, CAS-RN 1152951-06-8). Yield: 103 mg (55%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=2.14 (s, 3H), 2.17 (s, 3H), 5.37 (s, 2H), 7.31 (d, *J*=8.1 Hz, 2H), 7.77 (td, *J*=9.0, 2.6 Hz, 1H), 7.84 (d, *J*=8.1 Hz, 2H), 7.91 (dd, *J*=10.0, 2.5 Hz, 1H), 7.95 (b, 1H), 8.28 (s, 1H), 8.35 (dd, *J*=9.3, 6.1 Hz, 1H), 8.37 (b, 1H), 10.14 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=0.96 min, m/z 443.2 [M+H]$^+$.



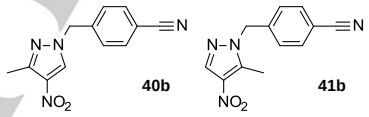
40 **41**

***N*⁴-[1-(4-Cyanobenzyl)-3-methyl-1*H*-pyrazol-4-yl]-7-fluoroquinoline-2,4-dicarboxamide (40)** and ***N*⁴-[1-(4-Cyanobenzyl)-5-methyl-1*H*-pyrazol-4-yl]-7-fluoroquinoline-2,4-dicarboxamide (41)**: Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (250.0 mg, 1.07 mmol, **70**) and a regioisomeric mixture of 4-[(4-amino-3-methyl-1*H*-pyrazol-1-yl)methyl]benzonitrile and 4-[(4-amino-5-methyl-1*H*-pyrazol-1-yl)methyl]benzonitrile (272 mg, 512 µmol, **40a** / **41a**). The regioisomeric products were separated by preparative HPLC to yield 265 mg (58%) of *N*⁴-[1-(4-cyanobenzyl)-3-methyl-1*H*-pyrazol-4-yl]-7-fluoroquinoline-2,4-dicarboxamide (**40**) and 239 mg (52%) of *N*⁴-[1-(4-cyanobenzyl)-5-methyl-1*H*-pyrazol-4-yl]-7-fluoroquinoline-2,4-dicarboxamide (**41**). Compound **40**: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.19 (s, 3H), 5.40 (s, 2H), 7.43 (d, *J*=8.3 Hz, 2H), 7.74 (ddd, *J*=9.3, 8.5, 2.8 Hz, 1H), 7.82-7.86 (m, 2H), 7.89-7.95 (m, 2H), 8.22 (s, 1H), 8.29 (dd, *J*=9.4, 6.2 Hz, 1H), 8.32 (s, 1H), 8.36 (br d, *J*=1.8 Hz, 1H), 10.46 ppm (s, 1H); LC-MS (ESI+, method 2): R_t=0.97 min, m/z 429.1 [M+H]$^+$. Compound **41**: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.21 (s, 3H), 5.44 (s, 2H), 7.30 (d, *J*=8.3 Hz, 2H), 7.73 (ddd, *J*=9.1, 8.8, 2.8 Hz, 1H), 7.81-7.85 (m, 3H), 7.87-7.94 (m, 2H), 8.24 (s, 1H), 8.31-8.38 (m, 2H), 10.36 ppm (s, 1H); LC-MS (ESI+, method 2): R_t=0.94 min, m/z 429.1 [M+H]$^+$.



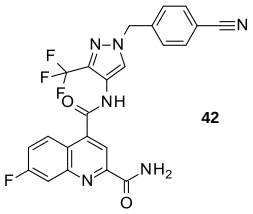
40a **41a**

4-[(4-Amino-3-methyl-1*H*-pyrazol-1-yl)methyl]benzonitrile (40a) / 4-[(4-amino-5-methyl-1*H*-pyrazol-1-yl)methyl]benzonitrile (41a): Prepared according to general procedure 2c from a regioisomeric mixture of 4-[(3-methyl-4-nitro-1*H*-pyrazol-1-yl)methyl]benzonitrile and 4-[(5-methyl-4-nitro-1*H*-pyrazol-1-yl)methyl]benzonitrile (7.27 g, 30.01 mmol, **40b** / **41b**). Yield: 4.42 g (69%) of regioisomeric mixture (55 + 45): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.99 (s, 3H), 3.67 (s, 2H), 5.16/5.26 (s, 1H), 6.98/7.06 (s, 1H), 7.17/7.27 (d, *J*=8.5, 2H), 7.78 (d, J=8.5 Hz, 2H); LC-MS (ESI+, method 1): R_t=0.55 min, m/z 213.1 [M+H]$^+$.



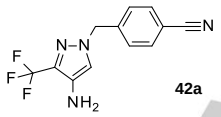
40b **41b**

4-[(3-Methyl-4-nitro-1*H*-pyrazol-1-yl)methyl]benzonitrile (40b) / 4-[(3-methyl-4-nitro-1*H*-pyrazol-1-yl)methyl]benzonitrile (41b): Prepared according to general procedure 2A from 3-methyl-4-nitro-1*H*-pyrazole (5.00 g, 39.34 mmol, CAS-RN 5334-39-4) and 4-(bromomethyl)benzonitrile (9.26 g, 47.2 mmol, **63**, CAS-RN 17201-43-3). Yield: 7.27 g, (76%) of regioisomeric mixture (60 + 40): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.40/2.60 (s, 3H), 5.43/5.56 (s, 2H), 7.37/7.48 (d, *J*=8.6 Hz, 2H), 7.83/7.85 (d, *J*=8.6 Hz, 2H), 8.30/9.00 (s, 1H); LC-MS (ESI+, method 1): R_t=1.01 min, 0.90 min, m/z 243.1 [M+H]$^+$.



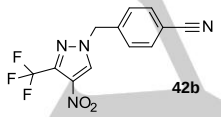
42

***N*⁴-[1-(4-Cyanobenzyl)-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-7-fluoroquinoline-2,4-dicarboxamide (42)**: Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (73.0 mg, 313 µmol, **70**) and 4-{[4-amino-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (100.0 mg, 376 µmol, **42a**). Yield: 42 mg (28%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=5.61 (s, 2H), 7.52 (d, *J*=8.4 Hz, 2H), 7.78 (ddd, *J*=9.1, 8.4, 2.6 Hz, 1H), 7.88-7.95 (m, 3H), 7.97 (br d, *J*=1.8 Hz, 1H), 8.24 (s, 1H), 8.29 (dd, *J*=9.4, 6.1 Hz, 1H), 8.40 (br d, *J*=1.8 Hz, 1H), 8.56 (d, *J*=0.8 Hz, 1H), 10.67 ppm (s, 1H); LC-MS (ESI+, method 1): *R*$_t$=1.12 min, m/z 483.1 [M+H]$^+$.



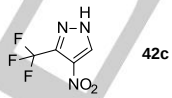
42a

4-{[4-Amino-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (42a): Prepared according to general procedure 3B from 4-{[4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (500 mg, 1.69 mmol, **42b**). Crude yield: 0.50 g: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=4.33 (s, 2H), 5.37 (s, 2H), 7.34-7.44 (m, 3H), 7.83-7.88 ppm (m, 2H); LC-MS (ESI+, method 1): *R*$_t$=0.93 min, m/z 267.1 [M+H]$^+$.



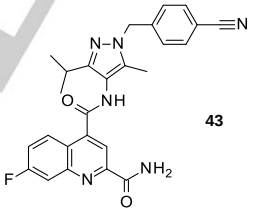
42b

4-{[4-Nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (42b): Prepared according to general procedure 2B from 4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (500 mg, 2.76 mmol, **42c**) and 4-(bromomethyl)benzonitrile (650 mg, 3.31 mmol, **63**, CAS-RN 17201-43-3). Yield: 0.63 g (77%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=5.61 (s, 2H), 7.53 (d, *J*=8.5 Hz, 2H), 7.84-7.90 (m, 2H), 9.34 ppm (d, *J*=0.6 Hz, 1H); LC-MS (ESI+, method 1): *R*$_t$=1.20 min, m/z 297.0 [M+H]$^+$.



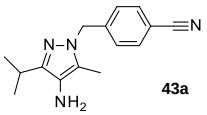
42c

4-Nitro-3-(trifluoromethyl)-1*H*-pyrazole (42c): Prepared according to general procedure 1 from 3-(trifluoromethyl)-1*H*-pyrazole (500 mg, 3.67 mmol, CAS-RN 1087160-38-0). Yield: 0.61 g (92%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=9.17 (s, 1H), 14.73 ppm (br s, 1H); LC-MS (ESI-, method 1): *R*$_t$=0.84 min, m/z 182.0 [M+H]$^+$.



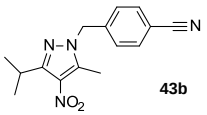
43

***N*⁴-[1-(4-Cyanobenzyl)-3-isopropyl-5-methyl-1*H*-pyrazol-4-yl]-7-fluoroquinoline-2,4-dicarboxamide (43)**: Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (125.0 mg, 534 µmol, **70**) and 4-{[4-amino-5-methyl-3-(propan-2-yl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (162.9 mg, 641 µmol, **43a**). Yield: 80 mg (32%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.23 (d, *J*=6.8 Hz, 6H), 2.13 (s, 3H), 2.98 (sept, *J*=7.0 Hz, 1H), 5.41 (s, 2H), 7.29 (d, *J*=8.6 Hz, 2H), 7.78 (ddd, *J*=9.4, 8.5, 2.6 Hz, 1H), 7.82-7.87 (m, 2H), 7.91 (dd, *J*=10.0, 2.7 Hz, 1H), 7.94 (br d, *J*=1.8 Hz, 1H), 8.25 (s, 1H), 8.31 (dd, *J*=9.4, 6.1 Hz, 1H), 8.37 (d, *J*=2.0 Hz, 1H), 10.07 ppm (s, 1H); LC-MS (ESI+, method 2): *R*$_t$=1.05 min, m/z 471.2 [M+H]$^+$.



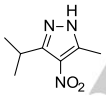
43a

4-{[4-Amino-5-methyl-3-(propan-2-yl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (43a): Prepared according to general procedure 3B from 4-{[5-methyl-4-nitro-3-(propan-2-yl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (2.20 g, 7.81 mmol, **43b**). Crude yield: 2.32 g: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.16 (d, *J*=6.8 Hz, 6H), 1.96 (s, 3H), 2.90 (spt, *J*=6.9 Hz, 1H), 5.21 (s, 2H), 7.14 (d, *J*=8.3 Hz, 2H), 7.77 ppm (d, *J*=8.3 Hz, 2H); LC-MS (ESI+, method 1): R_t=0.73 min, m/z 255.2 [M+H]$^+$.



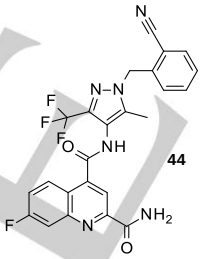
43b

4-{[5-Methyl-4-nitro-3-(propan-2-yl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (43b): Prepared according to general procedure 2B from 5-methyl-4-nitro-3-(propan-2-yl)-1*H*-pyrazole (2.00 g, 11.82 mmol, **43c**) and 4-(bromomethyl)benzonitrile (2.78 g, 14.19 mmol, **63**, CAS-RN 17201-43-3). Yield: 3.22 g (96%) containing ca. 20% of the regioisomer. Compound **43b**: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.21 (d, *J*=7.0 Hz, 6H), 2.53 (s, 3H), 3.47 (sept, *J*=6.8 Hz, 1H), 5.52 (s, 2H), 7.31 (d, *J*=8.5 Hz, 2H), 7.83 ppm (d, *J*=8.5 Hz, 2H); LC-MS (ESI+, method 1): R_t=1.25 min, m/z 285.1 [M+H]$^+$.



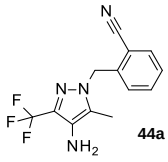
43c

5-Methyl-4-nitro-3-(propan-2-yl)-1*H*-pyrazole (43c): Prepared according to general procedure 1 from 5-methyl-3-(propan-2-yl)-1*H*-pyrazole (1.62 g, 13.01 mmol, CAS-RN 132558-01-1). Yield: 4.48 g (88%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.23 (d, *J*=7.1 Hz, 6H), 2.45 (br s, 3H), 3.50 (br s, 1H), 13.31 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=0.89 min, m/z 170.0 [M+H]$^+$.



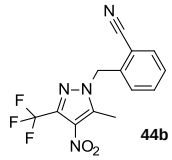
44

***N*^{4}-[1-(2-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-7-fluoroquinoline-2,4-dicarboxamide (44)**: Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (75.0 mg, 320 µmol, **70**) and 2-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (107.7 mg, 384 µmol, **44a**). Yield: 64.7 mg, (41%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.36 (s, 3H), 5.68 (s, 2H), 7.22 (d, *J*=7.6 Hz, 1H), 7.59 (td, *J*=7.7, 1.0 Hz, 1H), 7.75-7.85 (m, 2H), 7.91-7.97 (m, 2H), 7.98 (br d, *J*=1.8 Hz, 1H), 8.28-8.33 (m, 2H), 8.41 (br d, *J*=1.8 Hz, 1H), 10.52 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.12 min, m/z 497.3 [M+H]$^+$.



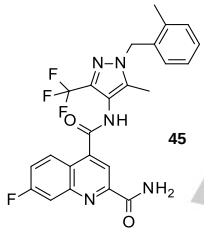
44a

2-{[4-Amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (44a): Prepared according to general procedure 3C from 2-{[5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (2.50 g, 8.06 mmol, **44b**). Yield: 1.97 g (87%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.14 (s, 3H), 4.09 (s, 2H), 5.45 (s, 2H), 6.99 (d, *J*=7.6 Hz, 1H), 7.49-7.56 (m, 1H), 7.70 (td, *J*=7.7, 1.3 Hz, 1H), 7.90 ppm (dd, *J*=7.7, 0.9 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.97 min, m/z 281.1 [M+H]$^+$.



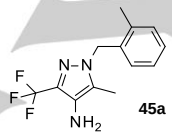
44b

2-{[5-Methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (44b): Prepared according to general procedure 2B from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (2.07 g, 10.62 mmol, CAS-RN 27116-80-9) and 2-(bromomethyl)benzonitrile (2.50 g, 12.75 mmol, CAS-RN 22115-41-9). Yield: 2.50 g (76%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.72 (s, 3H), 5.75 (s, 2H), 7.32 (d, *J*=7.9 Hz, 1H), 7.58 (td, *J*=7.7, 1.1 Hz, 1H), 7.73 (td, *J*=7.7, 1.3 Hz, 1H), 7.94 ppm (dd, *J*=7.9, 1.0 Hz, 1H); LC-MS (ESI+, method 1): R_t=1.19 min, m/z 311.1 [M+H]$^+$.



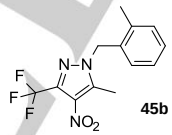
45

7-Fluoro-*N*^{4}-[5-methyl-1-(2-methylbenzyl)-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]quinoline-2,4-dicarboxamide (45): Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (104.4 mg, 446 µmol, **70**) and 5-methyl-1-(2-methylbenzyl)-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (100.0 mg, 371 µmol, **45a**). Yield: 59.5 mg (33%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.25 (s, 3H), 2.36 (s, 3H), 5.50 (s, 2H), 6.70 (d, *J*=7.4 Hz, 1H), 7.17-7.28 (m, 3H), 7.81 (ddd, *J*=9.3, 8.4, 2.8 Hz, 1H), 7.94 (dd, *J*=9.9, 2.5 Hz, 1H), 7.98 (br d, *J*=1.8 Hz, 1H), 8.31 (dd, *J*=9.4, 6.1 Hz, 1H), 8.41 (d, *J*=2.0 Hz, 1H), 10.49 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.20 min, m/z 486.4 [M+H]$^+$.



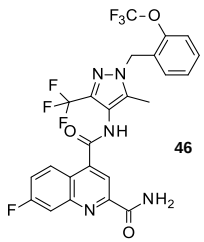
45a

5-Methyl-1-(2-methylbenzyl)-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (45a): Prepared according to general procedure 3B from 5-methyl-1-(2-methylbenzyl)-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (1.70 g, 5.68 mmol, **45b**). Yield: 1.02 g (67%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.04 (s, 3H), 2.28 (s, 3H), 4.02 (br s, 2H), 5.25 (s, 2H), 6.48 (d, *J*=7.5 Hz, 1H), 7.07-7.22 ppm (m, 3H); LC-MS (ESI+, method 2): R_t=1.14 min, m/z 270.2 [M+H]$^+$.



45b

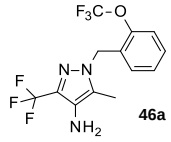
5-Methyl-1-(2-methylbenzyl)-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (45b): Prepared according to general procedure 2A from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (3.16 g, 16.21 mmol, CAS-RN 27116-80-9) and 1-(bromomethyl)-2-methylbenzene (1.81 g, 12.75 mmol, CAS-RN 22115-41-9). Yield: 1.92 g (48%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.31 (s, 3H), 2.61 (s, 3H), 5.53 (s, 2H), 6.74 (d, *J*=7.6 Hz, 1H), 7.12-7.18 (m, 1H), 7.20-7.27 (m, 2H); LC-MS (ESI+, method 2): R_t=1.36 min, m/z 300.1 [M+H]$^+$.



46

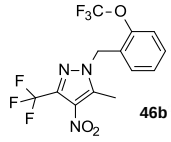
7-Fluoro-*N*^{4}-{5-methyl-1-[2-(trifluoromethoxy)benzyl]-3-(trifluoromethyl)-1*H*-pyrazol-4-yl}quinoline-2,4-dicarboxamide (46): Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (82.8 mg, 354 µmol, **70**) and 5-methyl-1-[2-(trifluoromethoxy)benzyl]-3-

(trifluoromethyl)-1*H*-pyrazol-4-amine and (100.0 mg, 295 µmol, **46a**). Yield: 95 mg (58%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.29 (s, 3H), 5.55 (s, 2H), 7.18 (dd, *J*=9.1, 1.3 Hz, 1H), 7.43-7.49 (m, 2H), 7.53 (ddd, *J*=8.9, 6.6, 1.8 Hz, 1H), 7.81 (ddd, *J*=9.4, 8.4, 2.5 Hz, 1H), 7.94 (dd, *J*=9.9, 2.5 Hz, 1H), 7.99 (br d, *J*=1.8 Hz, 1H), 8.26-8.34 (m, 2H), 8.42 (br d, *J*=1.8 Hz, 1H), 10.50 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.31 min, m/z 556.3 [M+H]$^+$.



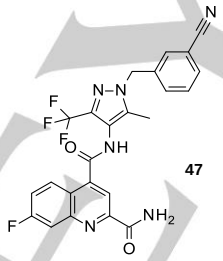
46a

5-Methyl-1-[2-(trifluoromethoxy)benzyl]-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (46a): Prepared according to general procedure 3A from 5-methyl-4-nitro-1-[2-(trifluoromethoxy)benzyl]-3-(trifluoromethyl)-1*H*-pyrazole (4.20 g, 11.38 mmol, **46b**). Yield: 1.86 g (48%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.07 (s, 3H), 4.03 (s, 2H), 5.31 (s, 2H), 6.88 (dd, *J*=7.7, 1.4 Hz, 1H), 7.33-7.50 ppm (m, 3H); LC-MS (ESI+, method 2): R_t=1.25 min, m/z 340.2 [M+H]$^+$.



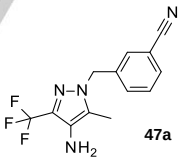
46b

5-Methyl-4-nitro-1-[2-(trifluoromethoxy)benzyl]-3-(trifluoromethyl)-1*H*-pyrazole (46b): Prepared according to general procedure 2A from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (2.78 g, 14.25 mmol, CAS-RN 27116-80-9) and 2-(chloromethyl)phenyl trifluoromethyl ether (2.50 g, 11.87 mmol, CAS-RN 198649-68-2). Yield: 4.03 g (92%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.66 (s, 3H), 5.61 (s, 2H), 7.33 (dd, *J*=7.7, 1.7 Hz, 1H), 7.40-7.47 (m, 2H), 7.50-7.57 ppm (m, 1H); LC-MS (ESI+, method 2): R_t=1.41 min, m/z 370.2 [M+H]$^+$.



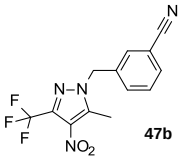
47

***N*^{4}-[1-(3-Cyanobenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-7-fluoroquinoline-2,4-dicarboxamide (47)**: Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (75.0 mg, 320 µmol, **70**) and 3-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (107.7 mg, 384 µmol, **47a**). Yield: 54.7 mg (34%): ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ=2.30 (s, 3H), 5.55 (s, 2H), 7.52-7.56 (m, 1H), 7.63 (t, *J*=7.9 Hz, 1H), 7.72-7.74 (m, 1H), 7.79 (ddd, *J*=9.3, 8.5, 2.7 Hz, 1H), 7.83 (dt, *J*=7.6, 1.4 Hz, 1H), 7.92 (dd, *J*=9.8, 2.5 Hz, 1H), 7.95 (br d, *J*=1.9 Hz, 1H), 8.26 (s, 1H), 8.29 (dd, *J*=9.5, 6.0 Hz, 1H), 8.38 (br d, *J*=1.9 Hz, 1H), 10.46 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.09 min, m/z 497.3 [M+H]$^+$.



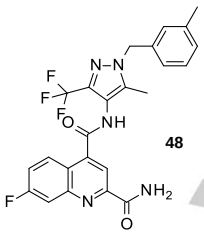
47a

3-{[4-Amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (47a): Prepared according to general procedure 3C from 3-{[5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (3.53 g, 11.38 mmol, **47b**). Yield: 2.89 g (91%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.08 (s, 3H), 4.03 (s, 2H), 5.33 (s, 2H), 7.36-7.39 (m, 1H), 7.54-7.59 (m, 2H), 7.74-7.79 ppm (m, 1H); LC-MS (ESI+, method 1): R_t=0.94 min, m/z 281.1 [M+H]$^+$.



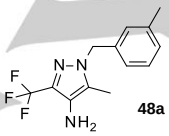
47b

3-{[5-Methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}benzonitrile (47b): Prepared according to general procedure 2A from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (2.49 g, 12.75 mmol, CAS-RN 27116-80-9) and 3-(bromomethyl)benzonitrile (3.00 g, 15.30 mmol, CAS-RN 28188-41-2). Yield: 3.53 g (89%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.67 (s, 3H), 5.63 (s, 2H), 7.58-7.63 (m, 2H), 7.75 (s, 1H), 7.81-7.85 ppm (m, 1H); LC-MS (ESI+, method 1): R_t=1.18 min, m/z 311.1 [M+H]$^+$.



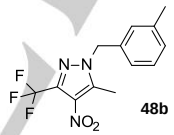
48

7-Fluoro-*N*^{4}-[5-methyl-1-(3-methylbenzyl)-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]quinoline-2,4-dicarboxamide (48): Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (104.4 mg, 446 µmol, **70**) and 5-methyl-1-(3-methylbenzyl)-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (100.0 mg, 371 µmol, **48a**). Yield: 12.3 mg (6.8%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.26 (s, 3H), 2.30 (s, 3H), 5.42 (s, 2H), 7.00 (d, *J*=7.8 Hz, 1H), 7.08 (s, 1H), 7.14 (d, *J*=7.6 Hz, 1H), 7.27 (t, *J*=7.3 Hz, 1H), 7.78 (td, *J*=8.8, 2.5 Hz, 1H), 7.92 (dd, *J*=9.9, 2.5 Hz, 1H), 7.94 (s, 1H), 8.25 (s, 1H), 8.28 (dd, *J*=9.4, 6.3 Hz, 1H), 8.37 (s, 1H), 10.42 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.21 min, m/z 486.3 [M+H]$^+$.



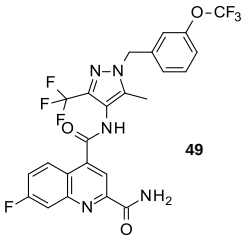
48a

5-Methyl-1-(3-methylbenzyl)-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (48a): Prepared according to general procedure 3B from 5-methyl-1-(3-methylbenzyl)-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (500 mg, 1.67 mmol, **48b**). Yield: 426 mg (95%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.07 (s, 3H), 2.28 (s, 3H), 4.01 (br s, 2H), 5.22 (s, 2H), 6.87 (d, *J*=7.6 Hz, 1H), 6.95 (s, 1H), 7.10 (d, *J*=7.6 Hz, 1H), 7.20-7.26 ppm (m, 1H); LC-MS (ESI+, method 2): R_t=1.15 min, m/z 270.2 [M+H]$^+$.



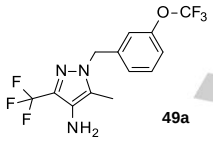
48b

5-Methyl-1-(3-methylbenzyl)-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (48b): Prepared according to general procedure 2A from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (2.85 g, 14.59 mmol, CAS-RN 27116-80-9) and 1-(bromomethyl)-3-methylbenzene (2.25 g, 12.16 mmol, CAS-RN 620-13-3). Yield: 3.50 g (96%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.28 (s, 3H), 2.64 (s, 3H), 5.49 (s, 2H), 7.01 (d, *J*=7.8 Hz, 1H), 7.07 (s, 1H), 7.14 (d, *J*=7.8 Hz, 1H), 7.25 ppm (t, *J*=7.5 Hz, 1H); LC-MS (ESI+, method 2): R_t=1.37 min, m/z 300.1 [M+H]$^+$.



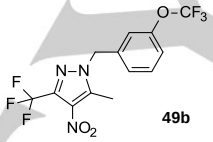
49

7-Fluoro-*N*^{4}-{5-methyl-1-[3-(trifluoromethoxy)benzyl]-3-(trifluoromethyl)-1*H*-pyrazol-4-yl}quinoline-2,4-dicarboxamide (49): Prepared according to general procedure 9B from 2-carbamoyl-5-fluoroquinoline-4-carboxylic acid (82.8 mg, 354 µmol, **70**) and 5-methyl-1-[3-(trifluoromethoxy)benzyl]-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (100.0 mg, 295 µmol, **49a**). Yield: 5.8 mg (3.5%): ^{1}H NMR (400 MHz, [D$_6$]Acetone): δ=2.40 (s, 3H), 5.60 (s, 2H), 7.06 (br s, 1H), 7.26-7.35 (m, 3H), 7.56 (t, *J*=8.0 Hz, 1H), 7.68 (ddd, *J*=9.2, 8.5, 2.7 Hz, 1H), 7.85 (dd, *J*=9.9, 2.5 Hz, 1H), 8.22 (br s, 1H), 8.42 (s, 1H), 8.49 (dd, *J*=9.4, 6.1 Hz, 1H), 9.58 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.35 min, m/z 556.3 $[M+H]^+$.



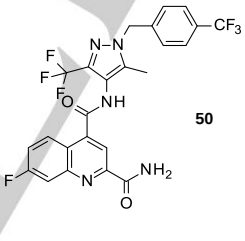
49a

5-Methyl-1-[3-(trifluoromethoxy)benzyl]-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (49a): Prepared according to general procedure 3B from 5-methyl-4-nitro-1-[3-(trifluoromethoxy)benzyl]-3-(trifluoromethyl)-1*H*-pyrazole (2.85 g, 7.72 mmol, **49b**). Yield: 2.39 g (91%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.09 (s, 3H), 4.05 (br s, 2H), 5.34 (s, 2H), 7.08-7.13 (m, 2H), 7.27-7.33 (m, 1H), 7.50 ppm (t, *J*=8.1 Hz, 1H); LC-MS (ESI+, method 2): R_t=1.24 min, m/z 340.3 $[M+H]^+$.



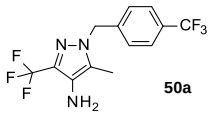
49b

5-Methyl-1-[3-(trifluoromethoxy)benzyl]-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (49b): Prepared according to general procedure 2A from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (2.30 g, 11.76 mmol, CAS-RN 27116-80-9) and 3-(bromomethyl)phenyl trifluoromethyl ether (2.50 g, 9.80 mmol, CAS-RN 159689-88-0). Yield: 2.80 g, (77%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.65 (s, 3H), 5.61 (s, 2H), 7.24 (d, *J*=8.3 Hz, 1H), 7.30-7.37 (m, 2H), 7.52 (t, *J*=7.8 Hz, 1H); LC-MS (ESI+, method 1): R_t=1.44 min, m/z 370.0 $[M+H]^+$.



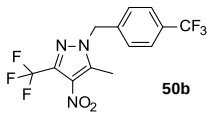
50

7-Fluoro-*N*^{4}-{5-methyl-3-(trifluoromethyl)-1-[4-(trifluoromethyl)benzyl]-1*H*-pyrazol-4-yl}quinoline-2,4-dicarboxamide (50): Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (100.0 mg, 427 µmol, **70**) and 5-methyl-3-(trifluoromethyl)-1-[4-(trifluoromethyl)benzyl]-1*H*-pyrazol-4-amine (165.6 mg, 512 µmol, **50a**). Yield: 123.4 mg (54%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.29 (s, 3H), 5.62 (s, 2H), 7.45 (d, *J*=8.1 Hz, 2H), 7.77-7.84 (m, 3H), 7.94 (dd, *J*=9.9, 2.5 Hz, 1H), 7.98 (br d, *J*=1.8 Hz, 1H), 8.28 (s, 1H), 8.30 (dd, *J*=9.3, 6.2 Hz, 1H), 8.41 (d, *J*=1.8 Hz, 1H), 10.49 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.30 min, m/z 540.3 $[M+H]^+$.



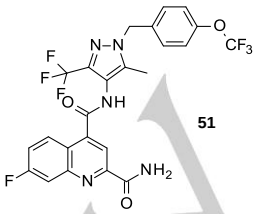
50a

5-Methyl-3-(trifluoromethyl)-1-[4-(trifluoromethyl)benzyl]-1*H*-pyrazol-4-amine (50a): Prepared according to general procedure 3B from 5-methyl-4-nitro-3-(trifluoromethyl)-1-[4-(trifluoromethyl)benzyl]-1*H*-pyrazole (500 mg, 1.42 mmol, **50b**). Yield: 441 mg (96%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.07 (s, 3H), 4.03 (s, 2H), 5.37 (s, 2H), 7.28 (d, *J*=8.1 Hz, 2H), 7.72 ppm (d, *J*=8.1 Hz, 2H); LC-MS (ESI+, method 1): R_t=1.18 min, m/z 324.2 [M+H]$^+$.



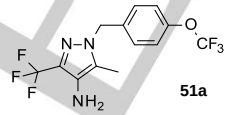
50b

5-Methyl-4-nitro-3-(trifluoromethyl)-1-[4-(trifluoromethyl)benzyl]-1*H*-pyrazole (50b): Prepared according to general procedure 2A from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (3.00 g, 15.38 mmol, CAS-RN 27116-80-9) and 1-(bromomethyl)-4-(trifluoromethyl)benzene (4.41 g, 18.45 mmol, CAS-RN 402-49-3). Yield: 2.80 g (77%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.64 (s, 3H), 5.67 (s, 2H), 7.45 (d, *J*=8.1 Hz, 2H), 7.75 ppm (d, *J*=8.1 Hz, 2H); LC-MS (ESI+, method 1): R_t=1.36 min, m/z 354.1 [M+H]$^+$.



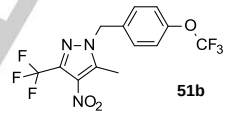
51

7-Fluoro-*N*^{4}-{5-methyl-1-[4-(trifluoromethoxy)benzyl]-3-(trifluoromethyl)-1*H*-pyrazol-4-yl}quinoline-2,4-dicarboxamide (51): Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (82.8 mg, 354 µmol, **70**) and 5-methyl-1-[4-(trifluoromethoxy)benzyl]-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (100.0 mg, 295 µmol, **51a**). Yield: 24.2 mg (15%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.29 (s, 3H), 5.54 (s, 2H), 7.36-7.46 (m, 4H), 7.80 ddd, *J*=9.2, 8.4, 2.5 Hz, 1H), 7.93 (dd, *J*=9.9, 2.5 Hz, 1H), 7.98 (br d, *J*= 1.5 Hz, 1H), 8.27 (s, 1H), 8.30 (dd, *J*=9.4, 6.1 Hz, 1H), 8.41 (d, *J*=1.8 Hz, 1H), 10.47 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.27 min, m/z 556.4 [M+H]$^+$.



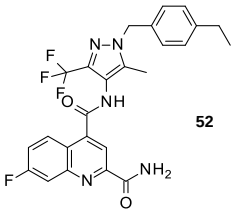
51a

5-Methyl-1-[4-(trifluoromethoxy)benzyl]-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (51a): Prepared according to general procedure 3B from 5-methyl-4-nitro-1-[4-(trifluoromethoxy)benzyl]-3-(trifluoromethyl)-1*H*-pyrazole (1.00 g, 2.71 mmol, **51b**). Yield: 854 mg (93%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.07 (s, 3H), 4.01 (s, 2H), 5.29 (s, 2H), 7.19-7.24 (m, 2H), 7.34 ppm (d, *J*=8.1 Hz, 2H); LC-MS (ESI+, method 2): R_t=1.25 min, m/z 340.2 [M+H]$^+$.



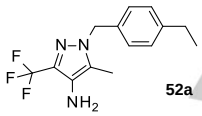
51b

5-Methyl-4-nitro-1-[4-(trifluoromethoxy)benzyl]-3-(trifluoromethyl)-1*H*-pyrazole (51b): Prepared according to general procedure 2A from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (2.30 g, 11.76 mmol, CAS-RN 27116-80-9) and 4-(bromomethyl)phenyl trifluoromethyl ether (2.50 g, 9.80 mmol, CAS-RN 50824-05-0). Yield: 3.08 g (85%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.65 (s, 3H), 5.59 (s, 2H), 7.38 ppm (m, 4H); LC-MS (ESI+, method 2): R_t=1.42 min, m/z 370.2 [M+H]$^+$.



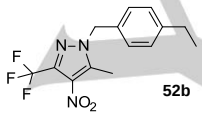
52

***N*⁴-[1-(4-Ethylbenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-7-fluoroquinoline-2,4-dicarboxamide (52)**: Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (75.0 mg, 320 µmol, **70**) and 1-(4-ethylbenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (108.9 mg, 384 µmol, **52a**). Yield: 65.8 mg (41%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.16 (t, *J*=7.6 Hz, 3H), 2.26 (s, 3H), 2.58 (q, *J*=7.6 Hz, 2H), 5.42 (s, 2H), 7.14-7.19 (m, 2H), 7.21-7.25 (m, 2H), 7.78 (ddd, *J*=9.3, 8.4, 2.8 Hz, 1H), 7.92 (dd, *J*=10.0, 2.7 Hz, 1H), 7.95 (br d, *J*=2.0 Hz, 1H), 8.25 (s, 1H), 8.28 (dd, *J*=9.4, 6.1 Hz, 1H), 8.37 (br d, *J*=1.5 Hz, 1H), 10.41 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.28 min, m/z 500.3 [M+H]$^+$.



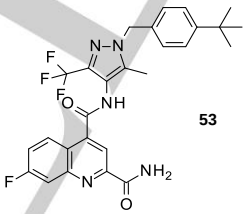
52a

1-(4-Ethylbenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (52a): Prepared according to general procedure 3A from 1-(4-ethylbenzyl)-5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (1.55 g, 4.95 mmol, **52b**). Yield: 1.23 g (88%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.15 (t, *J*=7.6 Hz, 3H), 2.08 (s, 3H), 2.57 (q, *J*=7.6 Hz, 3H), 4.00 (s, 2H), 5.21 (s, 2H), 7.03 (d, *J*=8.1 Hz, 2H), 7.18 ppm (d, *J*=8.4 Hz, 2H); LC-MS (ESI+, method 1): R_t=1.21 min, m/z 284.1 [M+H]$^+$.



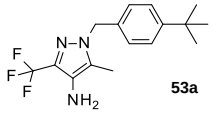
52b

1-(4-Ethylbenzyl)-5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (52b): Prepared according to general procedure 2B from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (1.50 g, 7.69 mmol, CAS-RN 27116-80-9) and 1-(chloromethyl)-4-ethylbenzene (1.43 g, 9.23 mmol, CAS-RN 57825-30-6). Yield: 1.55 g, (64%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.16 (t, *J*=7.6 Hz, 3H), 2.59 (q, *J*=7.6 Hz, 2H), 2.66 (s, 3H), 5.50 (s, 2H), 7.16-7.20 (m, 2H), 7.21-7.25 ppm (m, 2H); LC-MS (ESI+, method 1): R_t=1.42 min, m/z 314.1 [M+H]$^+$.



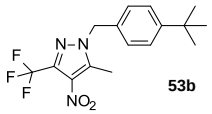
53

***N*⁴-[1-(4-*tert*-Butylbenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]-7-fluoroquinoline-2,4-dicarboxamide (53)**: Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (100.0 mg, 427 µmol, **70**) and 1-(4-*tert*-butylbenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (160.0 mg, 512 µmol, **53a**). Yield: 155 mg (67%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.26 (s, 9H), 2.27 (s, 3H), 5.42 (s, 2H), 7.15-7.22 (m, 2H), 7.38-7.45 (m, 2H), 7.79 (ddd, *J*=9.3, 8.6, 2.7 Hz, 1H), 7.92 (dd, *J*=10.0, 2.6 Hz, 1H), 7.95-8.01 (m, 1H), 8.23-8.31 (m, 2H), 8.37-8.44 (m, 1H), 10.44 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.39 min, m/z 528.2 [M+H]$^+$.



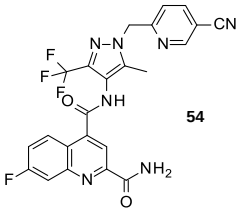
53a

1-(4-*tert*-Butylbenzyl)-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (53a): Prepared according to general procedure 3A from 1-(4-*tert*-butylbenzyl)-5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (1.50 g, 4.39 mmol, **53b**). Yield: 1.29 g (94%): ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=1.24 (s, 9H), 2.07 (s, 3H), 3.99 (s, 2H), 5.19 (s, 2H), 7.03 (d, *J*=8.2 Hz, 2H), 7.35 ppm (d, *J*=8.2 Hz, 2H); LC-MS (ESI+, method 1): R_t=1.34 min, m/z 312.1 [M+H]$^+$.



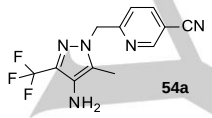
53b

1-(4-*tert*-Butylbenzyl)-5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (53b): Prepared according to general procedure 2B from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (1.17 g, 6.00 mmol, CAS-RN 27116-80-9) and 1-(bromomethyl)-4-*tert*-butylbenzene (1.50 g, 6.60 mmol, CAS-RN 18880-00-7). Yield: 1.59 g (78%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=1.25 (s, 9H), 2.65 (s, 3H), 5.49 (s, 2H), 7.18 (d, *J*=8.3 Hz, 2H), 7.36-7.42 ppm (m, 2H); LC-MS (ESI+, method 1): R_t=1.51 min, m/z 342.1 [M+H]$^+$.



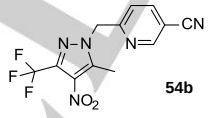
54

***N*^{4}-{1-[(5-Cyanopyridin-2-yl)methyl]-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl}-7-fluoroquinoline-2,4-dicarboxamide (54)**: Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (4.28 g, 18.28 mmol, **70**) and 6-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyridine-3-carbonitrile (6.17 g, 21.94 mmol, **54a**). Yield: 6.76 g (74%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.32 (s, 3H), 5.73 (s, 2H), 7.50 (d, *J*=8.3 Hz, 1H), 7.82 (ddd, *J*=9.2, 8.4, 2.8 Hz, 1H),, 7.94 (dd, *J*=9.8, 2.8 Hz, 1H), 7.99 (br d, *J*=1.8 Hz, 1H), 8.27-8.33 (m, 2H), 8.40 (dd, *J*=8.2, 2.2 Hz, 1H), 8.42 (br d, *J*=1.8 Hz, 1H), 9.02 (dd, *J*=2.0, 0.8 Hz, 1H), 10.50 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.04 min, m/z 498.4 [M+H]$^+$.



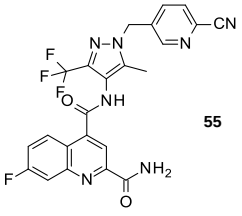
54a

6-{[4-Amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyridine-3-carbonitrile (54a): Prepared according to general procedure 3A from 6-{[5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyridine-3-carbonitrile (9.20 g, 28.38 mmol, **54b**) by using platinum (1 wt. %) / vanadium (2 wt. %) on carbon (0.005 equiv) and hydrogen pressure (73 psi). Yield: 7.54 g (94%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.11 (s, 3H), 4.08 (s, 2H), 5.48 (s, 2H), 7.20 (dd, *J*=8.1, 0.8 Hz, 1H), 8.31 (dd, *J*=8.2, 2.2 Hz, 1H), 8.99 ppm (dd, *J*=2.0, 0.8 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.78 min, m/z 282.1 [M+H]$^+$.



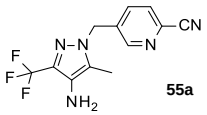
54b

6-{[5-Methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyridine-3-carbonitrile (54b): Prepared according to general procedure 2A from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (5.00 g, 25.63 mmol, CAS-RN 27116-80-9) and 6-(chloromethyl)nicotinonitrile (4.69 g, 30.75 mmol, CAS-RN 158626-15-4). Yield: 5.43 g (68%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.65 (s, 3H), 5.84 (s, 2H), 7.63 (dd, *J*=8.3, 0.6 Hz, 1H), 8.39 (dd, *J*=8.2, 2.2 Hz, 1H), 8.98 ppm (dd, *J*=2.0, 0.8 Hz, 1H); LC-MS (ESI+, method 1): R_t=1.12 min, m/z 312.1 [M+H]$^+$.



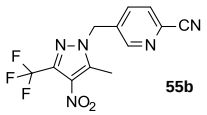
55

***N*^{4}-{1-[(6-Cyanopyridin-3-yl)methyl]-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl}-7-fluoroquinoline-2,4-dicarboxamide (55)**: Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (75.0 mg, 320 µmol, **70**) and 5-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyridine-2-carbonitrile (108.1 mg, 384 µmol, **55a**). Yield: 54.7 mg (34%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.34 (s, 3H), 5.68 (s, 2H), 7.81 (ddd, *J*=9.4, 8.4, 2.5 Hz, 1H), 7.88 (dd, *J*=8.0, 2.2 Hz, 1H), 7.94 (dd, *J*=9.9, 2.5 Hz, 1H), 7.98 (br d, *J*=1.8 Hz, 1H), 8.11 (dd, *J*=8.1, 0.8 Hz, 1H), 8.27-8.33 (m, 2H), 8.41 (br d, *J*=1.8 Hz, 1H), 8.70 (d, *J*=1.5 Hz, 1H), 10.50 ppm (s, 1H); LC-MS (ESI+, method 2): R_t=1.05 min, m/z 498.2 [M+H]$^+$.



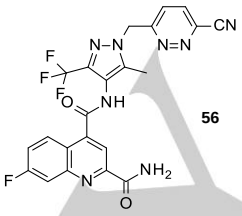
55a

5-{[4-Amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyridine-2-carbonitrile (55a): Prepared according to general procedure 3B from 5-{[5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyridine-2-carbonitrile (2.60 g, 8.35 mmol, **55b**). Yield: 0.67 g (29%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.12 (s, 3H), 4.09 (s, 2H), 5.45 (s, 2H), 7.66 (dd, *J*=8.1, 2.3 Hz, 1H), 8.03 (dd, *J*=7.8, 0.8 Hz, 1H), 8.57 ppm (d, *J*=1.5 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.82 min, m/z 282.1 [M+H]$^+$.



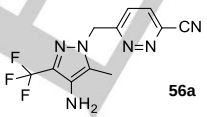
55b

5-{[5-Methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyridine-2-carbonitrile (55b): Prepared according to general procedure 2A from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (2.48 g, 12.69 mmol, CAS-RN 27116-80-9) and 5-(bromomethyl)pyridine-2-carbonitrile (3.00 g, 15.23 mmol, CAS-RN 308846-06-2). Yield: 3.10 g (78%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.69 (s, 3 H), 5.73 (s, 2H), 7.90 (dd, *J*=8.0, 2.2 Hz, 1H), 8.07 (dd, *J*=8.1, 0.5 Hz, 1H), 8.73 ppm (d, *J*=1.5 Hz, 1H); LC-MS (ESI+, method 1): R_t=1.10 min, m/z 312.1 [M+H]$^+$.



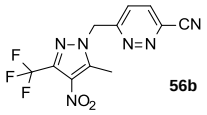
56

***N*^{4}-{1-[(6-Cyanopyridazin-3-yl)methyl]-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl}-7-fluoroquinoline-2,4-dicarboxamide (56)**: Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (22.1 mg, 94 µmol, **70**) and 6-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyridazine-3-carbonitrile (80.0 mg, 113 µmol, **56a**). Yield: 12.5 mg (27%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.36 (s, 3 H), 5.96 (s, 2H), 7.79-7.85 (m, 1H), 7.90-7.96 (m, 2H), 8.00 (br d, *J*=1.8 Hz, 1H), 8.27-8.33 (m, 2H), 8.40-8.45 (m, 2H), 10.53 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.01 min, m/z 499.3 [M+H]$^+$.



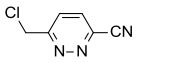
56a

6-{[4-Amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyridazine-3-carbonitrile (56a): Prepared according to general procedure 3C from 6-{[5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyridazine-3-carbonitrile (400.0 mg, 1.28 mmol, **56b**). Crude yield: 400 mg: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.15 (s, 3H), 4.12 (s, 2H), 5.73 (s, 2H), 7.63 (d, *J*=8.9 Hz, 1H), 8.34 ppm (d, *J*=8.6 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.76 min, m/z 283.1 [M+H]$^+$.



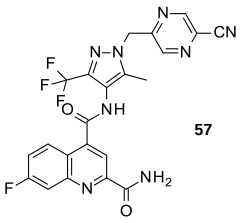
56b

6-{[5-Methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyridazine-3-carbonitrile (56b): Prepared according to general procedure 2A from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (1.68 g, 8.58 mmol, CAS-RN 27116-80-9) and 6-(chloromethyl)pyridazine-3-carbonitrile (2.26 g, 10.30 mmol, **56c**). Yield: 0.63 mg (20%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.69 (s, 3 H), 6.06 (s, 2H), 8.00 (d, *J*=8.9 Hz, 1H), 8.42 ppm (d, *J*=8.6 Hz, 1H); LC-MS (ESI+, method 1): R_t=1.07 min, m/z 313.1 [M+H]$^+$.



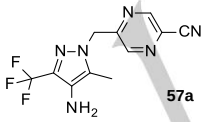
56c

6-(Chloromethyl)pyridazine-3-carbonitrile (56c): 6-methylpyridazine-3-carbonitrile (1.75 g, 14.69 mmol, CAS-RN 49840-90-6) was dissolved in 1,2-dichloroethane (100 mL) and after addition of trichloroisocyanuric acid (1.12 g, 4.85 mmol) the reaction mixture was stirred for 5 h at 90°C. The reaction mixture was evaporated and directly used in the next step.Crude yield: 2.50 g: LC-MS (ESI+, method 1): R_t=0.66 min, m/z 154.0 $[M+H]^+$.



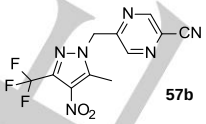
57

***N*⁴-{1-[(5-Cyanopyrazin-2-yl)methyl]-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl}-7-fluoroquinoline-2,4-dicarboxamide (57)**: Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (128.9 mg, 551 µmol, **70**) and 5-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyrazine-2-carbonitrile (259.0 mg, 459 µmol, **57a**). Yield: 22.3 mg (10%): ^{1}H NMR (400 MHz, [D$_6$]Acetone): δ=2.50 (s, 3 H), 5.87 (s, 2H), 7.14 (br s, 1H), 7.71 (ddd, *J*=9.4, 8.4, 2.5 Hz, 1H), 7.87 (dd, *J*=9.8, 2.7 Hz, 1H), 8.28 (br s, 1H), 8.45 (s, 1H), 8.52 (dd, *J*=9.4, 6.1 Hz, 1H), 8.85 (d, *J*=1.3 Hz, 1H), 9.14 (d, *J*=1.5 Hz, 1H), 9.66 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=1.02 min, m/z 499.1 $[M+H]^+$.



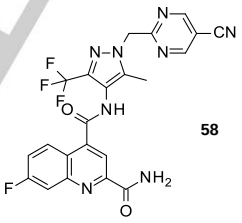
57a

5-{[4-Amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyrazine-2-carbonitrile (57a): Prepared according to general procedure 3B from 5-{[5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyrazine-2-carbonitrile (1.00 g, 3.20 mmol, **57b**). Yield: 259 mg (29%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.14 (s, 3 H), 4.08 (s, 2H), 5.60 (s, 2H), 8.69 (d, *J*=1.5 Hz, 1H), 9.17 ppm (d, *J*=1.5 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.82 min, m/z 283.1 $[M+H]^+$.



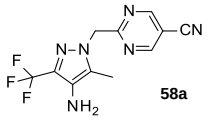
57b

5-{[5-Methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyrazine-2-carbonitrile (57b): Prepared according to general procedure 2A from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (3.05 g, 15.63 mmol, CAS-RN 27116-80-9) and 5-(chloromethyl)pyrazine-2-carbonitrile (2.00 g, 13.02 mmol, CAS-RN 1211526-07-6). Yield: 3.38 g (69%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.65 (s, 3 H), 5.96 (s, 2H), 8.95 (d, *J*=1.4 Hz, 1H), 9.16 ppm (d, *J*=1.4 Hz, 1H); LC-MS (ESI+, method 1): R_t=1.11 min, m/z 313.1 $[M+H]^+$.



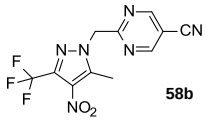
58

***N*⁴-{1-[(5-Cyanopyrimidin-2-yl)methyl]-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl}-7-fluoroquinoline-2,4-dicarboxamide (58)**: Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (100.0 mg, 427 µmol, **70**) and 2-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyrimidine-5-carbonitrile (144.6 mg, 512 µmol, **58a**). Yield: 25.6 mg (12%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.29 (s, 3 H), 5.87 (s, 2H), 7.82 (td, *J*=8.8, 2.7 Hz, 1H), 7.94 (dd, *J*=9.8, 2.7 Hz, 1H), 7.98 (br s, 1H), 8.27-8.34 (m, 2H), 8.41 (br s, 1H), 9.34 (s, 1H), 10.49 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.02 min, m/z 499.3 $[M+H]^+$.



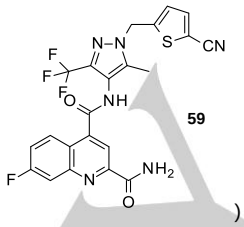
58a

2-{[4-Amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyrimidine-5-carbonitrile (58a): Prepared according to general procedure 3C from 2-{[5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyrimidine-5-carbonitrile (250.0 mg, 801 µmol, **58b**). Yield: 63 mg (27%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.08 (s, 3 H), 4.00 (s, 2H), 5.60 (s, 2H), 9.26 ppm (s, 2H); LC-MS (ESI+, method 1): R_t=0.74 min, m/z 283.1 [M+H]$^+$.



58b

2-{[5-Methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}pyrimidine-5-carbonitrile (58b): Prepared according to general procedure 2A from 3-methyl-4-nitro-5-(trifluoromethyl)-1*H*-pyrazole (2.05 g, 10.52 mmol, CAS-RN 27116-80-9) and 2-(bromomethyl)pyrimidine-5-carbonitrile (2.50 g, 12.62 mmol, CAS-RN 1799764-92-3). Yield: 2.90 g (88%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.61 (s, 3 H), 5.97 (s, 2H), 9.30 ppm (s, 2H); LC-MS (ESI-, method 1): R_t=1.09 min, m/z 313.1 [M+H]$^+$.



59

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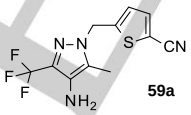
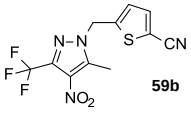
***N*^{4}-{1-[(5-Cyano-2-thienyl)methyl]-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl}-7-fluoroquinoline-2,4-dicarboxamide (59)**: Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (132.9 mg, 482 µmol, **70**) and 5-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}thiophene-2-carbonitrile (255.0 mg, 579 µmol, **59a**). Yield: 29.0 mg (6.5%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.34 (s, 3 H), 5.79 (s, 2H), 7.30 (d, *J*=3.8 Hz, 1H), 7.79 (ddd, J=9.2, 8.5, 7.8 Hz, 1H), 7.88-7.97 (m, 3H), 8.25-8.31 (m, 2H), 8.38 (br d, *J*=1.8 Hz, 1H), 10.46 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.12 min, m/z 503.3 [M+H]$^+$.



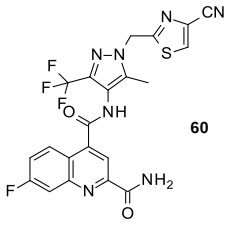
59a

5-{[4-Amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}thiophene-2-carbonitrile (59a): Prepared according to general procedure 3B from 5-{[5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}thiophene-2-carbonitrile (630.0 mg, 1.79 mmol, **59b**). Yield: 514 mg (90%): ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ=2.15 (s, 3H), 4.06 (s, 2H), 5.56 (s, 2H), 7.19 (d, *J*=3.8 Hz, 1H), 7.85 ppm (d, *J*=3.8 Hz, 1H); LC-MS (ESI+, method 1): R_t=0.95 min, m/z 287.1 [M+H]$^+$.



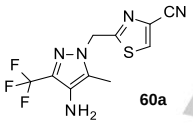
59b

5-{[5-Methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}thiophene-2-carbonitrile (59b): Prepared according to general procedure 2B from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (402.2 mg, 2.06 mmol, CAS-RN 27116-80-9) and 5-(bromomethyl)thiophene-2-carbonitrile (500.0 mg, 2.47 mmol, CAS-RN 134135-41-4). Yield: 630 mg (81%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.71 (s, 3 H), 5.88 (s, 2H), 7.32 (d, *J*=3.8 Hz, 1H), 7.91 ppm (d, *J*=3.8 Hz, 1H); LC-MS (ESI-, method 1): R_t=1.16 min, m/z 315.0 [M-H]$^-$.



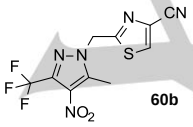
60

***N*⁴-{1-[(5-Cyano-2-thienyl)methyl]-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl}-7-fluoroquinoline-2,4-dicarboxamide (60)**: Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (111.9 mg, 406 µmol, **70**) and 2-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}-1,3-thiazole-4-carbonitrile (280.0 mg, 487 µmol, **60a**). Yield: 19.0 mg (3.9%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.37 (s, 3 H), 5.96 (s, 2H), 7.81 (ddd, *J*=9.2, 8.6, 2.8 Hz, 1H), 7.94 (dd, *J*=9.9, 2.8 Hz, 1H), 7.99 (br s, 1H), 8.27-8.35 (m, 2H), 8.42 (br d, *J*=1.8 Hz, 1H), 8.91 (s, 1H), 10.54 ppm (br s, 1H); LC-MS (ESI+, method 1): R_t=1.06 min, m/z 504.3 [M+H]$^+$.



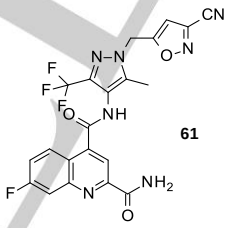
60a

2-{[4-Amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}-1,3-thiazole-4-carbonitrile (60a): Prepared according to general procedure 3B from 2-{[5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}-1,3-thiazole-4-carbonitrile (360.0 mg, 1.08 mmol, **60b**). Yield: 286 mg (88%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.20 (s, 3 H), 4.12 (br s, 2H), 5.72 (br s, 2H), 8.82 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=0.87 min, m/z 288.1 [M+H]$^+$.



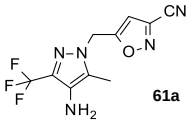
60b

2-{[5-Methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}-1,3-thiazole-4-carbonitrile (60b): Prepared according to general procedure 2B from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (275.4 mg, 1.41 mmol, CAS-RN 27116-80-9) and 2-(bromomethyl)-1,3-thiazole-4-carbonitrile (430.0 mg, 1.69 mmol, CAS-RN 454483-81-9). Yield: 365 mg (81%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.70 (s, 3 H), 6.03 (s, 2H), 8.90 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=1.13 min, m/z 318.1 [M+H]$^+$.



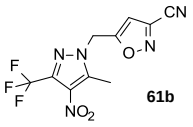
61

***N*⁴-{1-[(3-Cyano-1,2-oxazol-5-yl)methyl]-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl}-7-fluoroquinoline-2,4-dicarboxamide (61)**: Prepared according to general procedure 9B from 2-carbamoyl-7-fluoroquinoline-4-carboxylic acid (32.2 mg, 117 µmol, **70**) and 5-{[4-amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}-1,2-oxazole-3-carbonitrile (38.0 mg, 140 µmol, **61a**). Yield: 10.0 mg (15%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.37 (s, 3 H), 5.89 (s, 2H), 7.37 (s, 1H), 7.79 (ddd, *J*=9.2, 8.6, 2.7 Hz, 1H), 7.90-7.97 (m, 2H), 8.25-8.31 (m, 2H), 8.38 (br d, *J*=1.8 Hz, 1H), 10.49 ppm (s, 1H); LC-MS (ESI+, method 2): R_t=1.09 min, m/z 488.2 [M+H]$^+$.



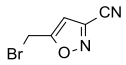
61a

5-{[4-Amino-5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}-1,2-oxazole-3-carbonitrile (61a): Prepared according to general procedure 3B from 5-{[5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}-1,2-oxazole-3-carbonitrile (200.0 mg, 598 µmol, **61b**). Yield: 173 mg (96%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.20 (s, 3 H), 4.11 (s, 2H), 5.66 (s, 2H), 7.23 ppm (s, 1H); LC-MS (ESI+, method 1): R_t=0.93 min, m/z 272.1 [M+H]$^+$.



61b

5-{[5-Methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]methyl}-1,2-oxazole-3-carbonitrile (61b): Prepared according to general procedure 2B from 5-methyl-4-nitro-3-(trifluoromethyl)-1*H*-pyrazole (1.09 g, 5.58 mmol, CAS-RN 27116-80-9) and 5-(bromomethyl)-1,2-oxazole-3-carbonitrile (1.79 g, 6.70 mmol, **61c**). Yield: 1.26 g (75%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=2.71 (s, 3 H), 6.00 (s, 2H), 7.37 ppm (s, 1H); LC-MS (ESI-, method 1): R_t=1.14 min, m/z 300.0 [M-H]$^-$.



61c

5-(Bromomethyl)-1,2-oxazole-3-carbonitrile (61c): 5-methyl-1,2-oxazole-3-carbonitrile (4.00 g, 37.00 mmol, CAS-RN 57351-99-2) was dissolved in tetrachloromethane (48 mL) and *N*-bromosuccinimide (26.34 g, 148.0 mmol) and benzoyl peroxide (1.34 g, 5.55 mmol) were added. The reaction mixture was stirred under reflux for 16 h. The reaction mixture was poured into sodium thiosulfate solution and extracted with methylene chloride. The combined organic layer was washed with sodium thiosulfate solution, dried over sodium sulfate, filtrated and evaporated to yield 6.91 g (100%) of the desired 5-(bromomethyl)-1,2-oxazole-3-carbonitrile ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ=4.94 (s, 2H), 7.33 ppm (s, 1H)