Relaxation of the rigid backbone of an oligoamide-foldamer-based $\alpha$-helix mimetic: identification of potent Bcl-$x_L$ inhibitors

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Supplementary Information

Chemistry

General
Anhydrous MeOH, THF, CHCl$_3$, toluene and EtOH were purchased from Sigma-Aldrich and used directly from their Sure-Seal bottles. Chemicals were purchased from Sigma-Aldrich or Alfa Aesar. All reactions were performed under an atmosphere of dry nitrogen in oven-dried glassware and were monitored for completeness by thin-layer chromatography (TLC) using silica gel (visualized by UV light, or developed by treatment with KMnO$_4$ stain, Hanessian’s stain or ninhydrin). $^1$H and $^{13}$C NMR spectra were recorded on Varian 400 MHz or 500 MHz spectrometers in either CDCl$_3$ or d$_6$-DMSO. Chemical shifts (δ) are reported in parts per million after calibration to residual isotopic solvent or TMS. Coupling constants (J) are reported in Hz. Mass spectrometry was performed using electrospray ionization on a Bruker IonTrap. “Sep” = septet.

3-Isopropanoyloxy-4-nitrobenzoic acid (7). 3-hydroxy-4-nitrobenzoic acid (9) was suspended in MeOH (0.1 M) and stirred at 0°C for 15 minutes. SOCl$_2$ (3 eq.) was carefully added drop-wise into the cold solution. The reaction flask was removed from the ice bath and heated to reflux overnight. The product was isolated by evaporating MeOH to give a yellow solid (methyl 3-hydroxy-4-nitrobenzoate; 10: $^1$H NMR (500 MHz; CDCl$_3$) δ 10.5 (1H, s, Ar-OH), 8.18 (1H, d, Ar-H, $J$ = 8.5 Hz), 7.83 (1H, s, Ar-H), 7.62 (1H, d, Ar-H, $J$ = 8.5 Hz), 3.96 (3H, s, Ar-CO$_2$Me)) in 100% yield. Product 10 was then dissolved in THF to a concentration of 0.1 M and stirred at RT. Isopropanol (1.3 eq.) was added followed by triphenylphosphine (1.35 eq.) and the reaction solution allowed to stir to full solvation. DIAD (1.3 eq.) was added portion-wise, and the reaction allowed to stir at RT overnight. The THF was removed in vacuo, and then the crude material was adsorbed onto silica gel and purified by flash column chromatography (eluent: Hex/EtOAc,
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Compound 11 was dissolved in a 3:1:1 mixture of THF/MeOH/H₂O (0.1 M), then LiOH·H₂O (2 eq.) was added to the solution, which was allowed to stir at RT until completion (within 1 h). Excess base in the reaction mixture was neutralized with equimolar amounts of HCl from a 1M stock solution and all the organic solvents were removed in vacuo. The crude solid was decanted with water to a separation funnel and acidified to pH 1 with 1M HCl. Pure 3-isopropoxy-4-nitrobenzoic acid 7 was extracted with ethyl acetate (3x) and concentrated: yield = 3.8 g, 95%; yellow solid; mp: 175–177°C; ¹H NMR (500 MHz; d₆-DMSO) δH 7.91 (1H, d, Ar-H, J = 9.0 Hz) 7.76 (1H, s, Ar-H) 7.61 (1H, d, Ar-H, J = 9.0 Hz) 4.89 (1H, sep, CH(CH₃)₂, J = 5.8 Hz), 1.29 (6H, d, CH(CH₃)₂, J = 5.8 Hz); ¹³C NMR (125 MHz; CDCl₃) δc 169.8, 151.0, 144.6, 133.4, 125.3, 122, 117.5, 73.3, 21.9; νmax/cm⁻¹ 2926, 1721, 1693, 1587, 1573, 1435; m/z (ESI) 248 (M + Na, 100%)⁺, 473 (2M + Na, 40%)⁺.

Methyl 4-amino-3-isopropoxybenzoate (8). Compound 11 was dissolved in MeOH to 0.1 M and allowed to stir at RT. The reaction flask was evacuated and purged with N₂ (3x), then 10 mol% of 10% Pd/C was carefully added to the reaction flask. The reaction flask was then purged with H₂ (bubbled through reaction mixture for a few minutes) then left under a balloon of H₂ at RT overnight. The solution was filtered through Celite, washing with MeOH. The crude material was dry-loaded onto silica gel, then purified by flash column chromatography (eluent: Hex/EtOAc, 5:1) to deliver the title compound methyl 4-amino-3-isopropoxybenzoate (8) as a light brown oil that solidified on standing: yield = 2.0 g, 95%; mp: 54–56°C; ¹H NMR (500 MHz; d₆-DMSO, TMS) δH 7.35 (1H, d, Ar-H, J = 8.0 Hz) 7.29 (1H, s, Ar-H), 6.64 (1H, d, Ar-H, J = 8.0 Hz), 5.53 (2H, s, Ar-NH₂), 4.52 (1H, sep, CH(CH₃)₂, J = 5.8 Hz), 3.73 (3H, s, Ar-CO₂Me), 1.27 (6H, d, CH(CH₃)₂, J = 5.8 Hz); ¹³C NMR (125 MHz; d₆-DMSO) δc 166.8, 150.8, 144.8, 124.3, 116.4, 114.5, 112.9, 70.8, 51.7, 22.2; νmax/cm⁻¹ 3496, 3375, 1687, 1605, 1587, 1573, 1518; m/z (ESI) 231.9 (M + Na, 45%)⁺, 441.1 (2M + Na, 100%)⁺.

6-Isopropoxy-5-nitropicolinic acid (12). 2,6-Dichloro-3-nitropyridine (14) was dissolved in toluene (0.1 M), then isopropanol (1.2 eq.) was added. The reaction mixture was allowed to stir at 0°C (ice bath) for 15 minutes, then NaH (1.4 eq.) was added portion-wise under an inert (N₂) atmosphere. The reaction flask was allowed to stir at 0°C for another 15 minutes then allowed to stir overnight at RT. TLC indicted the reaction was complete. The reaction was carefully quenched with brine, then the reaction mixture was diluted with further toluene, washed with water, dried (Na₂SO₄), filtered and concentrated to give the crude material as a yellow solid.
After adsorbing onto silica gel, the crude material was purified by column chromatography (eluent: Hex/EtOAc, 5:1) to give product 15 (6-chloro-2-isopropoxy-3-nitropyridine) in near-quantitative yield as an off-white solid and as a single regioisomer (1H NMR (500 MHz; CDCl3) δH 8.19 (1H, d, Ar-H, J = 8.0 Hz), 6.95 (1H, d, Ar-H, J = 8.0 Hz), 5.48 (1H, sep, CH(CH3)2, J = 6.0 Hz), 1.41 (6H, d, CH(CH3)2, J = 6.0 Hz)). Compound 15 was dissolved in toluene (0.1 M), and tributylvinyl tin (1.1 eq.) was added to the solution. The reaction flask was evacuated and purged with N2, and then Pd(PPh3)4 (5% mol eq.) was added. The reaction flask was evacuated and purged with N2 once more, then allowed to reflux under N2 overnight. TLC indicated the reaction was complete. The reaction was worked up by adding a 1 M solution of KF (aq.), and the product was extracted with EtOAc (3x). The EtOAc extracts were combined, washed with water, brine, dried (Na2SO4), filtered, and then concentrated. The crude product was dry-loaded onto silica gel, then column chromatography (eluent: Hex/EtOAc, 5:1) afforded product 16 (2-isopropoxy-3-nitro-6-vinylpyridine) as a yellow solid (98% yield): 1H NMR (500 MHz; CDCl3) δH 8.21 (1H, d, Ar-H, J = 8.0 Hz), 6.89 (1H, d, Ar-H, J = 8.0 Hz), 6.72 (1H, dd, CH=CH2, J = 17.0, 10.5 Hz), 6.37 (1H, d, CH=CH2, J = 17.0 Hz), 5.62 (1H, d, CH=CH2, J = 10.5 Hz), 5.57 (1H, sep, CH(CH3)2, J = 6.0 Hz), 1.43 (6H, d, CH(CH3)2, J = 6.0 Hz)). Vinyl compound 16 was dissolved in acetone (0.1 M), and KMnO4 (4 eq.) was added portion-wise. The reaction mixture was allowed to stir at RT until completion. MeOH was used to quench the excess KMnO4, then an equivalent volume of water was added into the crude mixture. The crude mixture was then concentrated to a thick, dark syrup and transferred with water to a separation funnel. The aqueous phase was made basic with 0.5 M NaOH, and then neutral organics were extracted into ether (3x). After acidification of the aqueous phase to pH 1, 6-isopropoxy-5-nitropicolinic acid 12 was extracted into EtOAc (3x). The extracted organic layers were combined, dried (Na2SO4), filtered and concentrated in vacuo to give the title compound as an off-white solid: yield = 306 mg, 74%; mp: 128–130°C; 1H NMR (500 MHz; CDCl3) δH 8.47 (1H, d, Ar-H, J = 8.5 Hz), 7.70 (1H, d, Ar-H, J = 8.5 Hz), 5.52 (1H, sep, CH(CH3)2, J = 5.8 Hz), 1.34 (6H, d, CH(CH3)2, J = 5.8 Hz); 13C NMR (125 MHz; CDCl3) δC 164.0, 154.5, 149.5, 138.1, 137.0, 118.1, 71.4, 21.9; νmax/cm⁻¹ 2926, 1721, 1693, 1600, 1573, 1526, 1435; m/z (ESI) 225.2 (M – H, 100%)*, 473.6 (2M + Na, 16%)*.  

![](image)

Methyl 5-amino-6-isopropoxypicolinate (13). 6-Isopropoxy-5-nitropicolinic acid (12) was dissolved in MeOH to 0.1 M and cooled to 0°C for 15 mins, and then SOCl2 (3 eq.) was added cautiously into the reaction flask. The flask was taken out of the ice bath, and heated to reflux overnight. The crude reaction mixture was concentrated in vacuo to furnish a yellow solid (6-isopropoxy-5-nitropicolinic acid), which was used without further purification. This material was dissolved in EtOAc (0.1 M), SnCl2·2H2O (5 eq.) was added, and then the reaction was allowed to stir overnight at 50°C. TLC confirmed all starting material had been consumed. The reaction mixture was diluted with further EtOAc, and the product was partitioned between EtOAc and saturated aqueous NaHCO3. EtOAc extractions (3x) were pooled, washed with sat. aq. NaHCO3, dried (Na2SO4), filtered and concentrated in vacuo to give the title compound 13 an orange-brown solid, which was used without further purification: yield = 263 mg, 96%; brown solid; mp: 117–119°C; 1H NMR (500MHz; d6-DMSO) δH 7.49 (1H, d, Ar-H, J = 10.0 Hz), 6.84 (1H, d, Ar-H, J = 10.0 Hz), 5.73 (2H, s, Ar-NH2), 5.3 (1H, sep, CH(CH3)2), J = 5.5 Hz), 3.75 (3H, s, Ar-CO2Me), 1.30 (6H, d, CH(CH3)2, J = 5.5 Hz); 13C NMR (125 MHz; d6-DMSO) δC 165.5,
150.1, 137.6, 129.9, 121.5, 116.8, 67.8, 51.8, 22.3; m/z (ESI) 232.9 (M + Na, 26%)*, 443.1 (2M + Na, 100%)*.  

**General Coupling Procedure.** Either benzoic acid 7 (1.2 eq) or picolinic acid 12 (1.2 eq) was dissolved in CHCl₃ (0.1 M) along with the required benzoate ester 8 (1 eq.) or picolinate ester 13 (1 eq.). PPh₃Cl₂ (3 eq.) was added, then the reaction was heated to reflux. The reaction was typically complete within 2-3 h, and there was no detrimental impact on yields if the reaction was left overnight under reflux. The crude reaction mixture was adsorbed directly onto silica gel, then purified by silica gel flash column chromatography, eluting with Hex/EtOAc, 1:1 or CH₂Cl₂/EtOAc, 99:1 as appropriate. Pure nitro dimers (17a – c) and nitro trimers (19a – f) were isolated with yields ≥ 90%.

**Methyl 6-isopropoxy-5-(6-isopropoxy-5-nitropicolamido)picolinate (17a):** yield = 236 mg, 90%; yellow solid; mp: 135–137°C; ¹H NMR (500 MHz; d₆-DMSO, TMS) δH 10.17 (1H, s, CONH), 8.81 (1H, d, Ar-H, J = 8.5 Hz), 8.65 (1H, d, Ar-H, J = 8.2 Hz), 7.91 (1H, d, Ar-H, J = 8.5 Hz), 7.81 (1H, d, Ar-H, J = 8.2 Hz), 5.62 (1H, sep, CH(CH₃)₂, J = 6.0 Hz), 5.49 (1H, sep, CH(CH₃)₂, J = 6.0 Hz), 3.86 (3H, s, Ar-CO₂Me), 1.46 (6H, d, CH(CH₃)₂, J = 6.0 Hz), 1.40 (6H, d, CH(CH₃)₂, J = 6.0 Hz); ¹³C NMR (125 MHz; d₆-DMSO); δC 164.8, 160.8, 154.1, 152.1, 149.1, 138.7, 137.8, 137.0, 125.8, 120.1, 115.8 (2), 71.8, 70.1, 52.7, 22.1, 22.0; m/z (ESI) 419.1 (M + H,100%)*, 859.1 (2M + Na, 90%)*.

**Methyl 3-isopropoxy-4-(3-isopropoxy-4-nitrobenzamido)benzoate (17b):** yield = 280 mg, 100%; yellow solid; mp: 106–108°C; ¹H NMR (500 MHz; d₆-DMSO, TMS) δH 9.67 (1H, s, CONH), 8.1 (1H, d, Ar-H, J = 7.7 Hz), 7.97 (1H, d, Ar-H, J = 9.7 Hz), 7.79 (1H, s, Ar-H), 7.62 (1H, d, Ar-H, J = 7.7 Hz), 7.58 (1H, s, Ar-H), 7.57 (1H, d, Ar-H, J = 9.7 Hz), 4.95 (1H, sep, CH(CH₃)₂, J = 6.0 Hz), 4.73 (1H, sep, CH(CH₃)₂, J = 5.6 Hz), 3.85 (3H, s, Ar-CO₂Me), 1.33 (6H, d, CH(CH₃)₂, J = 5.6 Hz), 1.32 (6H, d, CH(CH₃)₂, J = 5.6 Hz); ¹³C NMR (125 MHz; CDCl₃) δC 166.6, 163.2, 151.6, 145.9, 142.9, 139.5, 132.2, 125.8, 123.2, 119.0, 118.9, 117.2, 115.4, 113.1, 73.2, 71.9,
52.2, 22.2, 21.9; ν_{max}/cm^{-1} 3432, 3079, 2974, 2906, 2364, 1723, 1678, 1599, 1527; m/z (ESI) 417.1 (M + H, 100%)^+, 439.0 (M + Na, 70%)^+.

**Methyl 3-isopropoxy-4-(6-isopropoxy-5-nitropicolinamido)benzoate (17c):** yield = 580 mg, 92%; yellow solid; mp: 194–196°C; ^1H NMR (500 MHz; d_6-DMSO, TMS) δ_H 10.2 (1H, s, CONH), 8.63 (1H, d, Ar-H, J = 7.7 Hz), 8.61 (1H, d, Ar-H, J = 7.7 Hz), 7.92 (1H, d, Ar-H, J = 8.2 Hz), 7.66 (1H, d, Ar-H, J = 8.2 Hz), 7.63 (1H, s, Ar-H), 5.65 (1H, sep, CH(CH_3)_2, J = 5.8 Hz), 4.91 (1H, sep, CH(CH_3)_2, J = 5.8 Hz), 3.85 (3H, s, Ar-CO_2Me), 1.44 (6H, d, CH(CH_3)_2, J = 5.8 Hz), 1.37 (6H, d, CH(CH_3)_2, J = 5.8 Hz); ^13C NMR (125 MHz; CDCl_3) δ_C 166.9, 160.3, 154.9, 150.6, 146.4, 136.6, 132.1, 126.1, 123.3, 119.2 (2), 115.4, 113.2, 71.64, 71.50, 52.38, 22.33, 22.03; ν_{max}/cm^{-1} 3359, 2979, 1708, 1687, 1527, 1438; m/z (ESI) 418.1 (M + H, 100%)^+, 439.0 (M + Na, 70%)^+.

**Methyl 3-isopropoxy-4-(3-isopropoxy-4-(3-isopropoxy-4-nitrobenzamido)benzamido)benzoate (19b):** yield = 727 mg, 100%; cream-coloured solid; mp: 185–187°C; ^1H NMR (500 MHz; CDCl_3) δ_H 8.84 (1H, s, CONH), 8.75 (1H, s, CONH), 8.63 (1H, d, Ar-H, J = 8.4 Hz), 8.59 (1H, d, Ar-H, J = 8.4 Hz), 7.85 (1H, d, Ar-H, J = 8.2 Hz), 7.7 (1H, d, Ar-H, J = 8.4 Hz), 7.67 (1H, s, Ar-H), 7.61 (1H, s, Ar-H), 7.58 (1H, s, Ar-H), 7.40 (1H, d, Ar-H, J = 8.4 Hz), 7.35 (1H, d, Ar-H, J = 8.2 Hz), 4.86 – 4.71 (3H, m, 3xCH(CH_3)_2), 3.89 (3H, s, Ar-CO_2Me), 1.43 (18H, m, 3xCH(CH_3)_2); ^13C NMR (125 MHz; CDCl_3) δ_C 167.0, 164.6, 163.4, 151.8, 146.8, 145.9, 143.1, 139.6, 133.1, 131.5, 130.8, 126.0, 125.3, 123.5, 119.3, 118.9, 118.8, 117.4, 115.6, 113.3, 112.0, 73.3, 72.1, 72.0, 52.3, 22.5, 22.4, 22.1; ν_{max}/cm^{-1} 3430, 2977, 2358, 1714, 1685, 1594, 1521; m/z (ESI) 594.2 (M + H, 100%)^+, 1187 (2M + H, 50%)^+.
Methyl 3-isopropoxy-4-(3-isopropoxy-4-(6-isopropoxy-5-nitropicolinamido)benzamido)benzoate (19c): yield = 355 mg, 100%; yellow solid; mp: 260–262°C; $^1$H NMR (500 MHz; CDCl$_3$) $\delta$H 10.2 (1H, s, CONH), 8.85 (1H, s, CONH), 8.75 (1H, d, Ar-H, $J = 8.2$ Hz), 8.6 (1H, d, Ar-H, $J = 8.4$ Hz), 8.36 (1H, $d$, Ar-H, $J = 8.1$ Hz), 7.98 (1H, d, Ar-H, $J = 8.2$ Hz), 7.71 (1H, d, Ar-H, $J = 8.4$ Hz), 7.6 (1H, s, Ar-H), 7.58 (1H, s, Ar-H), 7.39 (1H, d, Ar-H, $J = 8.1$ Hz), 5.68 (1H, sep, CH(CH$_3$)$_2$, $J = 6.2$ Hz), 4.85 (1H, sep, CH(CH$_3$)$_2$, $J = 5.9$ Hz), 4.75 (1H, sep, CH(CH$_3$)$_2$, $J = 6.0$ Hz), 3.89 (3H, s, Ar-CO$_2$Me), 1.50 (6H, d, CH(C$_2$H$_3$)$_2$, $J = 6.0$ Hz), 1.46 – 1.42 (12H, m, 2xCH(CH$_3$)$_2$); $^{13}$C NMR (125 MHz; CDCl$_3$) $\delta$C 167.1, 164.6, 160.4, 154.9, 150.5, 147.2, 146.0, 141.8, 136.6, 133.2, 131.3, 130.8, 125.3, 123.5, 119.5, 118.8 (2), 115.4, 113.3, 112.1, 72.0, 71.7, 71.5, 52.3, 22.4, 22.3, 22.0; $\nu_{max}$/cm$^{-1}$ 3413, 3346, 2981, 2925, 2356, 1708, 1600, 1513, 1484; m/z (ESI) 595.2 (M + H, 100%)$^+$, 1188.9 (2M, 40%)$^+$. 

Methyl 3-isopropoxy-4-(6-isopropoxy-5(6-isopropoxy-5-nitropicolinamido)picolinamido)benzoate (19d): yield = 230 mg, 97%; pale-yellow solid; mp: 252–254°C; $^1$H NMR (500MHz; CDCl$_3$) $\delta$H 10.3 (1H, s, CONH), 10.1 (1H, s, CONH), 8.99 (1H, d, Ar-H, $J = 7.7$ Hz), 8.72 (1H, d, Ar-H, $J = 8.2$ Hz), 8.36 (1H, $d$, Ar-H, $J = 8.4$ Hz), 7.98 (1H, d, Ar-H, $J = 7.7$ Hz), 7.96 (1H, d, Ar-H, $J = 8.2$ Hz), 7.70 (1H, d, Ar-H, $J = 8.4$ Hz), 7.59 (1H, s, Ar-H), 5.75 – 5.60 (2H, m, 2xCH(CH$_3$)$_2$), 4.80 (1H, sep, CH(CH$_3$)$_2$, $J = 6.0$ Hz), 3.89 (3H, s, Ar-CO$_2$Me),
1.53 (6H, d, CH(CH₃)₂, J = 6.0 Hz), 1.49 (6H, d, CH(CH₃)₂, J = 6.0 Hz), 1.42 (6H, d, CH(CH₃)₂, J = 6.0 Hz); ¹³C-NMR (125 MHz; CDCl₃); δC 167.1, 162.1, 160.7, 154.9, 151.2, 149.9, 146.2, 141.2, 137.0, 136.8, 127.3, 125.7, 123.4, 119.1, 117.5, 115.4, 113.2, 71.8, 71.3, 69.7, 52.3, 22.4, 22.3, 22.1; νmax/cm⁻¹ 3365, 2985, 1695, 1600, 1511, 1481, 1340, 1265; m/z (ESI) 596 (M + H, 100%)⁺, 1213.3 (2M + Na, 20%).

Methyl 3-isopropoxy-4-(6-isopropoxy-5-(3-isopropoxy-4-nitrobenzamido)picolinamido)benzoate (19e): yield = 650 mg, 93%; white solid; mp: 197–200°C; ¹H NMR (500 MHz; CDCl₃) δH 10.2 (1H, s, CONH), 8.90 (1H, d, Ar-H, J = 8.1 Hz), 8.72 (1H, d, Ar-H, J = 8.4 Hz), 8.53 (1H, s, CONH), 7.98 (1H, d, Ar-H, J = 8.1 Hz), 7.86 (1H, d, Ar-H, J = 8.2 Hz), 7.70 (1H, d, Ar-H, J = 8.4 Hz), 7.67 (1H, s, Ar-H), 7.59 (1H, s, Ar-H), 7.33 (1H, d, Ar-H, J = 8.2 Hz), 5.64 (1H, sep, CH(CH₃)₂, J = 6.1 Hz), 4.83 – 4.76 (2H, m, 2xCH(CH₃)₂), 3.89 (3H, s, Ar-CO₂Me), 1.49 (6H, d, CH(CH₃)₂, J = 6.2 Hz), 1.45 – 1.41 (12H, m, 2xCH(CH₃)₂); ¹³C NMR (125 MHz; CDCl₃) δC 167.0, 163.8, 162.1, 151.8, 150.9, 146.3, 143.3, 141.3, 139.3, 132.9, 127.2, 126.0, 125.9, 125.2, 123.4, 119.2, 117.4, 117.3, 115.7, 113.2, 73.4, 71.3, 70.2, 52.3, 22.4, 22.3, 22.0; νmax/cm⁻¹ 3432, 3374, 3344, 2979, 2925, 1714, 1687, 1602, 1517, 1481; m/z (ESI) 595.2 (M + H, 100%)⁺, 1188 (2M, 20%)⁺.
Methyl 6-isopropoxy-5-(5-isopropoxypicolinamido)picolinate (19f): yield = 133 mg, 90%; white solid; mp: 240–241°C; \(^1\)H NMR (500 MHz; d\(_6\)-DMSO, TMS) \(\delta_H 10.2 \text{ (1H, s, CONH)}, 9.96 \text{ (1H, s, CONH)}, 8.84 \text{ (1H, d, Ar-H, } J = 8.7 \text{ Hz}), 8.51 \text{ (1H, d, Ar-H, } J = 8.7 \text{ Hz}), 7.99 \text{ (1H, d, Ar-H, } J = 8.7 \text{ Hz}), 7.87 \text{ (1H, d, Ar-H, } J = 8.2 \text{ Hz}), 7.79 \text{ (1H, s, Ar-H)}, 7.59 \text{ (1H, d, Ar-H, } J = 8.2 \text{ Hz)}, 5.50 \text{ (2H, m, 2xCH(CH\(_3\))\(_2\)}, 4.95 \text{ (1H, sep, CH(CH\(_3\))\(_2\)}, J = 5.5 \text{ Hz}), 3.86 \text{ (3H, s, Ar-CO\(_2\)Me)}, 1.46 \text{ (6H, d, CH(CH\(_3\))\(_2\)}, J = 5.5 \text{ Hz}), 1.41 \text{ (6H, d, CH(CH\(_3\))\(_2\)}, J = 6.5 \text{ Hz}), 1.35 \text{ (6H, d, CH(CH\(_3\))\(_2\)}, J = 6.5 \text{ Hz}); \(^13\)C NMR (125 MHz; CDCl\(_3\)) \(\delta_C 165.7, 163.9, 162.7, 152.2, 151.8, 151.3, 143.3, 140.6, 138.9, 138.4, 127.2, 126.6, 126.2, 126.0, 125.4, 120.2, 117.4, 117.3, 115.7, 73.4, 70.5, 69.7, 52.6, 22.4, 22.2, 22.1; m/z (ESI) 596.2 (M + H, 100%)\(^+\), 1189.8 (2M – H, 45%)\(^+\).

**General Reduction Procedure:** The nitro compound (1 eq.) was dissolved in EtOAc (0.1 M), or CHCl\(_3\)/EtOH (3:1; 0.05 M) if insoluble in EtOAc. SnCl\(_2\).2H\(_2\)O (5 eq.) was added, then the reaction was heated at 50°C overnight. Crude reaction mixtures were poured into a separatory funnel along with additional EtOAc or CHCl\(_3\), depending on the reaction solvent, and washed with sat. NaHCO\(_3\) (aq). The organics were extracted into EtOAc (or CHCl\(_3\)) (3x) with gentle shaking. The combined organic layers were washed with sat. NaHCO\(_3\) (aq), water, dried (Na\(_2\)SO\(_4\)), then filtered and concentrated. The crude residue was adsorbed onto silica gel, then purified by silica gel flash column chromatography, eluting with Hex/EtOAc, 1:1 or CH\(_2\)Cl\(_2\)/EtOAc, 96:1, as appropriate.

**Methyl 5-(5-amino-6-isopropoxypicolinamido)-6-isopropoxypicolinate (18a):** yield = 131 mg, 83%; yellow solid; mp: 202–203°C; \(^1\)H NMR (500 MHz; d\(_6\)-DMSO, TMS) \(\delta_H 10.1 \text{ (1H, s, }, \text{CONH} \),
CONH), 8.81 (1H, d, Ar-H, J = 8.0 Hz), 7.76 (1H, d, Ar-H, J = 7.7 Hz), 7.59 (1H, d, Ar-H, J = 8.0 Hz), 6.98 (1H, d, Ar-H, J = 7.7 Hz), 5.89 (2H, s, Ar-NH₂), 5.49 (1H, sep, CH(CH₃)₂, J = 6.3 Hz) 5.43 (1H, sep, CH(CH₃)₂, J = 6.3 Hz), 3.84 (3H, s, Ar-CON₂Me), 1.41 (12H, m, 2xCH(CH₃)₂); ¹³C NMR (125 MHz; d₆-DMSO) δc 165.3, 163.3, 151.6, 149.1, 138.1, 137.2, 131.3, 127.1, 124.3, 120.3, 118.5, 117.9, 69.6, 68.2, 52.6, 22.3, 22.2; m/z (ESI) 389.2 (M + H, 30%)+, 799.3 (2M + Na, 100%)⁺.

Methyl 4-(4-amino-3-isopropoxybenzamido)-3-isopropoxybenzoate (18b): yield = 230 mg, 89%; orange, sticky solid; mp: 146–148°C; ¹H NMR (500 MHz; d₆-DMSO, TMS) δh 8.95 (1H, s, CONH), 8.32 (1H, d, Ar-H, J = 10.0 Hz), 7.6 (1H, d, Ar-H, J = 7.7 Hz), 7.56 (1H, s, Ar-H), 7.34 (1H, s, Ar-H), 7.33 (1H, d, Ar-H, J = 10.0 Hz) 6.73 (1H, d, Ar-H, J = 7.7 Hz), 5.46 (2H, s, Ar-NH₂), 4.75 (1H, sep, CH(CH₃)₂, J = 6.0 Hz), 4.63 (1H, sep, CH(CH₃)₂, J = 6.0 Hz), 3.84 (3H, s, Ar-CON₂Me), 1.36 (6H, d, CH(CH₃)₂, J = 6.0 Hz), 1.32 (6H, d, CH(CH₃)₂, J = 6.0 Hz); ¹³C NMR (125 MHz; d₆-DMSO) δc 166.3, 164.9, 146.9, 143.9, 143.7, 134.0, 124.8, 122.8, 121.8, 121.1, 120.3, 113.9, 113.2, 113.0, 72.0, 70.8, 52.5, 22.4, 22.1; νmax/cm⁻¹ 3363, 2971, 2358, 1710, 1596, 1515, 1486, 1423; m/z (ESI) 387.1 (M + H, 100%)⁺, 772.5 (2M, 25%)⁺.

Methyl 4-(5-amino-6-isopropoxypicolinamido)-3-isopropoxybenzoate (18c): yield = 530 mg, 100%; pale yellow solid; mp: 173–174°C; ¹H NMR (500 MHz; CDCl₃, TMS) δh 10.3 (1H, s, CONH), 8.74 (1H, d, Ar-H, J = 8.2 Hz), 7.76 (1H, d, Ar-H, J = 7.7 Hz), 7.7 (1H, d, Ar-H, J = 8.2 Hz), 7.59 (1H, s, Ar-H), 6.96 (1H, d, Ar-H, J = 7.7 Hz), 5.57 (1H, sep, CH(CH₃)₂, J = 6.5 Hz), 4.79 (1H, sep, CH(CH₃)₂, J = 6.5 Hz), 4.2 (2H, s, Ar-NH₂), 3.9 (3H, s, Ar-CON₂Me), 1.44 (6H, d, CH(CH₃)₂, J = 6.5 Hz), 1.43 (6H, d, CH(CH₃)₂, J = 6.5 Hz); ¹³C NMR (125 MHz; CDCl₃) δc 167.2, 163.2, 149.9, 146.2, 135.6, 135.1, 133.6, 124.5, 123.4, 119.4, 118.7, 117.9, 113.2, 71.3, 68.6, 52.2, 22.4, 22.3; νmax/cm⁻¹ 3336, 2977, 2360, 1718, 1527, 1457; m/z 388.1 (M + H, 100%)⁺.
Methyl 4-(4-(4-amino-3-isopropoxybenzamido)-3-isopropoxybenzamido)-3-isopropoxybenzoate (20b): yield = 555 mg, 88%; pale cream-coloured solid; mp: 180–182°C; 
$^1$H NMR (500 MHz; CDCl$_3$) $\delta$: 8.86 (1H, s, CONH), 8.73 (1H, s, CONH), 8.69 (1H, d, Ar-H, $J = 10.0$ Hz), 8.63 (1H, d, Ar-H, $J = 9.0$ Hz), 7.72 (1H, d, Ar-H, $J = 9.0$ Hz), 7.62 (2H, m, 2xAr-H), 7.46 (1H, s, Ar-H), 7.4 (1H, d, Ar-H, $J = 8.2$ Hz), 7.3 – 7.24 (1H, m, Ar-H), 6.75 (1H, d, Ar-H, $J = 8.2$ Hz), 4.85 – 4.72 (2H, m, CH(CH$_3$)$_2$), 4.72 – 4.65 (1H, sep, CH(CH$_3$)$_2$, $J = 5.9$ Hz), 4.22 (2H, s, Ar-NH$_2$), 3.91 (3H, s, Ar-CO$_2$Me), 1.45 (12H, m, 2xCH$_2$(C$_2$H$_3$)$_2$), 1.41 (6H, d, CH$_2$(C$_2$H$_3$)$_2$, $J = 5.9$ Hz); $^{13}$C NMR (125 MHz; CDCl$_3$) $\delta$: 167.3, 165.8, 165.5, 146.8, 146.0, 145.6, 142.0, 133.7, 133.4, 129.7, 125.2, 124.6, 123.8, 120.4, 119.5, 119.1, 118.9, 114.0, 113.5, 112.9, 112.4, 72.0, 71.9, 71.1, 52.2, 22.0, 21.8, 21.7; $\nu_{max}$/cm$^{-1}$: 3486, 3430, 3338, 2975, 2356, 1712, 1596, 1511, 1486; m/z (ESI) 586.2 (M + Na, 100%), 1149.4 (2M + Na, 70%).

Methyl 4-(4-(5-amino-6-isopropoxypicolinamido)-3-isopropoxybenzamido)-3-isopropoxybenzoate (20c): yield = 276 mg, 89%; pale-yellow solid; mp: 228–230°C; $^1$H NMR (500 MHz; CDCl$_3$) $\delta$: 10.3 (1H, s, CONH), 8.88 (1H, s, CONH), 8.80 (1H, d, Ar-H, $J = 7.9$ Hz), 8.63 (1H, d, Ar-H, $J = 8.4$ Hz), 7.77 (1H, d, Ar-H, $J = 8.0$ Hz), 7.72 (1H, d, Ar-H, $J = 8.4$ Hz), 7.62 (1H, s, Ar-H), 7.59 (1H, s, Ar-H), 7.39 (1H, d, Ar-H, $J = 8.0$ Hz), 6.96 (1H, d, Ar-H, $J = 7.9$ Hz), 5.57 (1H, sep, CH(CH$_3$)$_2$, $J = 6.2$ Hz), 4.84 (1H, sep, CH(CH$_3$)$_2$, $J = 6.2$ Hz), 4.76 (1H, m, CH(CH$_3$)$_2$, $J = 6.0$ Hz), 4.22 (2H, s, Ar-NH$_2$), 3.91 (3H, s, Ar-CO$_2$Me), 1.48 – 1.41 (18H, m,
3xCH(CH₃)₂; ¹³C NMR (125 MHz; CDCl₃) δC 167.0, 164.9, 163.3, 149.9, 146.9, 145.9, 135.5, 135.2, 133.4, 129.2, 125.7, 123.5, 119.3, 118.9 (2), 118.7, 117.9, 113.3, 112.2, 72.1, 71.3, 68.6, 52.2, 22.43, 22.39, 22.35; νmax/cm⁻¹ 3496, 3425, 3371, 2977, 2929, 1708, 1672, 1591, 1519, 1483, 1263; m/z (ESI) 565.3 (M + H, 80%)⁺, 1129 (2M + H, 100%)⁺.

Methyl 4-(5-(5-amino-6-isopropoxypicolinamido)-6-isopropoxypicolinamido)-3-isopropoxybenzoate (20d): yield = 250 mg, 99%; off-white solid; mp: 237–239°C; ¹H NMR (500MHz; CDCl₃) δH 10.30 (1H, s, CONH), 9.02 (1H, d, Ar-H, J = 7.8 Hz), 8.75 (1H, d, Ar-H, J = 8.1 Hz), 7.96 (1H, d, Ar-H, J = 8.2 Hz), 7.75 (1H, d, Ar-H, J = 7.8 Hz), 7.72 (1H, d, Ar-H, J = 8.2 Hz), 7.63 (1H, s, Ar-H), 6.96 (1H, d, Ar-H, J = 8.1 Hz), 5.69 (1H, sep, CH(CH₃)₂, J = 6.0 Hz), 4.81 (1H, sep, CH(CH₃)₂, J = 6.0 Hz), 4.25 (2H, s, Ar-NH₂), 3.91 (3H, s, Ar-CO₂Me), 1.52 – 1.41 (18H, m, 3xCH(CH₃)₂); ¹³C NMR (125 MHz; CDCl₃) δC 167.1, 163.6, 162.5, 151.0, 149.8, 146.2, 139.7, 135.4, 134.8, 133.2, 127.1, 126.1, 124.9, 123.4, 119.3, 118.9, 118.0, 117.6, 113.2, 71.4, 69.2, 68.8, 52.2, 22.4, 22.3, 22.2; νmax/cm⁻¹ 3504, 3369, 2977, 2360, 1708, 1677, 1596, 1510, 1465; m/z (ESI) 588.2 (M + Na, 100%)⁺.

Methyl 4-(5-(4-amino-3-isopropoxybenzamido)-6-isopropoxypicolinamido)-3-isopropoxybenzoate (20e): yield = 588 mg, 100%; white solid; mp: 208–210°C; ¹H NMR (500 MHz; CDCl₃) δH 10.30 (1H, s, CONH), 9.02 (1H, d, Ar-H, J = 7.8 Hz), 8.75 (1H, d, Ar-H, J = 8.1 Hz), 7.96 (1H, d, Ar-H, J = 8.2 Hz), 7.75 (1H, d, Ar-H, J = 7.8 Hz), 7.72 (1H, d, Ar-H, J = 8.2 Hz), 7.63 (1H, s, Ar-H), 6.96 (1H, d, Ar-H, J = 8.1 Hz), 5.69 (1H, sep, CH(CH₃)₂, J = 6.0 Hz), 4.81 (1H, sep, CH(CH₃)₂, J = 6.0 Hz), 4.25 (2H, s, Ar-NH₂), 3.91 (3H, s, Ar-CO₂Me), 1.52 – 1.41 (18H, m, 3xCH(CH₃)₂); ¹³C NMR (125 MHz; CDCl₃) δC 167.1, 163.6, 162.5, 151.0, 149.8, 146.2, 139.7, 135.4, 134.8, 133.2, 127.1, 126.1, 124.9, 123.4, 119.3, 118.9, 118.0, 117.6, 113.2, 71.4, 69.2, 68.8, 52.2, 22.4, 22.3, 22.2; νmax/cm⁻¹ 3504, 3369, 2977, 2360, 1708, 1677, 1596, 1510, 1465; m/z (ESI) 588.2 (M + Na, 100%)⁺.
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Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

should be concentrated before the work-up procedure is initiated. Note: For saponifications on a large scale (>500 mg), it is recommended that the reaction mixture should be neutralized with 1 M HCl and then the solvent should be concentrated before the work-up procedure is initiated.
5-(5-(5-amino-6-isopropoxypicolinamido)-6-isopropoxypicolamido)-6-isopropoxypicolinic acid (1): yield = 94 mg, 100%; pale-yellow solid; $^1$H NMR (500 MHz; d$_6$-DMSO) $\delta$ 10.71 (1H, s, CO$_2$H), 10.20 (1H, s, CONH), 10.1 (1H, s, CONH), 8.90 (1H, d, Ar-H, $J = 7.5$ Hz), 8.78 (1H, d, Ar-H, $J = 7.5$ Hz), 7.83 (1H, d, Ar-H, $J = 8.0$ Hz), 7.74 (1H, d, Ar-H, $J = 8.0$ Hz), 7.56 (1H, d, Ar-H, $J = 8.0$ Hz), 6.97 (1H, d, Ar-H, $J = 7.5$ Hz), 5.87 (2H, s, NH$_2$), 5.59 – 5.53 (2H, m, 2xCH(CH$_3$)$_2$), 5.41 (1H, sep, CH(CH$_3$)$_2$, $J = 6.0$ Hz), 1.46 (6H, d, CH(CH$_3$)$_2$, $J = 6.0$ Hz), 1.40 (6H, d, CH(CH$_3$)$_2$, $J = 6.0$ Hz); $^{13}$C NMR (125 MHz; CDCl$_3$) $\delta$ 165.5, 162.7, 161.8, 151.3, 150.3, 148.6, 138.5, 137.9, 137.7, 130.9, 126.9, 125.6, 124.8, 124.5, 119.4, 118.1, 117.4, 116.9, 69.4, 69.2, 67.8, 21.9, 21.8, 21.8; m/z (ESI) 552.2 (M + H, 100%), 574.2 (M + Na, 55%)$^*$. 

4-(4-(4-Amino-3-isopropoxybenzamido)-3-isopropoxybenzamido)-3-isopropoxybenzoic acid (2): yield = 50 mg, 95%; white solid; mp: 228–230°C; $^1$H NMR (500 MHz; d$_6$-DMSO, TMS) $\delta$ 9.28 (1H, s, CONH), 8.95 (1H, s, CONH), 8.30 (1H, d, Ar-H, $J = 8.0$ Hz), 8.16 (1H, d, Ar-H, $J = 7.5$ Hz), 7.57 (4H, m, 4xAr-H), 7.34 (2H, m, 2xAr-H), 6.72 (1H, d, Ar-H, $J = 8.0$ Hz), 5.44 (2H, s, Ar-NH$_2$), 4.80 (1H, sep, CH(CH$_3$)$_2$, $J = 6.1$ Hz), 4.72 (1H, sep, CH(CH$_3$)$_2$, $J = 6.0$ Hz), 4.61 (1H, sep, CH(CH$_3$)$_2$, $J = 6.0$ Hz), 1.39 (6H, d, CH(CH$_3$)$_2$, $J = 6.1$ Hz), 1.35 (6H, d,
CH(CH₃)₂, J = 6.0 Hz), 1.32 (6H, d, CH(CH₃)₂, J = 6.0 Hz); ¹³C NMR (125 MHz; d₆-DMSO) δ C
167.0, 164.5, 164.3, 147.6, 147.1, 143.3, 143.2, 132.8, 132.2, 129.2, 126.7, 122.1, 121.4, 121.3,
120.7, 120.3, 120.2, 113.9, 112.7, 112.6, 112.1, 71.4, 71.3, 70.3, 21.9, 21.8, 21.7; νmax/cm⁻¹
3401, 2975, 2364, 1683, 1592, 1517, 1486, 1413; m/z (ESI) 550.2 (M + H, 95%) *, 1099.3 (2M +
H, 100%) *.

4-(4-(5-Amino-6-isopropoxypicolinamido)-3-isopropoxybenzamido)-3-isopropoxybenzoic
acid (3): yield = 50 mg, 96%; off-white solid; mp: 260–262°C; ¹H NMR (500 MHz; d₆-DMSO,
TMS) δ H 10.21 (1H, s, CONH), 9.28 (1H, s, CONH), 8.65 (1H, d, Ar-H, J = 9.1 Hz), 8.18 (1H, d,
Ar-H, J = 8.6 Hz), 7.64 (1H, s, Ar-H), 7.60 – 7.57 (4H, m, 4xAr-H), 6.98 (1H, d, Ar-H, J = 8.6 Hz),
5.81 (2H, s, Ar-NH₂), 5.47 (1H, sep, CH(CH₃)₂, J = 5.5 Hz), 4.92 (1H, sep, CH(CH₃)₂, J = 5.5
Hz), 4.72 (1H, sep, CH(CH₃)₂, J = 5.5 Hz), 1.41 (12H, m, 2xCH(CH₃)₂), 1.36 (6H, d, CH(CH₃)₂, J
= 5.5 Hz); ¹³C NMR (125 MHz; d₆-DMSO) δ C 167.2, 164.6, 162.7, 149.1, 147.9, 146.0, 137.7,
132.3, 132.1, 131.9, 128.7, 127.3, 125.4, 122.4, 120.6, 118.2, 117.9, 117.8, 114.3, 111.9, 71.8,
71.4, 68.0, 22.3, 22.2, 22.1; νmax/cm⁻¹ 3349, 2971, 2923, 2860, 1675, 1591, 1517, 1481; m/z
(ESI) 551.2 (M + H, 100%) *, 573.2 (M + Na, 60%) *, 1123.4 (2M + Na, 90%) *.
4-(5-(5-Amino-6-isopropoxypicolinamido)-6-isopropoxypicolinamido)-3-isopropoxybenzoic acid (4): yield = 50 mg, 100%; pale-yellow solid; mp: 260–262°C; $^1$H NMR (500 MHz; $d_6$-DMSO, TMS) $\delta$H 10.29 (1H, s, CONH), 10.11 (1H, s, CONH), 8.92 (1H, d, Ar-H, $J = 8.2$ Hz), 8.61 (1H, d, Ar-H, $J = 8.2$ Hz), 7.87 (1H, d, Ar-H, $J = 7.9$ Hz), 7.65 – 7.58 (3H, m, 3xAr-H), 6.98 (1H, d, Ar-H, $J = 7.9$ Hz), 5.89 (2H, s, Ar-NH$_2$), 5.64 (1H, sep, CH(CH$_3$)$_2$, $J = 6.0$ Hz), 5.45 (1H, sep, CH(CH$_3$)$_2$, $J = 6.0$ Hz), 4.87 (1H, sep, CH(CH$_3$)$_2$, $J = 6.0$ Hz), 1.48 (6H, d, CH(CH$_3$)$_2$, $J = 6.0$ Hz), 1.43 (6H, d, CH(CH$_3$)$_2$, $J = 6.0$ Hz), 1.39 (6H, d, CH(CH$_3$)$_2$, $J = 6.0$ Hz); $^{13}$C NMR (125 MHz; $d_6$-DMSO) $\delta$C 166.9, 162.7, 161.2, 150.3, 148.6, 145.6, 138.5, 137.7, 131.9, 130.8, 125.7, 125.0, 124.5, 122.6, 118.1, 117.8, 117.4, 116.9, 113.2, 71.0, 69.2, 67.8, 21.9, 21.8, 21.7; $\nu_{max}$/cm$^{-1}$ 3411, 3357, 2975, 2929, 2360, 2337, 1685, 1598, 1517, 1465; m/z (ESI) 552.2 (M + H, 100%), 1125.4 (2M + Na, 100%).

4-(5-(4-Amino-3-isopropoxybenzamido)-6-isopropoxypicolinamido)-3-isopropoxybenzoic acid (5): yield = 53 mg, 100%; pale-yellow solid; mp: 238–240°C; $^1$H NMR (500 MHz; $d_6$-DMSO, TMS) $\delta$H 12.81 (1H, s, CO$_2$H), 10.33 (1H, s, CONH), 9.07 (1H, s, CONH), 8.61 (2H, m, 2xAr-H), 7.83 (1H, d, Ar-H, $J = 8.2$ Hz), 7.63 – 7.61 (2H, m, 2xAr-H), 7.37 (2H, m, 2xAr-H), 6.72 (1H, d, Ar-H, $J = 8.2$ Hz), 5.56 – 5.49 (3H, m, CH(CH$_3$)$_2$, Ar-NH$_2$), 4.87 (1H, sep, CH(CH$_3$)$_2$, $J = 5.6$ Hz), 4.61 (1H, sep, CH(CH$_3$)$_2$, $J = 5.6$ Hz), 1.47 (6H, d, CH(CH$_3$)$_2$, $J = 5.6$ Hz), 1.38 (6H, d, CH(CH$_3$)$_2$, $J = 5.6$ Hz); $^{13}$C NMR (125 MHz; $d_6$-DMSO) $\delta$C 167.4,
5-(5-(4-Amino-3-isopropoxybenzamido)-6-isopropoxypicolinamido)-6-isopropoxypicolinic acid (6): yield = 30 mg, 98%; off-white solid; mp: 225–227°C; $^1$H NMR (500 MHz; $d_6$-DMSO, TMS) $\delta$H 10.2 (1H, s, CONH), 9.08 (1H, s, CONH), 8.82 (1H, d, Ar-H, $J$ = 7.7 Hz), 8.61 (1H, d, Ar-H, $J$ = 8.2 Hz), 7.83 (1H, d, Ar-H, $J$ = 7.7 Hz), 7.76 (1H, d, Ar-H, $J$ = 8.2 Hz), 7.37 (2H, m, 2xAr-H), 6.72 (1H, d, Ar-H, $J$ = 8.1 Hz), 5.59 – 5.45 (4H, m, 2xCH(CH$_3$)$_2$, Ar-NH$_2$), 4.61 (1H, sep, CH(CH$_3$)$_2$, $J$ = 5.9 Hz), 1.49 (6H, d, CH(CH$_3$)$_2$, $J$ = 5.9 Hz), 1.41 (6H, d, CH(CH$_3$)$_2$, $J$ = 5.9 Hz); $^{13}$C NMR (125 MHz; $d_6$-DMSO) $\delta$c 165.9, 165.6, 162.4, 152.5, 151.8, 144.1, 143.7, 139.2, 139.1, 128.8, 127.7, 126.0, 125.1, 122.3, 120.7, 119.9, 116.8, 113.4, 113.1, 70.9, 70.1, 69.7, 22.4, 22.3, 22.1; m/z (ESI) 551.3 (M, 50%)*, 574.3 (M + Na, 100%)*, 1125.3 (2M + Na, 50%)*. 
Computational details

A CHARMM-compatible force field for compounds 1, 2 and 5 was constructed in the framework of the CHARMM General Force Fields (CGenFF) version 2b6. Atom types and charges were assigned manually using analogy with existing CGenFF model compounds and standard CHARMM force field charge assignment rules. This manual procedure allowed us to define the benzene- and pyridine-based monomers of the oligoamide backbone as different CHARMM residues and the isopropyl groups as side chain patches, thus providing basic building block for convenient generation of a variety of oligoamide-foldamers for present and future research. Bond, angle, dihedral and improper dihedral parameters were obtained from the CGenFF program version 0.9.1 beta through the ParamChem website. The parameters by analogy assigned by this program were critically examined and a better analogy was manually chosen for a few select parameters; the resulting CHARMM-compatible stream file is available in the Electronic Supplementary Information. Solution phase calculations of compounds 1, 2 and 5 were performed by placing a minimized conformation of the solute in a pre-equilibrated cubic cell with edge length ~ 49 Å containing 3504 TIP3P water molecules. All water molecules with atoms within 2 Å from any solute atom were removed and an arbitrary water molecule was replaced by a sodium ion in order to neutralize the oligoamide’s free backbone carboxylate. In the presence of periodic boundary conditions, the system was then partially minimized for 200 steepest decent steps in order to alleviate any bad contacts or other strong interaction. Finally, the system was gradually heated to 298.15K during a 20ps MD simulation and then equilibrated for 100 ps. This equilibration was followed by a 50 ns production simulation during which snapshots were taken at 2 ps intervals. The particle mesh Ewald method was used for the treatment of the Coulomb interactions with a real space cutoff of 12 Å, a 6th order cubic spline and a kappa value of 0.32. For the Lennard-Jones (LJ) interactions, a force-switching function was applied over the range of 10-12 Å, and a long-range correction was used to account for LJ interactions beyond the cutoff distance. A timestep of 1 fs was used in conjunction with the “Leapfrog” algorithm to integrate the equations of motion. The SHAKE algorithm was applied to constrain the length of covalent bonds to hydrogen atoms to their equilibrium values. The Nosé-Hoover thermostat and the Langevin piston barostat were used to generate the isothermal-isobaric ensemble (NPT) with continuous dynamics.

Probability distributions for distances were generated by measuring the distance at each snapshot and creating a histogram of the resulting 25000 measurements using 0.1 Å bins, which was then normalized so that the area under the curve integrates to 1. For angles and dihedral angles, bin sizes of 5° and 15° were used, respectively.

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* Keyword “PRES” in the CHARMM Residue Topology File (rtf) format specification.
† An effort is underway to improve the accuracy of assignment of parameters by analogy, which will significantly decrease the incidence of non-optimal analogies.
**Figure A:** Measurements of select distances and angles in Sattler et al's Bak–Bcl-xL NMR structure compared to probability distributions from 50ns MD simulations on compounds 1 (red), 2 (green) and 5 (blue). O1, O2 and O3 respectively correspond to the N-terminal, middle and C-terminal ether oxygens in the oligoamide foldamers.

**Figure B:** Left: same probability distribution as Figure 2 in the main article, but the N-terminal bifurcated hydrogen bond lengths were measured instead of the C-terminal ones. Right: same probability distribution as Figure 3 in the main article, but for the N-terminal virtual dihedral instead of the C-terminal one.
Fluorescence Polarization In Vitro Assay

Fluorescence polarization experiments were conducted using a BMG PHERAstar FS multimode microplate reader equipped with two PMTs for simultaneous measurements of the perpendicular and parallel fluorescence emission with a 485 nm excitation and 520 nm emission filters. Human Bcl-xL was expressed and purified as previously described minus the C-terminal transmembrane domain (amino acids 205 – 234),\(^{13}\) and was stored in 1x PBS, pH 7.4 at -78°C. A 6-aminohexanoic acid linker was conjugated to the N-terminus of the Bak BH3 peptide GQVGRQLAIIGDDINR which was then capped with fluorescein (on the amino group of the linker) and the peptide was amidated on the C-terminus to give FITC-Ahx-GQVGRQLAIIGDDINR-CONH\(_2\), hereafter referred to as “FITC-Bak” (synthesized by Neo BioScience in >95% purity). To determine the \(K_d\) of the FITC-Bak peptide, the assay was performed in black polypropylene 384-well microplate (Costar) with a final volume of 50 µL containing varying concentrations of Bcl-xL in the presence of 15 nM FITC-Bak peptide in PBS (pH 7.4) at room temperature. The fluorescence polarization assays (FPCA) were performed using 15 nM Bcl-xL in the same buffer (hence, 15 nM FITC-Bak) with varying concentrations of inhibitors. Regression analysis was carried out using Origin (OriginLab, Northampton, MA) to fit the data to the Hill equation (1) to determine the binding affinity \((K_d)\) of Bcl-xL for the binding of the FITC-Bak peptide and to determine the IC\(_{50}\) in the FPCA. The Cheng-Prusoff equation (1) was then used to determine the \(K_i\) for the inhibitors.

\[
K_i = \frac{IC_{50}}{1 + \frac{[L_{total}^{FITC-Bak}]}{K_{d}^{FITC-Bak}}}
\]

\((IC_{50} = \text{determined using Hill equation, } [L_{total}^{FITC-Bak}] = \text{total ligand } (15 \text{ nM FITC-Bak}), K_{d}^{FITC-Bak} = 12.5 \text{ nM the affinity of Bcl-xL for FITC-Bak peptide under the assay conditions.})

Figure C: Binding of fluorescent peptide FITC-Bak (15 nM) to Bcl-xL.
Figure D: Competitive inhibition fluorescence polarization assay for binding of compound 2 to Bcl-xL.

**XTT Whole Cell Toxicity Assay**

The effects of the inhibitor on cell viability were assessed in quadruplicate samples using the 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino) carbonyl]-2H-tetrazolium hydroxide (XTT) assay (Roche). Cancer cells as well as human normal lung microvesicular endothelial cells were seeded (3000 cells/well) and incubated in 96-well, flat-bottomed plates in 10% FBS-supplemented culture mediums 24 hours before inhibitor treatment. The cells were then exposed to individual Bcl-xL inhibitors at the indicated concentrations in 10% FBS-supplemented culture mediums at 37°C in 5% CO₂ for 72 hours. The medium was removed and replaced with fresh medium containing 150 µl of XTT, and the cells were further cultured in the CO₂ incubator at 37°C for 5 hours. Absorbance was determined on a plate reader at 480 nm. Each sample point represents the average of quadruplication.
References

3 https://www.paramchem.org/