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SUPPLEMENTARY INFORMATION

Structure-based design, synthesis and evaluation *in vitro* of aryl-naphthyridinones, arylpyridopyrimidinones and their tetrahydro derivatives as inhibitors of the tankyrases

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Chemistry experimental

1-Iodo-4-phenylmethoxybenzene (19h). BnBr (389 mg, 4.7 mmol) was added to **19i** (1.00 g, 4.6 mmol) and Cs₂CO₃ (1.50 g, 4.6 mmol) in dry DMF (10 mL) and the mixture was stirred for 90 min. The mixture was diluted with water (10 mL) and extracted thrice with EtOAc. The combined extracts were washed (water, brine). Drying and chromatography (petroleum ether / EtOAc, 99:1) gave **19h** (1.20 g, 82%) as white crystals: mp 59-61°C (lit.¹ mp 56.5-57°C); IR ν_{\max} 1582 cm⁻¹; ¹H NMR (CDCl₃) δ 4.99 (2 H, s, CH₂), 6.76 (2 H, d, *J* = 9.0 Hz, 3,5-H₂), 7.31-7.43 (5 H, m, Ph 2,3,4,5,6-H₅), 7.56 (2 H, d, *J* = 9.0 Hz, 2,6-H₂); ¹³C NMR (CDCl₃) δ 70.06 (CH₂), 83.01 (4-C), 117.29 (2,6-C₂), 127.37 (Ph 3,5-C₂), 128.06 (Ph 4-C), 128.59 (Ph 2,6-C₂), 136.50 (Ph 1-C), 138.21 (3,5-C₂), 158.61 (1-C).

4-Methoxy-1-trimethylsilylethynylbenzene (20c). Et₃N (10 mL) and THF (10 mL) were added to 4-methoxyiodobenzene **19c** (1.05 g, 4.5 mmol), CuI (87 mg, 450 μ mol), (Ph₃P)₂PdCl₂ (158 mg, 225 μ mol) and Na ascorbate (89 mg, 450 μ mol) under Ar. The mixture was stirred at 40°C for 30 min. Me₃SiC \equiv CH (1.03 g, 10.5 mmol) was added and the mixture was stirred at 40°C for 16 h. The evaporation residue, in CH₂Cl₂, was washed (water, 2 \times) and dried. Chromatography (petroleum ether / EtOAc 99:1) gave **20c** (909 mg, 99%) as an oil (lit.² oil): ¹H NMR (CDCl₃) δ 0.23 (9 H, s, SiMe₃), 3.79 (3 H, s, OMe), 6.80 (2 H, d, *J* = 6.8 Hz, 3,5-H₂), 7.40 (2 H, d, *J* = 4.9 Hz, 2,6-H₂); ¹³C NMR (CDCl₃) δ -0.002 (SiMe₃), 55.17 (OMe), 92.34 (ethyne 1-C), 105.15 (ethyne 2-C), 113.75 (2,6-C₂), 115.25 (4-C), 133.39 (3,5-C₂), 159.70 (1-C); MS *m/z* 205.1037 (M + H)⁺ (C₁₂H₁₇OSi requires 205.1049).

4-Trifluoromethyl-1-trimethylsilylethynylbenzene (20d). 4-Trifluoromethyl-1-iodobenzene **19d** was treated with CuI, (Ph₃P)₂PdCl₂, Na ascorbate and Me₃SiC \equiv CH in THF and Et₃N, as for the synthesis of **20c**, to give **20d** (92%) as a colourless oil (lit.³ oil): IR ν_{\max} 2161, 2063, 1614, 1511, 1323 cm⁻¹; ¹H NMR (CDCl₃) δ 0.27 (9 H, s, SiMe₃), 7.54 (4 H, s, 2,3,5,6-H₄); ¹³C NMR (CDCl₃) δ -0.02 (SiMe₃), 88.07 (ethyne 2-C), 97.13 (ethyne 1-C), 123.90 (q, *J* = 272 Hz, CF₃), 125.13 (q, *J* = 3.9 Hz, 3,5-C₂), 126.99 (q, *J* = 1.4 Hz, 1-C), 130.19 (q, *J* = 32.7 Hz, 4-C), 132.17 (2,6-C₂); ¹⁹F NMR (CDCl₃) δ -62.94 (s, CF₃).

4-Chloro-1-trimethylsilylethynylbenzene (20e). 4-Chloroiodobenzene **19e** was treated with CuI, (Ph₃P)₂PdCl₂, Na ascorbate and Me₃SiC \equiv CH in THF and Et₃N, as for the synthesis of **20c**, to give **20e** (96%) as a pale buff powder: mp 42-45°C (lit.⁴ mp 43-45°C); IR ν_{\max} 2157, 1643, 1588, 825, 756 cm⁻¹; ¹H NMR (CDCl₃) δ 0.24 (9 H, s, SiMe₃), 7.26 (2 H, d, *J* = 8.8 Hz, 2,6-C₂), 7.37 (2 H, d, *J* = 8.9 Hz, 3,5-C₂); ¹³C NMR (CDCl₃) δ 0.00 (SiMe₃), 95.47 (ethyne 2-C), 121.78 (ethyne 1-C), 115.08 (4-C), 128.65 (2,6-C₂), 133.29 (3,5-C₂), 134.62 (1-C).

1-Amino-4-trimethylsilylethynylbenzene (20g). 4-Iodoaniline **19g** was treated with CuI, (Ph₃P)₂PdCl₂, Na ascorbate and Me₃SiC \equiv CH in THF and Et₃N, as for the synthesis of **20c**, to give **20g** (74%) as an off-white solid: mp 94-98°C (lit.⁵ mp 93-95°C); IR ν_{\max} 3467, 2158, 1622, 1510 cm⁻¹; ¹H NMR (CDCl₃) δ 0.22 (9 H, s, SiMe₃), 3.77 (2 H, br, NH₂), 6.56 (2 H, d, *J* = 8.6 Hz, 2,6-H₂), 7.27 (2 H, d, *J* = 8.2 Hz, 3,5-H₂); ¹³C NMR (CDCl₃) δ -0.002 (SiMe₃), 91.22 (ethyne 2-C), 105.86 (ethyne 1-C), 112.45 (4-C), 114.38 (2,6-C₂), 133.24 (3,5-C₂), 146.63 (1-C).

(4-Phenylmethoxyoxyphenylethynyl)trimethylsilane (20h). Compound **19h** was treated with CuI, (Ph₃P)₂PdCl₂, Na ascorbate and Me₃SiC \equiv CH in THF and Et₃N, as for the synthesis of **20c**, to give **20h** (92%) as a white solid: mp 45-47°C (lit.⁶ mp 50°C); IR ν_{\max} 2157, 1602

cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 0.25 (9 H, s, SiMe_3), 5.06 (2 H, s, CH_2), 6.89 (2 H, d, $J = 6.8$ Hz, 3,5- H_2), 7.25-7.40 (7 H, m, 2,6- H_2 , Ph 2,3,4,5,6- H_5); $^{13}\text{C NMR}$ (CDCl_3) δ -0.002 (SiMe_3), 69.96 (CH_2), 92.50 (ethyne 2-C), 105.09 (ethyne 1-C), 114.71 (3,5- C_2), 115.25 (1-C), 127.39 (Ph 2,6- C_2), 128.01 (Ph 4-C), 128.55 (Ph 3,5- C_2), 133.42 (2,6- C_2), 136.54 (Ph 1-C), 158.87 (4-C).

4-(Trimethylsilylethynyl)pyridine (20l). CuI (95 mg, 0.50 mmol), $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ **3** (174 mg, 0.25 mmol), Na ascorbate (98 mg, 0.50 mmol) and 4-bromopyridine hydrochloride **22** (970 mg, 5.0 mmol) were placed in a flask, which was degassed and filled with Ar. Pr^i_2NH (10 mL) and THF (10 mL) were added. The mixture was stirred at 40°C for 30 min. $\text{Me}_3\text{SiC}\equiv\text{CH}$ (532 mg, 5.0 mmol) was added and the mixture was stirred at 40°C for 10 h. Evaporation and chromatography (petroleum ether / EtOAc 5:1 \rightarrow 3:1) gave **20l** (767 mg, 89%) as a pale buff oil (lit.⁷ yellow liquid); $^1\text{H NMR}$ (CDCl_3) δ 0.27 (9 H, s, SiMe_3), 7.29 (2 H, d, $J = 4.4$ Hz, 3,5- H_2) 8.55 (2 H, d, $J = 4.4$ Hz, 2,6- H_2); $^{13}\text{C NMR}$ (CDCl_3) δ -0.002 (SiMe_3), 100.24 (ethyne 2-C), 102.31 (ethyne 1-C), 126.16 (3,5- C_2), 131.52 (4-C), 150.03 (2,6- C_2).

1-Ethynyl-4-methoxybenzene (21c). Compound **20c** (1.00 g, 4.9 mmol) in THF (100 mL) was stirred with Bu_4NF in THF (1.0 M, 10 mL) for 16 h. Saturated aq. NaHCO_3 was added and the mixture was extracted (Et_2O , 3 \times). Drying and chromatography (petroleum ether / EtOAc 19:1) gave **21c** (595 mg, 92%) as a pale yellow oil (lit.⁸ oil): IR ν_{max} 2158, 1607, 1570, 1507 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 2.98 (1 H, s, $\text{C}\equiv\text{CH}$), 3.80 (3 H, s, Me), 6.83 (2 H, d, $J = 9.5$ Hz, 3,5- H_2), 7.42 (2 H, d, $J = 9.4$ Hz, 2,6- H_2); $^{13}\text{C NMR}$ (CDCl_3) δ 55.20 (OMe), 67.89 (ethyne 2-C), 83.60 (ethyne 1-C), 113.88 (2,6- C_2), 114.14 (4-C), 133.52 (3,5- C_2), 159.90 (1-C).

1-Ethynyl-4-trifluoromethylbenzene (21d). Compound **20d** was treated with Bu_4NF , as for the synthesis of **21c**, to give **21d** (66%) as a colourless oil (lit.⁹ oil): IR ν_{max} 1519, 1323 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 3.18 (1 H, s, $\text{C}\equiv\text{CH}$), 7.58 (4 H, s, 2,3,5,6- H_4), $^{13}\text{C NMR}$ (CDCl_3) δ 79.51 (ethyne 2-C), 82.13 (ethyne 1-C), 123.81 (q, $J = 288$ Hz, CF_3), 125.24 (2,6- C_2), 125.88 (4-C), 130.57 (q, $J = 33$ Hz, 4-C), 132.33 (3,5- C_2); $^{19}\text{F NMR}$ (CDCl_3) δ -62.96 (s, CF_3).

1-Chloro-4-ethynylbenzene (21e). Compound **20e** was treated with Bu_4NF , as for the synthesis of **21c**, to give **21e** (57%) as a pale amber powder: mp $41\text{-}44^\circ\text{C}$ (lit.¹⁰ mp $43\text{-}44.5^\circ\text{C}$): IR ν_{max} 2154, 1645, 1589, 1488, 756 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 3.09 (1 H, s, $\text{C}\equiv\text{CH}$), 7.29 (2 H, d, $J = 8.8$ Hz, 3,5- H_2), 7.41 (2 H, d, $J = 8.9$ Hz, 2,6- H_2); $^{13}\text{C NMR}$ (CDCl_3) δ 78.07 (ethyne 2-C), 85.45 (ethyne 1-C), 120.55 (4-C), 128.61 (3,5- C_2), 133.28 (2,6- C_2), 134.86 (1-C).

1-Amino-4-ethynylbenzene (21g). Compound **20g** (423 mg, 2.2 mmol) in THF (100 mL) was stirred with Bu_4NF in THF (1.0 M, 6.7 mL) for 16 h at 35°C . Saturated aq. NaHCO_3 was added. The mixture was extracted (Et_2O , 3 \times). Drying and chromatography (petroleum ether / EtOAc 1:3) gave **21g** (230 mg, 81%) as a pale green powder: mp $81\text{-}85^\circ\text{C}$ (lit.¹¹ mp $88\text{-}90^\circ\text{C}$): IR ν_{max} 3486, 3388, 2095, 1619, 1513 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 2.95 (1 H, s, $\text{C}\equiv\text{CH}$), 3.79 (2 H, s, NH_2), 6.58 (2 H, d, $J = 7.6$ Hz, 2,6- H_2), 7.28 (2 H, d, $J = 7.7$ Hz, 3,5- H_2); $^{13}\text{C NMR}$ (CDCl_3) δ 74.79 (ethyne 2-C), 84.32 (ethyne 1-C), 111.34 (4-C), 114.52 (2,6- C_2), 133.41 (3,5- C_2), 146.95 (1-C).

4-Ethynylpyridine (21l). Compound **20l** (2.30 g, 13.1 mmol) in THF (30 mL) was stirred at 40°C with Bu_4NF in THF (1.0 M, 30 mL) for 10 h. Sat. aq. NaHCO_3 was added and the mixture was extracted (EtOAc, 3 \times). Drying, evaporation and chromatography (petroleum ether / EtOAc 3:1) gave **21l** (550 mg, 42%) as an off-white powder with a strong unpleasant

odour: mp 51-54°C (lit.¹² 62-63°C); IR ν_{\max} 3378, 1641, 1594 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.28 (1 H, s, $\text{C}\equiv\text{CH}$), 7.33 (2 H, d, $J = 5.8$ Hz, 3,5- H_2), 8.59 (2 H, m, 2,6- H_2); ^{13}C NMR (CDCl_3) δ 60.29 (ethyne 1-C), 80.88 (ethyne 2-C), 126.16 (3,5- C_2), 130.25 (4-C), 149.74 (2,6- C_2).

2-Bromo-3-cyanopyridine (24). 2-Chloro-3-cyanopyridine **23** (3.68 mg, 26 μmol) was boiled under reflux with AcOH (100 mL) for 12 h. The evaporation residue, in THF (80 mL) and H_2O (20 mL), was boiled under reflux for 4 h. Evaporation gave 3-cyanopyridin-2-one (3.12 g, quant.) as white crystals: mp 110-114°C (lit.¹³ 174-175°C); ^1H NMR δ 6.47 (1 H, t, $J = 6.6$ Hz, 5-H), 7.91 (1 H, dd, $J = 6.5, 2.1$ Hz, 4-H), 8.14 (1 H, dd, $J = 7.0, 2.1$ Hz, 6-H), 11.48 (1 H, s, 1-H); ^{13}C NMR δ 105.80 (3-C), 124.05 (5-C), 141.87 (CN), 144.50 (6-H), 150.02 (4-C), 154.20 (2-C); MS m/z 143.0214 ($\text{M} + \text{Na}$)⁺ ($\text{C}_6\text{H}_4\text{N}_2\text{NaO}$ requires 143.0222). Bu_4NBr (8.55 g, 26 μmol) and P_2O_5 (3.67 g, 26 μmol) were heated in PhMe (250 mL) at 80°C for 30 min. The above 3-cyanopyridin-2-one (1.59 g, 13 μmol) was added and the mixture was boiled under reflux for 12 h. The mixture was cooled, poured into cold water and extracted (EtOAc , 2 \times). Drying and evaporation gave **24** (2.24 g, 94%) as off-white crystals: mp 114-118°C (lit.¹⁴ mp 105°C); IR ν_{\max} 2236, 1574, 1550, 1472 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.42 (1 H, dd, $J = 7.7, 4.8$ Hz, 5-H), 8.01 (1 H, dd, $J = 7.8, 2.0$ Hz, 4-H), 8.57 (1 H, dd, $J = 4.9, 2.0$ Hz, 6-H); ^{13}C NMR δ 114.27 (3-C), 115.63 (CN), 122.37 (5-C), 142.53 (4-C), 143.84 (2-C), 152.92 (6-C).

3-Bromopyridine-4-carboxylic acid (31). 3-Bromopyridine **30** (164 mg, 1.0 μmol) was added to LiNPr_2^i in dry THF (1.0 M, 15 mL, 1.5 μmol) and the mixture was stirred at -78°C for 30 min under Ar. Crushed solid CO_2 was added under Ar, and the cooling was removed. The mixture was stirred until reaching 20°C. Water (10 mL) was added. The organic solvents were evaporated. The solution was washed thrice with Et_2O . Aq. HCl (9 M) was added to pH 3. The mixture was stirred for 1 h and extracted (EtOAc , 3 \times). The combined extracts were washed (brine) and dried. Evaporation gave **31** (20 mg, 10%) as white needles: mp 175-176°C (decomp.) (lit.¹⁵ mp 240°C); ^1H NMR δ 7.71 (1 H, d, $J = 4.8$ Hz, 6-H), 8.70 (1 H, d, $J = 4.9$ Hz, 5-H), 8.91 (1 H, s, 2-H) 12.56 (1 H, br, OH); ^{13}C NMR (CDCl_3) δ 117.26 (4-C), 123.77 (6-C), 148.94 (5-C), 152.61 (2-C), 165.00 (C=O), 166.07 (3-C); MS m/z 202 / 200 ($\text{M} - \text{H}$)⁻.

3-Bromopyridine-4-carboxamide (32) and ethyl 3-bromopyridine-4-carboxylate (33). EtO_2CCl (0.58 g, 5.4 μmol) was added dropwise to an ice-cold mixture of **31** (1.00 g, 4.6 μmol), dry THF (15 mL) and dry Et_3N (1.0 mL). The mixture was stirred for 1 h at 0°C, then NH_3 was bubbled through the suspension for 15 min. The mixture was filtered. The solids were washed with hot Me_2CO . The solvent was evaporated from the combined filtrate and washings. Recrystallisation (EtOH) gave **32** as an off-white powder (777 mg, 78%): mp 149-150°C; ^1H NMR (CDCl_3) δ 7.48 (1 H, d, $J = 4.8$ Hz, 5-H), 7.88 (1 H, br, NH), 8.11 (1 H, br, NH), 8.65 (1 H, d, $J = 4.8$ Hz, 6-H), 8.84 (1 H, s, 2-H); ^{13}C NMR (CDCl_3) δ 116.82 (3-C), 122.73 (5-C), 146.02 (4-C), 148.58 (6-C), 151.68 (2-C), 167.03 (C=O); MS m/z 224.9469 ($\text{M} + \text{Na}$)⁺ ($\text{C}_6\text{H}_5^{81}\text{BrN}_2\text{NaO}$ requires 224.9457), 222.9485 ($\text{M} + \text{Na}$)⁺ ($\text{C}_6\text{H}_5^{79}\text{BrN}_2\text{NaO}$ requires 222.9477). Evaporation of the solvent from the mother liquor gave **33** (60 mg, 5%) as a yellow liquid: ^1H NMR (CDCl_3) δ 1.41 (3 H, t, $J = 7.2$ Hz, Me), 4.43 (2 H, q, $J = 7.3$ Hz, CH_2), 7.59 (1 H, d, $J = 4.9$ Hz, 5-H), 8.59 (1 H, d, $J = 4.9$ Hz, 6-H), 8.83 (1 H, s, 2-H); ^{13}C NMR (CDCl_3) δ 14.04 (Me), 62.33 (CH_2), 118.71 (3-C), 124.15 (5-C), 139.34 (4-C), 148.41 (6-C), 153.64 (2-C), 164.47 (C=O); MS m/z 253.9623 ($\text{M} + \text{Na}$)⁺ ($\text{C}_8\text{H}_8^{81}\text{BrNNaO}_2$ requires 253.9611), 251.9638 ($\text{M} + \text{Na}$)⁺ ($\text{C}_8\text{H}_8^{79}\text{BrNNaO}_2$ requires 251.9631), 224.9469 ($\text{M} + \text{H}$)⁺ ($\text{C}_6\text{H}_5^{81}\text{BrN}_2\text{O}$ requires 224.9457), 222.9485 ($\text{M} + \text{H}$)⁺ ($\text{C}_6\text{H}_5^{79}\text{BrN}_2\text{O}$ requires 222.9477).

3-Bromo-4-cyanopyridine (34). Compound **32** (687 mg, 3.4 mmol) was stirred at reflux with POCl₃ (5.0 mL) for 2 h. The mixture was cooled, poured onto ice (100 g) and neutralised with aq. NaOH (5 M, 60 mL). The mixture was extracted Et₂O (2 ×). The combined extracts were washed (sat. aq. NaHCO₃), treated with charcoal and filtered. Evaporation and recrystallisation (petroleum ether) gave **34** as an off-white powder (292 mg, 42%): mp 79-81°C (lit.¹⁶ mp 96.6-98.2°C); ¹H NMR (CDCl₃) δ 7.53 (1 H, d, *J* = 4.9 Hz, 5-H), 8.69 (1 H, d, *J* = 4.9 Hz, 6-H), 8.92 (1 H, s, 2-H); ¹³C NMR (CDCl₃) δ 114.79 (C≡N), 122.14 (4-C), 124.17 (3-C), 126.75 (5-C), 148.76 (6-C), 152.69 (2-C); MS *m/z* 182.9541 (M + H)⁺ (C₆H₄N₂⁷⁹Br requires 182.9552).

1,3-Bis(4-methylphenyl)propane-1,3-dione (37b). NaH (2.00 g, 50 mmol, 60% in oil) was washed free from oil with dry hexane (10 mL) at 0°C under Ar. Dry THF (30 mL) was added, followed by methyl 4-methylbenzoate (3.30 g, 22 mmol) in dry THF (10 mL) and 4-methyl-1-acetylbenzene (2.66 g, 20 mmol) in dry THF (10 mL) at 0°C under Ar. The suspension was stirred under reflux for 16 h. The mixture was cooled and filtered (Celite®). The solid was washed with EtOH (20 mL). The combined filtrates were poured into Et₂O (20 mL) and aq. HCl (1 M, 20 mL). The aq. layer was extracted (Et₂O, 2 ×). The combined extracts were washed (brine, 3 ×) and dried. Evaporation and recrystallisation (EtOH) gave **37b** (2.50 g, 50%) as yellow needles: mp 112-113°C (lit.¹⁷ 117-118°C); ¹H NMR (CDCl₃) (enol) δ 2.46 (6 H, s, 2 × Me), 6.84 (1 H, s, CH), 7.31 (4 H, d, *J* = 8.0 Hz, 2 × Ph 3,5-H₂), 7.91 (4 H, d, *J* = 8.5 Hz, 2 × Ph 2,6-H₂); ¹³C NMR (CDCl₃) δ 21.65 (2 × Me), 92.50 (CH), 127.18 (2 × Ph 2,6-C₂), 129.39 (2 × Ph 3,5-C₂), 132.94 (2 × Ph 1-C), 143.11 (2 × Ph 4-C), 185.50 (C=O, C-OH); MS *m/z* 527.2193 (2 M + Na)⁺ (C₃₄H₃₂NaO₄ requires 527.2188), 275.1055 (M + Na)⁺ (C₁₇H₁₆NaO₂ requires 275.1043).

1,3-Bis(4-methoxyphenyl)propane-1,3-dione (37c). Methyl 4-methoxybenzoate was treated with 4-methoxy-1-acetylbenzene and NaH, as for the synthesis of **37b**, to give **37c** (46%) as an off-white powder: mp 110-111°C (lit.¹⁸ 111.5-113.5°C); ¹H NMR (CDCl₃) (enol form) δ 3.90 (6 H, s, 2 × Me), 6.76 (1 H, s, =CH), 6.99 (4 H, d, *J* = 8.5 Hz, 2 × Ph 3,5-H₂), 8.01 (4 H, d, *J* = 9.0 Hz, 2 × Ph 2,6-H₂); ¹³C NMR (CDCl₃) δ 55.49 (2 × Me), 91.50 (=CH), 113.95 (2 × Ph 3,5-C₂), 128.23 (2 × Ph 1-C), 128.09 (2 × Ph 2,6-C₂), 163.03 (2 × Ph 4-C), 184.63 (C=O, C-OH); MS *m/z* 591.1950 (2 M + Na)⁺ (C₃₄H₃₂NaO₈ requires 591.1984), 307.0933 (M + Na)⁺ (C₁₇H₁₆NaO₄ requires 307.0941).

1,3-Bis(4-trifluoromethylphenyl)propane-1,3-dione (37d). Methyl 4-trifluoromethylbenzoate was treated with 4-trifluoromethyl-1-acetylbenzene and NaH, as for the synthesis of **37b**, to give **37d** (57%) as an off-white powder: mp 116-117°C (lit.¹⁹ 130°C); ¹H NMR (CDCl₃) (enol) δ 6.91 (1 H, s, CH), 7.80 (4 H, s, 2 × Ph 3,5-H₂), 8.12 (4 H, s, 2 × Ph 2,6-H₂); ¹³C NMR (CDCl₃) δ 94.15 (CH), 122.53 (2 × Ph 1-C), 124.66 (q, *J* = 270.8 Hz, 2 × CF₃), 125.81 (q, *J* = 3.5 Hz, 2 × Ph 3,5-C₂), 127.62 (2 × Ph 2,6-C₂), 134.26 (q, *J* = 32.8 Hz, 2 × Ph 4-C), 184.70 (C=O, C-OH); MS *m/z* 383.0495 (M + Na)⁺ (C₁₇H₁₀F₆NaO₂ requires 383.0477).

1,3-Bis(4-chlorophenyl)propane-1,3-dione (37e). Methyl 4-chlorobenzoate was treated with 4-chloro-1-acetylbenzene and NaH, as for the synthesis of **37b**, to give **37e** (68%) as a pale pink plates: mp 130-131°C (lit.²⁰ 158-159°C); ¹H NMR (CDCl₃) (enol) δ 6.70 (1 H, s, CH), 7.40 (4 H, d, *J* = 8.5 Hz, 2 × Ph 3,5-H₂), 7.85 (4 H, d, *J* = 8.5 Hz, 2 × Ph 2,6-H₂); ¹³C NMR (CDCl₃) δ 92.84 (CH), 128.49 (2 × Ph 2,6-C₂), 129.01 (2 × Ph 3,5-C₂), 133.69 (2 × Ph 1-C), 138.87 (2 × Ph 4-C), 184.71 (C=O, C-OH); MS *m/z* 316.9863 (M + Na)⁺ (C₁₅H₁₀³⁵Cl³⁷ClNaO₂ requires 316.9923), 314.9948 (M + Na)⁺ (C₁₅H₁₀³⁵Cl₂NaO₂ requires 314.9950).

1,3-Bis(4-bromophenyl)propane-1,3-dione (37f). Methyl 4-bromobenzoate was treated with 4-bromo-1-acetylbenzene and NaH, as for the synthesis of **37b**, to give **37f** (30%) as an off-white powder: mp 198-200°C (lit.²¹ 197-198.5°C); ¹H NMR (CDCl₃) (enol) δ 6.70 (1 H, s, CH), 7.55 (4 H, d, *J* = 9.0 Hz, 2 × Ph 3,5-H₂), 7.77 (4 H, d, *J* = 8.5 Hz, 2 × Ph 2,6-H₂); ¹³C NMR (CDCl₃) δ 92.50 (CH), 126.80 (2 × Ph 4-C), 128.63 (2 × Ph 2,6-C₂), 131.99 (2 × Ph 3,5-C₂), 134.00 (2 × Ph 1-C), 184.71 (C=O, C-OH); MS *m/z* 406.8946 (M + Na)⁺ (C₁₅H₁₀⁸¹Br₂NaO₂ requires 406.8901), 404.8966 (M + Na)⁺ (C₁₅H₁₀⁷⁹Br⁸¹BrNaO₂ requires 404.8920), 402.8960 (M + Na)⁺ (C₁₅H₁₀⁷⁹Br₂NaO₂).

1,3-Di(pyridin-4-yl)propane-1,3-dione (37l). NaH (1.00 g, 25 mmol, 60% in oil) was washed free from oil with dry hexane (10 mL) at 0°C under Ar. Dry THF (30 mL) was added. Methyl pyridine-4-carboxylate (1.51 g, 11 mmol) in dry THF (10 mL) and 4-acetylpyridine (1.21 g, 10 mmol) in dry THF (10 mL) at 0°C under Ar were added. The suspension was stirred under reflux for 16 h. The cooled mixture was filtered (Celite[®]). The filtrate was poured into Et₂O and water. Aq. HCl (9 M) was added to pH 4. The precipitate was collected and was washed (petroleum ether) to give **37l** (960 mg, 42%) as pale buff needles: mp 158-159°C (lit.²² 156-157°C); ¹H NMR (enol) δ 7.77 (1 H, s, CH), 8.34 (4 H, d, *J* = 5.0 Hz, 2 × pyridine 3,5-H₂), 9.01 (4 H, d, *J* = 5.6 Hz, 2 × pyridine 2,6-H₂); ¹³C NMR δ 97.50 (CH), 121.84 (2 × pyridine 3,5-C₂), 144.00 (2 × pyridine 4-C), 148.68 (2 × pyridine 2,6-C₂), 184.0 (C=O, C-OH); MS *m/z* 227.0826 (M + H)⁺ (C₁₃H₁₁N₂O₂ requires 227.0815).

4-Phenylethynylbenzonitrile (42j). CuI (52 mg, 0.3 mmol), (Ph₃P)₄Pd (162 mg, 0.14 mmol), Na ascorbate (33 mg, 0.16 mmol) and **42f** (500 mg, 2.75 mmol) were placed in a flask, which was degassed and filled with Ar. Pr^{*i*}₂NH (5 mL) and THF (10 mL) were added. The mixture was stirred at 40°C for 30 min. PhC≡CH **21a** (281 mg, 2.75 mmol) was added and the mixture was stirred at 40°C for 16 h. Evaporation and chromatography (petroleum ether / EtOAc 199:1 → 99:1) gave **42j** (480 mg, 87%) as an off-white powder: mp 84-86°C (lit.³ mp 78-79°C); ¹H NMR (CDCl₃) δ 7.33-7.41 (3 H, m, Ph 3,4,5-H₃), 7.50-7.56 (2 H, m, Ph 2,6-H₂), 7.59-7.65 (NCPH 2,3,5,6-H₄); ¹³C NMR (CDCl₃) δ 87.67 (ethyne 1-C), 93.72 (ethyne 2-C), 111.39 (C≡N), 118.53 (NCPH 1-C), 122.15 (Ph 1-C), 128.19 (NCPH 4-C), 128.47 (Ph 3,5-C₂), 129.10 (Ph 4-C), 131.75 (Ph 2,6-C₂), 132.02 (NCPH 2,6-C₂), 132.03 (NCPH 3,5-C₂).

N-Methoxy-4-methylbenzimidamide (43b). 4-Methylbenzonitrile **42b** (234 mg, 2.0 mmol) in MeOH (10 mL) was stirred with MeONH₂.HCl (167 mg, 2.0 mmol) and Na₂CO₃ (212 mg, 2.0 mmol) in water (5 mL) for 24 h. MeONH₂.HCl (83.5 mg, 1.0 mmol) was added and the mixture was stirred for 2 d. The mixture was filtered. The evaporation residue, in CH₂Cl₂, was dried. Evaporation and recrystallisation (CHCl₃ / petroleum ether) gave **43b** (10 mg, 3%) as a white powder: mp 89-91°C (lit.²³ 85°C); ¹H NMR (CD₃OD) δ 2.43 (3 H, s, PhMe), 3.89 (3 H, s, OMe), 7.27 (2 H, d, *J* = 8.2 Hz, Ph 3,5-H₂), 7.59 (2 H, d, *J* = 8.2 Hz, Ph 2,6-H₂); ¹³C NMR (CDCl₃) δ 21.82 (PhMe), 61.39 (OMe), 125.71 (2,6-C₂), 129.28 (3,5-C₂); MS *m/z* 165.1036 (M + H)⁺ (C₉H₁₃N₂O requires 165.1028).

N-Methoxy-4-trifluoromethylbenzimidamide (43d). Compound **42d** (342 mg, 2.0 mmol) in MeOH (5 mL) was added to MeONH₂.HCl (167 mg, 2.0 mmol) and Na₂CO₃ (212 mg, 2.0 mmol) in water (5 mL). The mixture was sonicated at 55°C for 30 min, then stirring continued at 20°C for 20 h. MeONH₂.HCl (83.5 mg, 1.0 mmol) was added and the mixture was stirred at 25°C for 24 h. The mixture was filtered. The evaporation residue, in CH₂Cl₂, was dried. Evaporation and recrystallisation (CHCl₃ / petroleum ether) gave **43d** (85 mg, 20%) as a white powder: mp 92-94°C; ¹H NMR (CD₃OD) δ 3.95 (3 H, s, Me), 7.76 (2 H, d, *J* = 8.7 Hz, Ph 3,5-H₂), 7.90 (2 H, d, *J* = 8.8 Hz, Ph 2,6-H₂), 13.99 (2 H, br, NH₂); ¹³C NMR (CDCl₃) δ

125.61 (3,5-C₂), 127.32 (1-C), 129.24 (2,6-C₂), 139.99 (4-C), 152.72 (C=N); MS *m/z* 219.0730 (M + H)⁺ (C₉H₁₀FN₂O requires 219.0745).

N-Hydroxy-4-methylbenzimidamide (44b). 4-Methylbenzonitrile **42b** (940 mg, 8.0 mmol) in EtOH (30 mL) was added to NH₂OH.HCl (3.34 g, 48 mmol) and NaHCO₃ (2.54 g, 24 mmol) in water (30 mL) and the mixture was boiled under reflux for 3 h. The EtOH was evaporated and the residue was poured into water. The precipitate was collected, washed (water) and dried to give **44b** (940 mg, 78%) as a white powder: mp 138-139°C (lit.²⁴ 136-137°C); ¹H NMR δ 2.37 (3 H, s, Me), 5.77 (2 H, br, NH₂), 7.22 (2H, d, *J* = 8.0 Hz, Ph 3,5-H₂), 7.61 (2 H, d, *J* = 8.0 Hz, Ph 2,6-H₂), 9.55 (1H, s, OH); ¹³C NMR δ 20.78 (Me), 125.24 (2,6-C₂), 128.60 (3,5-C₂), 130.55 (1-C), 138.21 (4-C), 150.74 (C=N); MS *m/z* 151.0888 (M + H)⁺ (C₈H₁₁N₂O requires 151.0871).

N-Hydroxy-4-trifluoromethylbenzimidamide (44d). Compound **44d** was prepared as previously described.²⁵

4-Chloro-N-hydroxybenzimidamide (44e). Compound **44e** was prepared as previously described.²⁵

4-Bromo-N-hydroxybenzimidamide (44f). 4-Bromobenzonitrile **42f** was treated with NH₂OH.HCl and NaHCO₃, as for the synthesis of **44b**, to give **44f** (90%) as a white powder: mp 140-141°C (lit.²⁶ 139-140°C); ¹H NMR δ 5.90 (2 H, br, NH₂), 7.60 (2 H, d, *J* = 8.8 Hz, Ph 3,5-H₂), 7.67 (2 H, d, *J* = 8.8 Hz, Ph 2,6-H₂), 9.77 (1 H, s, OH); ¹³C NMR (HSQC / HMBC) δ 122.06 (4-C), 127.39 (3,5-C₂), 131.02 (2,6-C₂), 132.56 (1-C), 149.97 (C=N); MS *m/z* 216.9792 (M + H)⁺ (C₇H₈⁸¹BrN₂O requires 216.9780), 214.9814 (M + H)⁺ (C₇H₈⁷⁹BrN₂O requires 214.9820).

4-Amino-N-hydroxybenzimidamide (44g). 4-Aminobenzonitrile **42g** (472 mg, 4.0 mmol) in EtOH (15 mL) was added to NH₂OH.HCl (1.67 g, 24 mmol) and NaHCO₃ (1.27 g, 12 mmol) in water (15 mL). The mixture boiled under reflux for 8 h and cooled. The EtOH was evaporated. The residue was poured into water and extracted (EtOAc, 3 ×). The combined extracts were dried. Evaporation gave **44g** (90 mg, 15%) as a white powder: mp 157-158°C (lit.²⁷ 166-168°C); ¹H NMR δ 5.30 (2 H, br, NH₂), 5.62 (2 H, br, NH₂), 6.57 (2 H, d, *J* = 8.6 Hz, Ph 3,5-H₂), 7.38 (2 H, d, *J* = 8.6 Hz, Ph 2,6-H₂), 9.25 (1 H, s, OH); ¹³C NMR (CDCl₃) δ 113.04 (3,5-C₂), 120.36 (1-C), 126.31 (2,6-C₂), 149.57 (4-C), 151.49 (C=N); MS *m/z* 174.0649 (M + Na)⁺ (C₇H₉N₃NaO requires 174.0643), 152.0853 (M + H)⁺ (C₇H₁₀N₃O requires 152.0824).

N-Hydroxy-4-nitrobenzimidamide (44k). 4-Nitrobenzonitrile **42k** was treated with NH₂OH.HCl and NaHCO₃, as for the synthesis of **44b**, to give **44k** (97%) as a white powder: mp 174-176°C (lit.²⁸ 176°C); ¹H NMR δ 4.62 (2 H, br, NH₂), 7.95 (2 H, d, *J* = 8.7 Hz, Ph 2,6-H₂), 8.32 (2 H, d, *J* = 8.7 Hz, Ph 3,5-H₂); ¹³C NMR δ 124.53 (3,5-C₂), 128.19 (2,6-C₂), 137.00 (1-C), 149.00 (4-C), 163.00 (C=N); MS *m/z* 182.0562 (M + H)⁺ (C₇H₈N₃O₃ requires 182.0566).

N-Hydroxypyridine-4-carboximidamide (44l). 4-Cyanopyridine **42l** was treated with NH₂OH.HCl and NaHCO₃, as for the synthesis of **44b**, to give **44l** (83%) as a white powder: mp 181-184°C (lit.²⁹ 178-179°C); ¹H NMR (CDCl₃) δ 6.04 (2 H, br, NH₂), 7.69 (2 H, d, *J* = 4.6 Hz, 3,5-H₂), 8.62 (2 H, d, *J* = 4.8 Hz, 2,6-H₂), 10.08 (1 H, s, OH); ¹³C NMR (CDCl₃) δ 121.9 (3,5-C₂), 143.07 (4-C), 150.37 (2,6-C₂), 152.22 (C=N); MS *m/z* 138.0683 (M + H)⁺ (C₆H₈N₃O requires 138.0667).

4-Methylbenzimidamide (45b). Compound **44b** (150 mg, 1.0 mmol) was boiled under reflux with HCOONH₄ (403 mg, 6.3 mmol) and Pd/C (10%, 150 mg) in AcOH (5 mL) for 4 d under Ar. The cooled mixture was filtered (Celite[®]). Aq. NaOH (1.0 M, 20 mL) was added to the evaporation residue and the mixture was extracted (EtOAc, 3 ×). Drying and evaporation gave **44b** (82 mg, 61%) as a white powder: mp 53-55°C (lit.³⁰ 68°C); ¹H NMR δ 2.42 (3 H, s, Me), 6.72 (3 H, br, NH + NH₂), 7.25 (2 H, d, *J* = 8.4 Hz, Ph 3,5-H₂), 7.72 (2 H, d, *J* = 8.3 Hz, Ph 2,6-H₂); ¹³C NMR δ 20.08 (Me), 126.46 (2,6-C₂), 128.56 (3,5-C₂), 133.16 (1-C), 139.44 (4-C), 162.57 (C=N); MS *m/z* 135.1018 (M + H)⁺ (C₈H₁₁N₂ requires 135.0922).

4-Trifluoromethylbenzimidamide (45d). Compound **45d** was prepared as previously described.²⁵

4-Chlorobenzimidamide (45e). Compound **45e** was prepared as previously described.²⁵

4-Bromobenzimidamide (45f). Compound **44f** was treated with HCOONH₄ and Pt/C, as for the synthesis of **45e**, to give **45f** (94 mg, 68%) as a white powder: mp 257-259°C (lit.³¹ 258.5-259.5°C); ¹H NMR δ 7.51 (2 H, br, NH₂), 7.53 (2 H, d, *J* = 7.6 Hz, 3,5-H₂), 7.79 (2 H, d, *J* = 7.2 Hz, 2,6-H₂), 7.93 (1 H, br, NH); ¹³C NMR δ 126.73 (3,5-C₂), 128.22 (2,6-C₂), 129.59 (4-C), 131.20 (1-C), 166.90 (C=N); MS *m/z* 200.9851 (M + H)⁺ (C₇H₈⁸¹BrN₂ requires 200.9851), 198.9877 (M + H)⁺ (C₇H₈⁷⁹BrN₂ requires 198.9871).

4-Aminobenzimidamide (45g). Compound **44g** (151 mg, 1.0 mmol) was stirred under reflux in AcOH (5 mL) with Pd/C (1%, 362 mg) and HCOONH₄ (800 mg, 12.6 mmol) for 4 d, before being cooled and filtered (Celite[®]). The evaporation residue was basified with aq. NaOH (5 M, 20 mL) and extracted thrice with EtOAc. Drying and evaporation gave **45g** (80 mg, 59%) as a white powder: mp 200-201°C (lit.³² 171°C); ¹H NMR δ 6.70 (3 H, br, NH & NH₂), 7.35 (2 H, br, NH₂), 7.66 (2 H, d, *J* = 8.6 Hz, Ph 3,5-H₂), 7.73 (2 H, d, *J* = 8.6 Hz, Ph 2,6-H₂); ¹³C NMR δ 117.80 (3,5-C₂), 127.21 (2,6-C₂), 133.0 (1-C), 140.0 (4-C), 152.0 (C=N); MS *m/z* 136.0898 (M + H)⁺ (C₇H₁₀N₃ requires 136.0875).

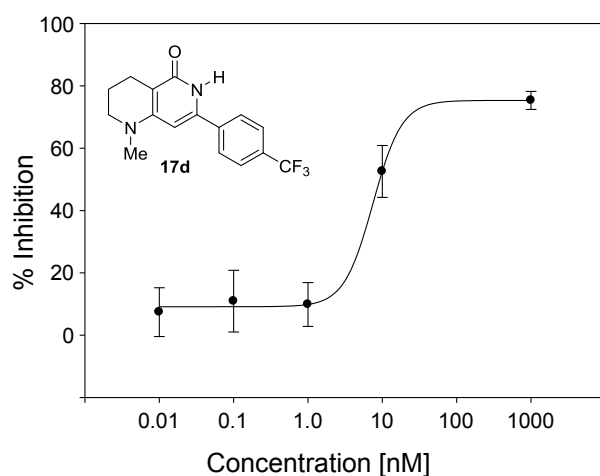
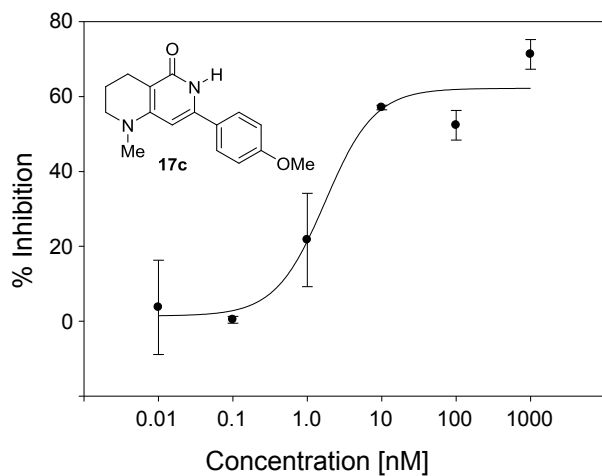
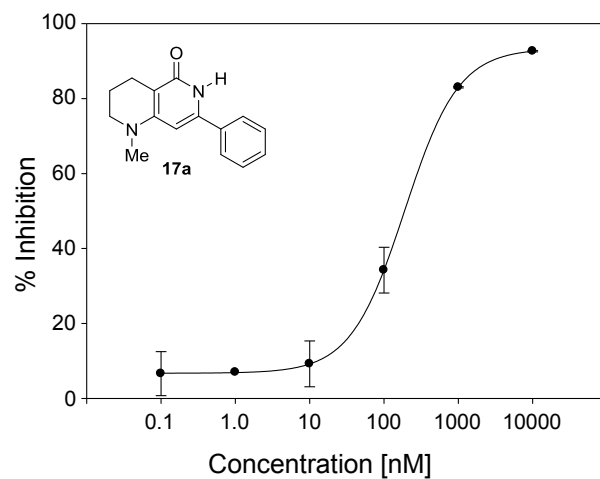
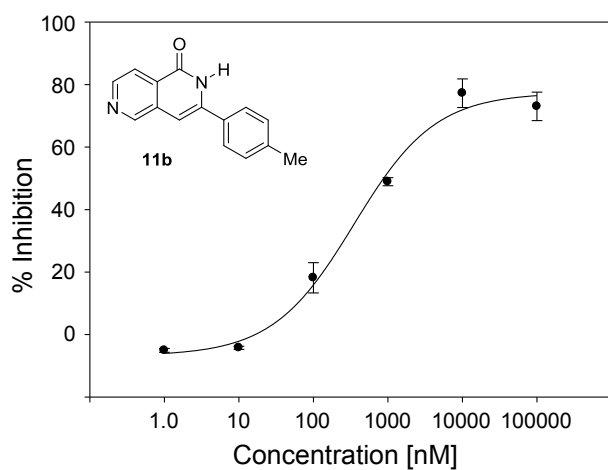
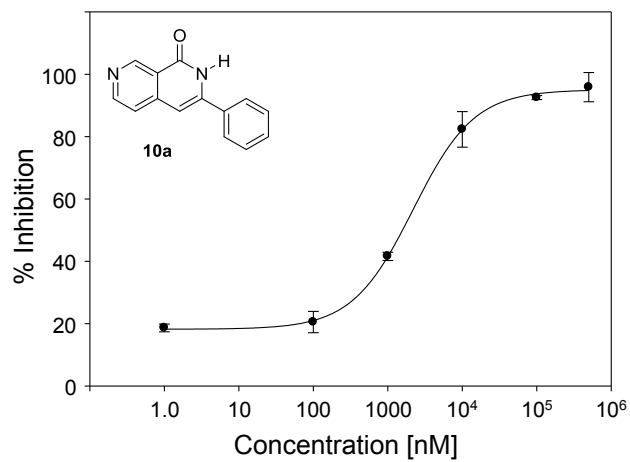
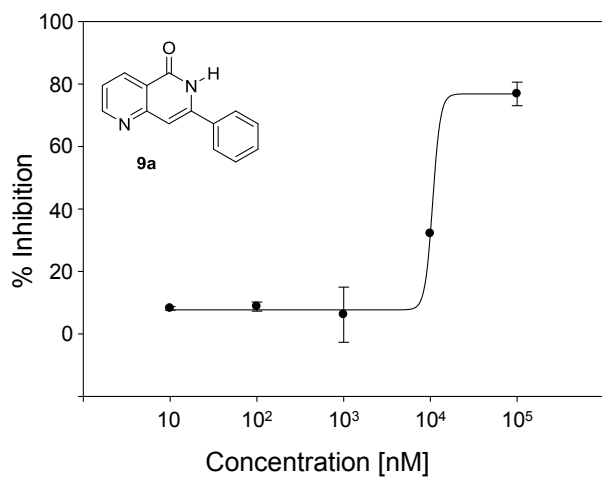
4-Phenylethynylbenzimidamide (45j). NaOMe (134 mg, 2.5 mmol) was stirred under reflux for 2 h with **44j** (480 mg, 2.36 mmol) in dry MeOH (15 mL). NH₄Cl (278 mg, 5.2 mmol) was added and stirring under reflux continued for 2 h. Evaporation and recrystallisation (water) gave **45j** (355 mg, 68%) as an off-white powder: mp 90-91°C; ¹H NMR d 7.51-7.54 (3 H, m, Ph 3,4,5-H₃), 7.67 (2 H, m, Ph 2,6-H₂), 7.81 (2 H, m, amidine Ph 2,6-H₂), 7.89 (1 H, br, NH), 7.97 (2 H, m, amidine-Ph 3,5-H₂), 9.06 (1 H, br, NH), 9.45 (1 H, br, NH); ¹³C NMR d 88.30 (ethyne 1-C), 93.60 (ethyne 2-C), 111.05 (amidine Ph 1-C), 118.44 (amidine Ph 4-C), 121.39 (Ph 1-C), 128.88 (Ph 3,4,5-C₃), 129.55 (Ph 4-C), 131.63 (Ph 2,6-C₂), 132.15 (amidine Ph 3,5-C₂), 132.62 (amidine Ph 2,6-C₂); MS *m/z* 242 (M + Na)⁺, 221.1090 (M + H)⁺ (C₁₅H₁₃N₂ requires 221.1073).

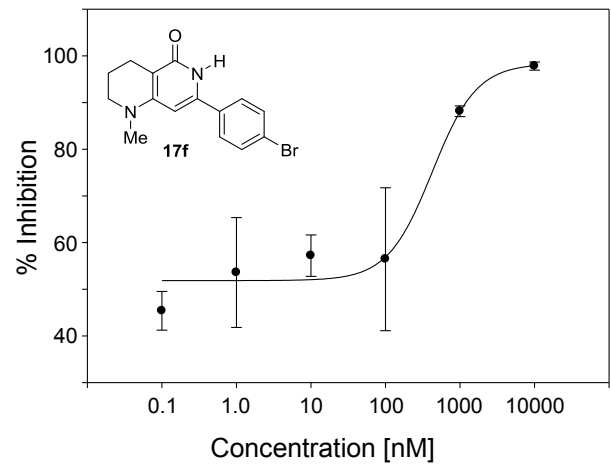
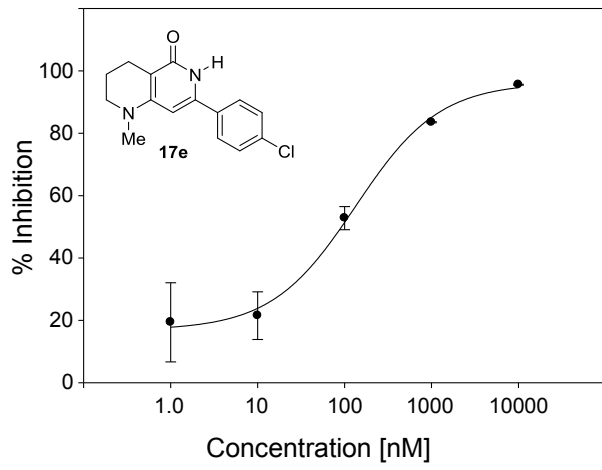
Pyridine-4-carboximidamide (45l). Compound **44l** (137 mg, 1.0 mmol) was boiled under reflux with Pd/C (1%, 150 mg) and HCOONH₄ (400 mg, 6.3 mmol) in AcOH (5 mL) for 4 d. The suspension was filtered (Celite[®]). The evaporation residue was basified with aq. NaOH (5 M, 20 mL) and extracted (EtOAc, 3 ×). Evaporation and drying gave **45l** (30.5 mg, 25%) as a white powder: mp >200°C (decomp.) (lit.³³ 235-238°C); ¹H NMR δ 7.78 (2 H, d, *J* = 5.5 Hz, 3,5-H₂), 8.87 (2 H, d, *J* = 5.0 Hz, 2,6-H₂), 9.52 (3 H, br, NH and NH₂); ¹³C NMR δ 121.39 (3,5-C₂), 141.24 (4-C), 150.24 (2,6-C₂), 166.38 (C=N); MS *m/z* 122.0710 (M + H)⁺ (C₆H₈N₃ requires 122.0718).

Data collection and refinement statistics for the tankyrase-2 crystal structures

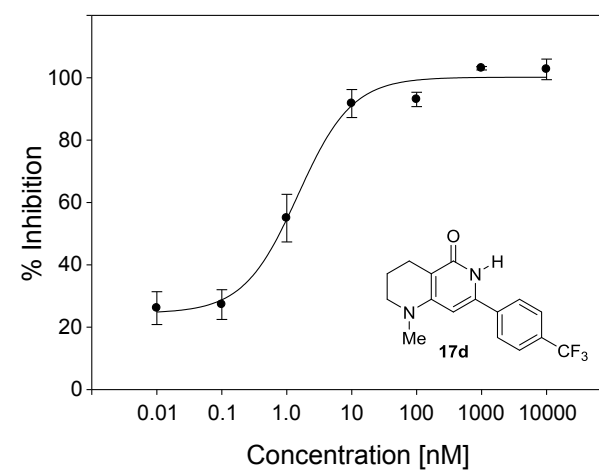
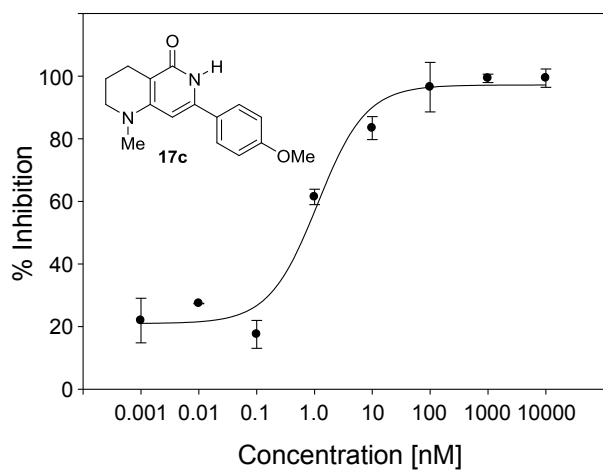
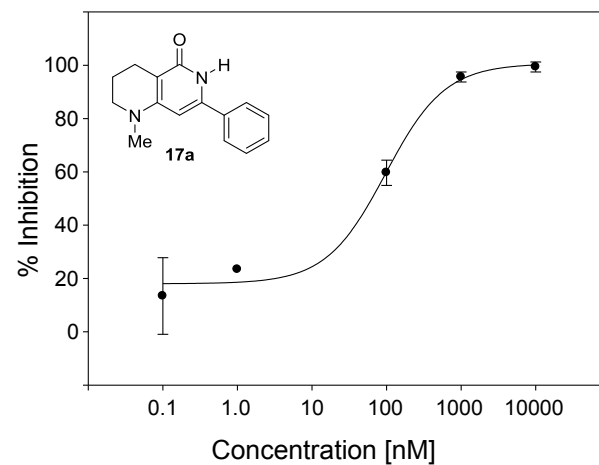
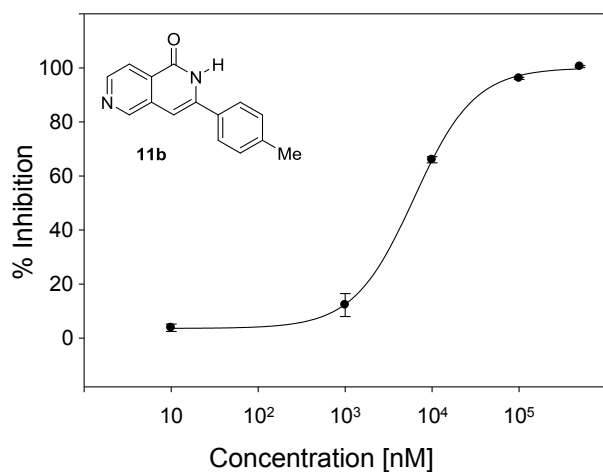
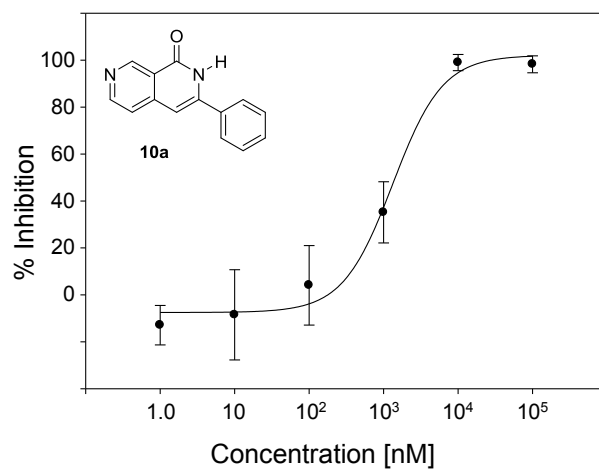
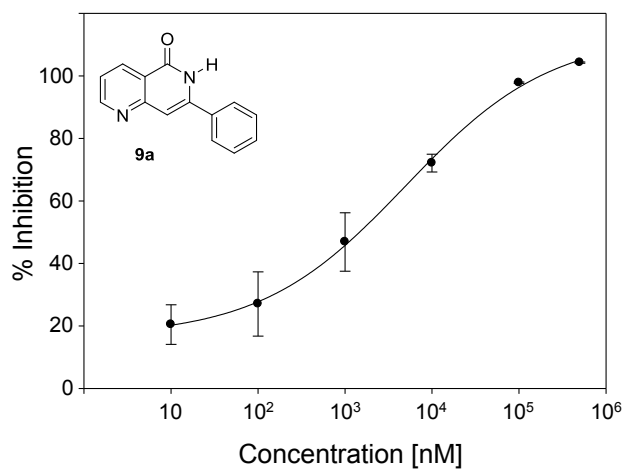
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Data		
Beam line	Diamond I04-1	Diamond I04-1
Wavelength (Å)	0.92000	0.92000
Space group	C222 ₁	C222 ₁
<i>Cell dimensions</i>		
a, b, c (Å)	91.55, 98.12, 119.22	91.56, 97.89, 118.47
Resolution (Å)	30-1.95 (2.00-1.95)	50-1.80 (1.85-1.80)
R _{merge}	13.2 (86.4)	6.3 (83.6)
I / σ I	9.87 (2.15)	18.80 (2.17)
Completeness (%)	99.8 (100)	99.9 (100)
Redundancy	6.7 (6.9)	6.8 (7.0)
Refinement		
R _{work} / R _{free}	0.162/0.200	0.162/0.198
<i>B-factors</i>		
Protein	27.2	28.3
Inhibitor	18.1	34.3
<i>R.m.s.d.</i>		
Bond lengths (Å)	0.011	0.012
Bond angles (°)	1.4	1.5
<i>Ramachandran plot (%)</i>		
Favoured regions	99.3	99.3
Additionally allowed regions	0.7	0.7

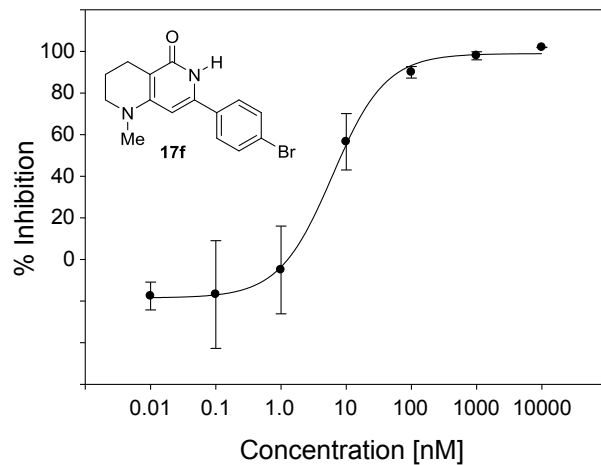
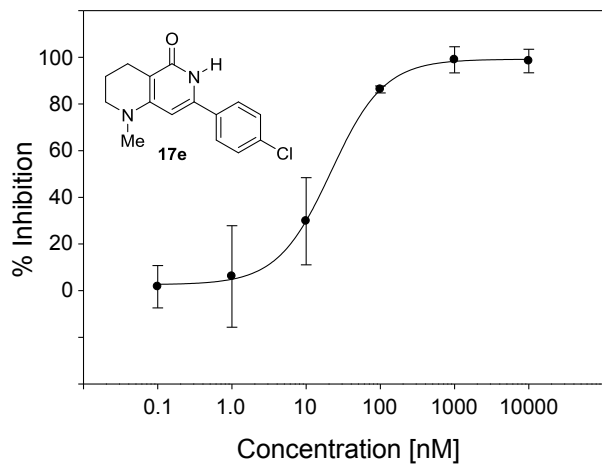
Examples of concentration-inhibition graphs for inhibition of TNKS-1



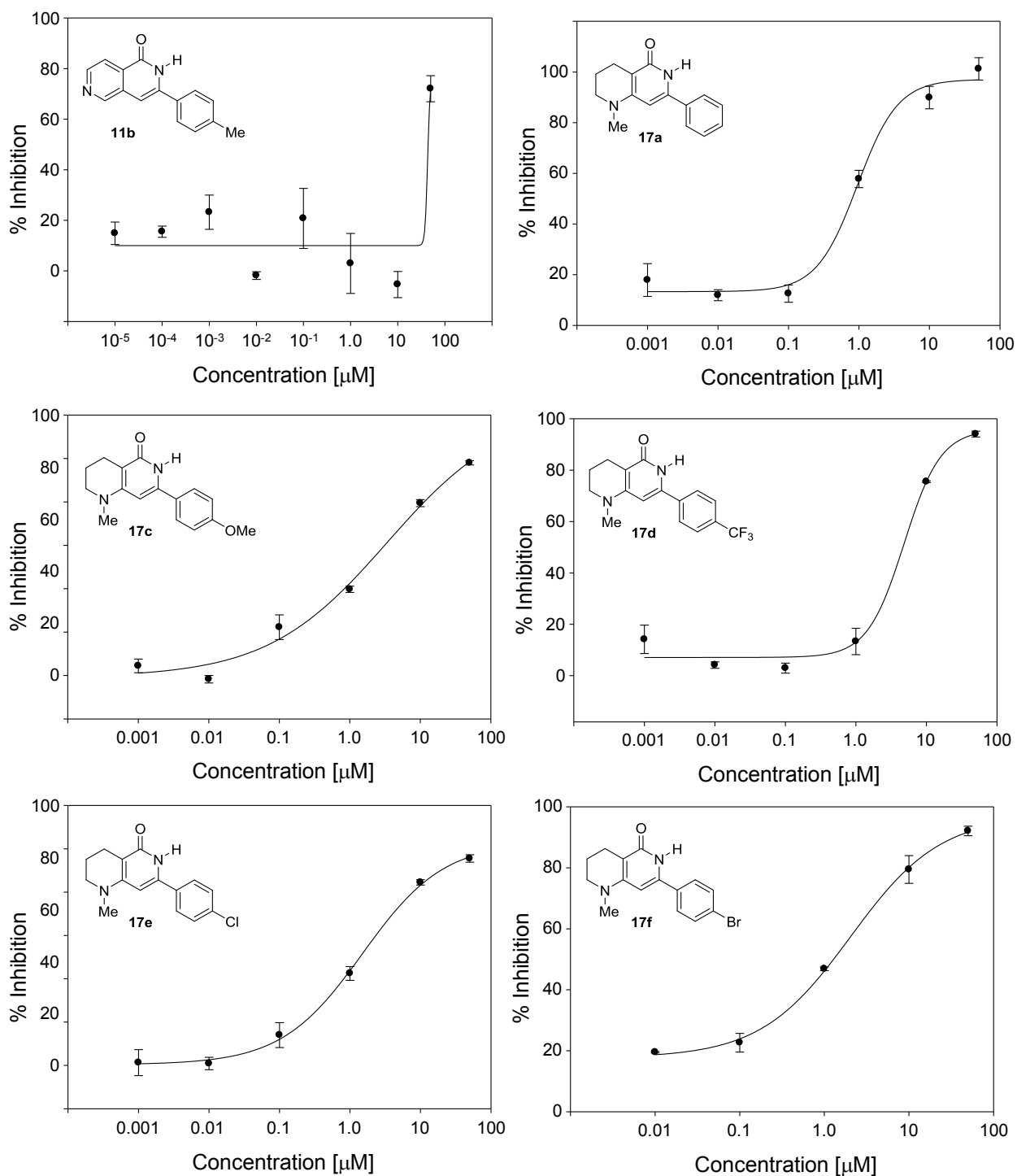


Examples of concentration-inhibition graphs for inhibition of TNKS-2





Examples of concentration-inhibition graphs for inhibition of PARP-1



References for Supplementary Information

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