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SUPPORTING INFORMATION

Title: Synthesis of an Oxazole–Pyrrole–Piperazine Scaffold as an α-Helix Mimetic
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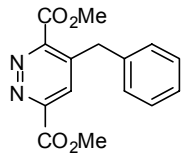
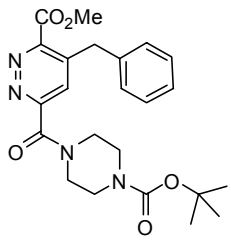
Ref. No.: O200701164

General methods

Solvents and reagents were of reagent-grade, purchased from commercial suppliers, and used without further purification unless otherwise stated. Substituted NBoc-protected piperazines were purchased from Anaspec. Thin-layer chromatography (TLC) was performed on Kieselgel 60 F_{254} coated plates (Merck). Preparative TLC was performed on Partisil® PK6F silica gel 60 Å, coated plates 1000 μm (Whatman). ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 250 MHz, Varian Mercury 300 MHz or Bruker DRX 600 MHz spectrometers. Chemical shifts are expressed in ppm (δ), referenced to the protio impurity of the solvent as internal standard for ^{1}H and ^{13}C nuclei. High resolution mass spectra were recorded on an Agilent ESI-TOF mass spectrometer by Scripps Center for Mass Spectrometry.

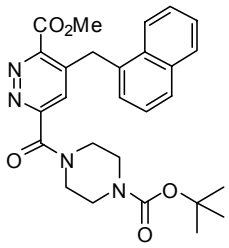


3,6-Dimethyl-4-benzyl-1,2-pyridazine dicarboxylate 3b; To a solution of tetrazine **5** (1.125 g, 5.7 mmol) in 1,4-dioxane (30 mL) was added 3-Phenyl-1-propyne **6b** (850 µL, 6.8 mmol). The reaction vessel was sealed and heated to 90 ºC for 24 h. The volatiles were evaporated under reduced pressure and the crude residue purified by silica gel chromatography (CH_2Cl_2/EtOAc 9/1) to give **3b** (1.415 g, 87%) as a yellow oil. ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.32 (m, 2H), 7.27 (m, 1H), 7.13 (d, J = 7.4 Hz, 2H), 4.30 (s, 2H), 4.03 (s, 3H), 3.99 (s, 3H); ^{13}C NMR: (150 MHz, $CDCl_3$) δ 165.3, 164.3, 154.2, 152.0, 122, 142.3, 136.4, 129.4, 129.3, 129.2, 127.6, 53.7, 53.3; HRMS: (ESI-TOF) $C_{15}H_{14}N_2O_4H^+$ expected: 287.1026, found: 287.1022.



Methyl 4-benzyl-6-(4-(*tert*-butoxycarbonyl)piperazine-1-carbonyl)pyridazine-3-carboxylate 13a; Following the Method A procedure for the piperazine coupling described below: starting from **3b** (252 mg, 0.88 mmol), column AcOEt/Hexane 1/1 to 3/2, yield: 174 mg (52%). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.33–7.22 (m, 3H), 7.14–7.12 (m, 2H), 4.29 (s, 2H), 3.99 (s, 3H), 3.76–3.72 (m, 2H), 3.66–3.63 (m, 2H), 3.55–3.47 (m, 4H), 1.43 (s, 9H); ^{13}C NMR: (150 MHz, $CDCl_3$) δ 164.5, 163.9, 156.5, 154.0, 152.1, 142.5, 135.9, 129.0, 128.8, 128.6, 126.9, 79.8, 52.8, 46.9, 42.3, 37.0, 27.9; HRMS: (ESI-TOF) $C_{23}H_{28}N_4O_5H^+$ expected: 441.2132. found: 441.2132.

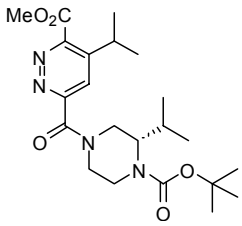
<u>Method B: Typical procedure for the piperazine coupling</u>



Methyl 6-(4-(*tert*-butoxycarbonyl)piperazine-1-carbonyl)-4-(naphthalen-1-ylmethyl)pyridazine-3-carboxylate 13b; To a stirred solution of pyridazine **3c** (300 mg, 0.89 mmol) and $MgCl_2$ (170 mg, 1.78 mmol) in CH_3CN (5 mL) was added dropwise a solution of *N*-Bocpiperazine (249 mg, 1.34 mmol) in CH_3CN (3 mL) at rt. The mixture was then sonicated for 1 h and let 24 h under nitrogen. The mixture was poured into water (10 mL) and the aqueous layer was extracted with EtOAc (3x10 mL). The organic layers were collected, dried over Na_2SO_4, filtered and concentrated in vacuo. The

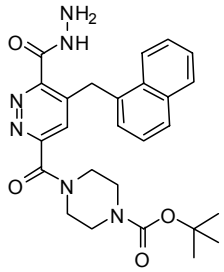
crude residue was purified on silica (CH_2Cl_2/AcOEt 1/0 to 8/2) to afford compound **13b** (196 mg, 45%) as a yellow foam; ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.54-7.45 (m, 3H), 7.35 (m, 2H), 4.80 (s, 2H), 4.11 (s, 3H), 3.70 (m, 2H), 3.58 (m, 2H), 3.52 (m, 2H), 3.46 (m, 2H), 1.48 (m, 9H); ^{13}C NMR: (150 MHz, $CDCl_3$) δ 165.0, 164.2, 156.8, 154.4, 152.0, 142.9, 134.0, 131.6, 131.5, 129.1, 128.6, 128.5, 126.7, 126.1, 125.6, 123.4, 80.3, 53.4, 47.2, 42.5, 34.7, 28.3; HRMS: (ESI-TOF) $C_{27}H_{30}N_4O_5H^+$ expected: 491.2289. found: 491.2280.

Method A: Typical procedure for the piperazine coupling



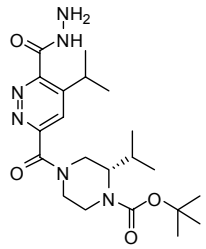
(*S*)-Methyl 6-(4-(*tert*-butoxycarbonyl)-3-isopropylpiperazine-1-carbonyl)-4-isopropylpyridazine-3-carboxylate 13c; To a stirring solution of the dimethyl ester **3d** (719 mg, 3.02 mmol) in THF (10 mL) at 0 °C was added dropwise a cold solution of LiOH•H_2O (139 mg, 3.3 mmol) in water (5 mL). The reaction was stirred at 0 °C until disappearance of the starting material according to TLC. The pH was then made acidic (pH 1-2) with careful addition of a 3% HCl solution and the organic phase was extracted with EtOAc (3 x 30 mL). The fractions were combined, dried with Na_2SO_4, filtered and the solvent was removed in vacuo. The desired monosaponified pyridazine was obtained as a pale yellow solid (510 mg, 2.27 mmol, 75%). The carboxylic acid was used directly in the next step without further purification. To a solution of the acid (340 mg, 1.5 mmol) in CH_2Cl_2 (15 mL), was added NEt_3 (0.422 mL, 3 mmol), *N*-Boc-Isopropyl-piperazine (350 mg, 1.5 mmol) and PyBroP (707 mg, 1.5 mmol). After stirring 18 h under nitrogen, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with a solution of HCl (0.1 M, 10 mL) and saturated $NaHCO_3$ (10 mL). The organic layer was then dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (Hexane/AcOEt 1/0 to 6/4) and the desired piperazine adduct **13c** was obtained as a pale yellow foam (452 mg, 1.04 mmol, 69%); ^{1}H NMR: (250 MHz, $CDCl_3$) δ 7.89 (s, 0.7H), 7.84 (s, 0.3H), 4.85 (m, 0.7H), 4.62 (m, 0.3H), 4.18 (m, 1H), 4.03 (s, 3H), 3.90 (m, 1H), 3.47 (hept, *J* = 6.8 Hz, 1H), 3.36 (m, 1H), 3.15 (m, 1H), 2.94 (m, 2H), 2.16-1.87 (m, 1H), 1.44 (s, 5H), 1.43 (s, 4H), 1.32-1.22 (m, 6H), 1.05 (d, *J* = 6.9 Hz, 2H), 0.85 (d, *J* = 6.8 Hz, 2H), 0.79 (d, *J* = 6.9 Hz, 1H), 0.59 (d, *J* = 6.8 Hz, 1H);

^{13}C NMR: (62.5 MHz, $CDCl_3$) δ 165.1, 164.9, 156.9, 154.6, 152.7, 149.1, 148.9, 125.9, 125.4, 53.2, 47.8, 47.5, 43.9, 42.4, 28.8, 28.3, 25.9, 25.6, 22.6, 22.5, 20.3, 19.9, 18.6; HRMS: (ESI-TOF) $C_{22}H_{34}N_4O_5H^+$ expected: 435.2602. found: 435.2598.

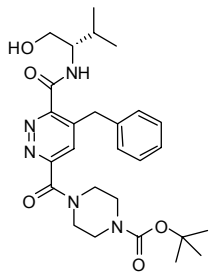


***Tert*-butyl 4-(6-(hydrazinecarbonyl)-5-(naphthalen-1-ylmethyl)pyridazine-3-carbonyl)piperazine-1-carboxylate 14b;** Following the typical procedure for the acylhydrazide formation described below: starting from **13b** (186 mg, 0.37 mmol), column CH_2Cl_2/MeOH 1/0 to 95/5, yield: 174 mg, (93%); ^{1}H NMR: (250 MHz, $CDCl_3$) δ 9.29 (m, 1H), 7.84 (m, 2H), 7.69 (m, 1H), 7.49-7.29 (m, 4H), 7.22 (m, 1H), 5.04 (s, 2H), 3.62 (m, 2H), 3.48-3.32 (m, 6H), 1.43 (m, 9H); ^{13}C NMR: (62.5 MHz, $CDCl_3$) δ 164.2, 164.1, 156.9, 154.2, 150.5, 143.9, 133.9, 132.2, 131.5, 129.0, 128.9, 128.5, 128.3, 126.5, 125.9, 125.6, 123.5, 80.3, 47.0, 43.2, 43.0, 42.2, 34.5, 28.2; HRMS: (ESI-TOF) $C_{26}H_{30}N_6O_4H^+$ expected: 491.2401. found: 491.2388.

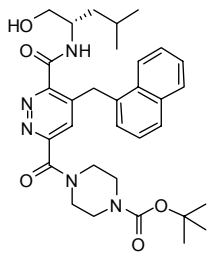
<u>Method C: Typical procedure for the acylhydrazide formation:</u>



(*S*)-*Tert*-butyl 4-(6-(hydrazinecarbonyl)-5-isopropylpyridazine-3-carbonyl)-2-isopropylpiperazine-1-carboxylate 14c; To a solution of methylester **13c** (224 mg, 0.51 mmol) in MeOH (10 mL), was added hydrazine hydrate (206 mg, 4.1 mmol). The reaction mixture was stirred at rt under nitrogen for 20 h, and then the volatiles removed under reduced pressure. The crude product was purified using silica gel chromatography (CH_2Cl_2/MeOH 1/0 to 95/5) to give the desired acylhydrazide **14c** as a pale yellow foam (211 mg, 0.48 mmol, 94%); ^{1}H NMR: (250 MHz, $CDCl_3$) δ 9.02 (m 1H), 7.90 (s, 0.7H), 7.82 (s, 0.3H), 4.82 (m, 0.7H), 4.61 (m, 0.3H), 4.28-3.50 (m, 5H), 3.42-2.84 (m, 2H), 2.14-1.86 (m, 1H), 1.43 (s, 5H), 1.42 (s, 4H), 1.32-1.20 (m, 6H), 1.05 (d, J = 6.9 Hz, 2H), 0.84 (d, J = 6.8 Hz, 2H), 0.79 (d, J = 6.9 Hz, 1H), 0.53 (d, J = 6.8 Hz, 1H); ^{13}C NMR: (62.5 MHz, $CDCl_3$) δ 165.1, 164.9, 156.9, 154.6, 152.7, 149.1, 148.9, 125.9, 125.4, 53.2, 47.8, 47.5, 43.9, 42.4, 28.8, 28.3, 25.9, 25.6, 22.6, 22.5, 20.3, 19.9, 18.6; HRMS: (ESI-TOF) $C_{21}H_{34}N_6O_4H^+$ expected: 435.2714. found: 435.2732.



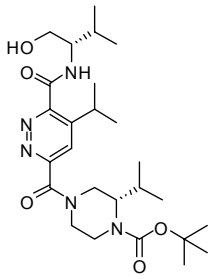
(*S*)-*Tert*-butyl 4-(5-benzyl-6-(1-hydroxy-3-methylbutan-2-ylcarbamoyl)pyridazine-3-carbonyl)piperazine-1-carboxylate 15a; To a solution of methylester **13a** (275 mg, 0.624 mmol) in a THF/H_2O mixture (3/1, 4 ml) was added dropwise a solution of LiOH•H_2O (45 mg, 1.074 mmol) in H_2O (1 ml). After stirring for 1.5 h at rt the solution was poured into a solution of 0.5 M HCl and extracted four times with AcOEt. The organic phases were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (4 mL). L-Valinol (72 mg, 0.745 mmol, 1.2 eq.) was added followed by PyBroP (320 mg, 0.686 mmol) and *i*Pr_2NEt (0.5 ml). The resulting mixture was stirred overnight at rt, and then a solution of 0.5 M HCl was added and the mixture was extracted several times with AcOEt. The combined organic phases were washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (AcOEt/CH_2Cl_2 1:1) to give the diamide **15a** (135 mg, 0.264 mmol, 42%) as a pale yellow oil. ^{1}H NMR: (600 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.2 Hz, 2H), 7.66 (s, 1H), 7.32–7.30 (m, 3H), 7.25–7.22 (m, 2H), 4.59-4.52 (m, 2H), 4.02–3.97 (m, 2H), 3.82–3.78 (m, 1H), 3.75–3.71 (m, 3H), 3.56–3.44 (m, 6H), 2.12-2.06 (m, 1H), 1.44 (s, 9H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR: (150 MHz, CD_3COCD_3) δ 166.5, 166.2, 159.4, 156.0, 144.7, 140.1, 131.3, 130.9, 130.5, 130.5, 128.6, 111.4, 81.1, 63.9, 58.6, 48.7, 43.8, 38.5, 30.9, 29.5, 21.1, 20.1; HRMS: (ESI-TOF) $C_{27}H_{37}N_5O_5H^+$ expected 512.2867. found 512.2865.



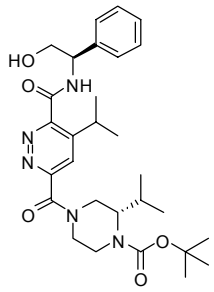
(*S*)-*Tert*-butyl 4-(6-(1-hydroxy-4-methylpentan-2-ylcarbamoyl)-5-(naphthalen-1-ylmethyl)pyridazine-3-carbonyl)piperazine-1-carboxylate 15b; Following the typical procedure for the amino alcohol coupling described below: starting from **14b** (174 mg, 0.35 mmol), column CH_2Cl_2/MeOH 1/0 to 97/3, yield: 159 mg, (77%); ^{1}H NMR: (250 MHz, $CDCl_3$) δ 8.24 (m, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.52-7.30 (m, 4H), 7.22 (m, 1H), 5.08 (s, 2H), 4.35 (m, 1H), 3.84 (m, 1H), 3.78-3.60 (m, 3H), 3.52-3.32 (m, 6H), 1.90-1.40 (m, 3H), 1.44 (m, 9H), 0.98 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR: (62.5 MHz, $CDCl_3$) δ 164.3, 156.9, 154.3,

150.9, 144.3, 134.0, 132.5, 131.7, 129.2, 129.1, 128.9, 128.6, 128.3, 126.5, 125.9, 125.7, 123.7, 80.3, 65.9, 50.2, 47.0, 43.3 (broad), 42.3, 40.1, 34.8, 28.2, 24.9, 23.0, 22.1; HRMS: (ESI-TOF) $C_{32}H_{41}N_5O_5H^+$ expected: 576.3180. found: 576.3169.

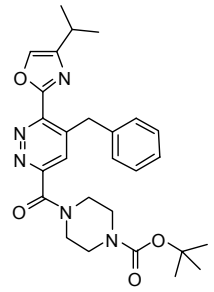
Method C: Typical procedure for the amino alcohol coupling



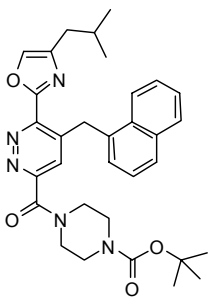
(*S*)-*Tert*-butyl 4-(6-((*S*)-1-hydroxy-3-methylbutan-2-ylcarbamoyl)-5-isopropylpyridazine-3-carbonyl)-2-isopropylpiperazine-1-carboxylate 15c; To a solution of $NaNO_2$ (67 mg, 0.97 mmol), and acetic acid (87 mg, 1.45 mmol) in water (3.5 mL) at 0 °C was added dropwise a HCl solution (1 M, 1.944 mL, 1.94 mmol). After 10 min a solution of acyl hydrazide **14c** (211 mg, 0.48 mmol) in THF (10 mL) was added slowly and the reaction mixture was stirred at 0 °C for 20 min. The acidic solution was made basic (pH 10) with a saturated solution of $NaHCO_3$ and extracted with cold Et_2O (3x15 mL). The organic fractions were collected in a second flask at 0 °C, and a cold solution of L-valinol (100 mg, 0.97 mmol) in Et_2O (5 mL) was added. The reaction was allowed to warm to rt and stirred overnight. The solvent was evaporated, and the crude residue was purified by silica gel chromatography (CH_2Cl_2/MeOH 1/0 to 95/5). The desired amido-alcohol **15c** was obtained as a pale yellow foam (235 mg, 0.46 mmol, 95%); ^{1}H NMR: (250 MHz, $CDCl_3$) δ 8.07 (m, 1H), 7.88 (m, 0.7H), 7.84 (m, 0.3H), 4.85 (m, 0.7H), 4.66 (m, 0.3H), 4.32-4.16 (m, 1H), 4.10-3.90 (m, 2H), 3.88-3.68 (m, 2H), 3.61 (m, 1H), 3.37 (m, 1H), 3.26-3.04 (m, 1H), 3.02-2.88 (m, 1H), 2.71 (m, 1H), 2.16-1.86 (m, 2H), 1.44 (s, 9H), 1.36-1.16 (m, 7H), 1.15-0.92 (m, 7H), 0.86 (d, J = 6.8 Hz, 2H), 0.79 (d, J = 6.9 Hz, 1H), 0.52 (d, J = 6.8 Hz, 1H); ^{13}C NMR: (62.5 MHz, $CDCl_3$) δ 165.6, 165.1, 164.5, 157.2, 154.6, 151.6, 151.3, 126.5, 126.1, 80.2, 80.1, 63.6, 57.3, 47.8, 47.4, 43.7, 42.3, 38.6 (broad), 29.1, 28.3, 27.9, 25.9, 25.5, 22.7, 22.6, 22.5, 20.3, 19.8, 19.5, 18.7; (ESI-TOF) $C_{26}H_{43}N_5O_5H^+$ expected: 506.3337. found: 506.3322.



(*S*)-*Tert*-butyl 4-(6-((*R*)-2-hydroxy-1-phenylethylcarbamoyl)-5-isopropylpyridazine-3-carbonyl)-2-isopropylpiperazine-1-carboxylate 15d; Following Method C procedure for the amino alcohol coupling described above: starting from **14c** (210 mg, 0.48 mmol), column CH_2Cl_2/MeOH 1/0 to 95/5, white foam, yield: 152 mg (58%); ^{1}H NMR: (600 MHz, $CDCl_3$) δ 8.67 (m, 1H), 7.95 (m, 0.7H), 7.90 (m, 0.3H), 7.46 (m, 2H), 7.42 (m, 2H), 7.35 (m, 1H), 5.32 (m, 1H), 4.90 (m, 0.7H), 4.70 (m, 0.3H), 4.30 (m, 1H), 4.160-4.02 (m, 4H), 3.43 (m, 0.3H), 3.30-2.98 (m, 2.7H), 2.34-1.94 (m, 2H), 1.50 (s, 5H), 1.49 (s, 4H), 1.35-1.27 (m, 6H), 1.13 (d, J = 6.8 Hz, 2H), 0.92 (d, J = 6.8 Hz, 2H), 0.85 (d, J = 6.9 Hz, 1H), 0.58 (m, 1H); ^{13}C NMR: (150 MHz, $CDCl_3$) δ 165.1, 164.0, 157.4, 154.7, 151.7, 151.2, 138.5, 128.9, 128.0, 126.8, 126.7, 126.3, 80.2, 66.4, 56.1, 47.9, 47.4, 43.8, 42.4, 28.3, 27.9, 26.0, 25.6, 22.8, 22.7, 22.6, 20.3, 20.2; HRMS: (ESI-TOF) $C_{29}H_{41}N_5O_5H^+$ expected: 540.3180. found: 540.3172.



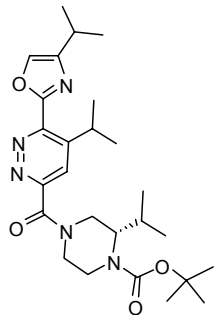
***Tert*-butyl 4-(5-benzyl-6-(4-isopropyloxazol-2-yl)pyridazine-3-carbonyl)piperazine-1-carboxylate 16a;** Following the typical procedure for the oxazole formation described below: starting from **15a** (135 mg, 0.26 mmol), column CH_2Cl_2/AcOEt 5/1 to 2/1, yield: 71 mg, (40%). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.60 (s, 1H), 7.33–7.20 (m, 5H), 4.65 (s, 2H), 3.77 (m, 2H), 3.75 (m, 2H), 3.57 (m, 2H), 3.53 (m, 2H), 2.98 (m, 1H), 1.47 (s, 9H), 1.33 (d, J = 6.9 Hz, 6H); ^{13}C NMR: (150 MHz, $CDCl_3$): 164.6, 157.1, 155.2, 154.5, 149.5, 148.9, 142.0, 136.7, 134.5, 129.5, 129.1, 128.9, 127.1, 80.3, 47.4, 42.7, 38.1, 28.3, 26.5, 21.4; HRMS: (ESI-TOF) $C_{27}H_{33}N_5O_4H^+$ expected: 492.2605. found: 492.2607.



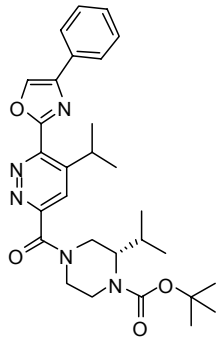
***Tert*-butyl 4-(6-(4-isobutyloxazol-2-yl)-5-(naphthalen-1-ylmethyl)pyridazine-3-carbonyl)piperazine-1-carboxylate 16b;** Following the typical procedure for the oxazole formation described below: starting from **15b** (139 mg, 0.24 mmol), column Hexane/AcOEt 1/0 to 7/3, yield: 70 mg, (52%); ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.92 (d, J = 8.6 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.70 (m,

1H), 7.53-7.46 (m, 2H), 7.43 (m, 1H), 7.37 (m, 2H), 5.11 (s, 2H), 3.70 (m, 2H), 3.64 (m, 2H), 3.52 (m, 2H), 3.47 (m, 2H), 2.53 (d, J = 6.9 Hz, 2H), 2.02 (hept, J = 6.7 Hz, 1H), 1.48 (s, 9H), 0.96 (d, J = 6.6 Hz, 6H); ^{13}C NMR: (150 MHz, $CDCl_3$) δ 164.6, 157.2, 155.2, 154.4, 148.7, 142.4, 141.8, 136.5, 134.1, 132.5, 131.7, 129.0, 128.5, 128.4, 128.3, 126.5, 125.9, 125.6, 123.7, 80.3, 47.3, 43.7, 43.6, 43.5 (broad), 42.5, 35.7, 35.2, 28.3, 27.7, 22.2; HRMS: (ESI-TOF) $C_{32}H_{37}N_5O_4H^+$ expected: 556.2918. found: 556.2905.

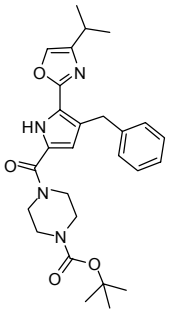
Typical procedure for the oxazole formation



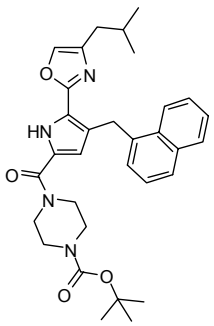
(*S*)-*Tert*-butyl 2-isopropyl-4-(5-isopropyl-6-(4-isopropyloxazol-2-yl)pyridazine-3-carbonyl)piperazine-1-carboxylate 16c; To a stirred solution of alcohol **15c** (235 mg, 0.46 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Dess-Martin periodinane (296 mg, 0.69 mmol). The mixture was stirred at 0 °C for 30 min and at rt for 2 h and then washed with aqueous $NaHCO_3/Na_2S_2O_3$ (1:1, 10 mL), dried (Na_2SO_4), filtered and concentrated to afford the crude aldehyde. The aldehyde was then immediately dissolved in CH_2Cl_2 (6 mL) cooled to 0 °C, and treated with Ph_3P (732 mg, 2.79 mmol) and 2,6-di-*tert*-butyl pyridine (2.055 mL, 9.3 mmol). Then $BrCCl_2CCl_2Br$ (907 mg, 2.79 mmol) was added. After 1 h, CH_3CN (10 mL) and then DBU (1.389 mL, 9.3 mmol) were added. The mixture was then warmed to rt for 2 h and concentrated. The crude residue was purified by flash chromatography with (Hexane/AcOEt 1/0 to 7/3) to afford the desired oxazole **16c** as a pale yellow solid (181 mg, 0.37 mmol, 80%); ^{1}H NMR: (250 MHz, $CDCl_3$) δ 7.94 (s, 0.6H), 7.89 (s, 0.4H), 7.57 (s, 1H), 4.87 (m, 0.7H), 4.66 (m, 0.3H), 4.30 (m, 1H), 4.21 (hept, J = 6.9 Hz, 1H), 3.95 (m, 2H), 3.67 (m, 0.7H), 3.41 (m, 0.3H), 3.18 (m, 1H); 2.94 (m, 2H), 2.20-1.88 (m, 1H), 1.46 (s, 6H), 1.45 (s, 3H), 1.30 (d, J = 6.9 Hz, 12H), 1.08 (d, J = 6.9 Hz, 2H), 0.87 (d, J = 6.9 Hz, 2H), 0.80 (d, J = 6.9 Hz, 1H), 0.58 (m, 1H); ^{13}C NMR: (62.5 MHz, $CDCl_3$) δ 165.8, 165.2, 156.9, 155.6, 155.5., 154.7, 149.4, 149.1, 148.8, 134.3, 125.7, 125.3, 80.1, 80.0, 58.3 (broad), 47.9, 47.6, 44.0, 42.5, 38.9 (broad) 30.0, 28.3, 26.4, 25.9, 25.7, 22.2, 21.4, 20.3, 19.9, 18.7, 18.7 (broad); HRMS: (ESI-TOF) $C_{26}H_{39}N_5O_4H^+$ expected: 486.3075. found: 486.3075.



(*S*)-*T*ert-butyl 2-isopropyl-4-(5-isopropyl-6-(4-phenyloxazol-2-yl)pyridazine-3-carbonyl)piperazine-1-carboxylate 16d; Following the typical procedure for the oxazole formation described above: starting from **15d** (152 mg, 0.28 mmol), column Hexane/AcOEt 1/0 to 7/3, yield: 117 mg, (80%); ^{1}H NMR: (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.99 (s, 0.8H), 7.90 (s, 0.2H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.45 (t_{app}, *J* = 7.7 Hz, 2H), 7.36 (t_{app}, *J* = 7.4 Hz, 1H), 7.32 (m, 1H), 6.45 (d, *J* = 2.6 Hz, 0.7H), 4.67 (m, 0.3H), 4.35 (m, 2H), 3.96 (m, 2H), 3.44 (m, 0.3H), 3.20 (m, 0.6H), 3.05-2.95 (m, 1.1H), 2.12 (m, 0.7H), 1.99 (m, 0.3H), 1.47 (s, 9H), 1.41-1.35 (m, 6H), 1.09 (d, *J* = 6.5 Hz, 2H), 0.89 (d, *J* = 6.7 Hz, 2H), 0.82 (d, *J* = 6.7 Hz, 1H), 0.62 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR: (150 MHz, $CDCl_3$) δ 165.1, 157.5, 155.8, 155.7, 154.7, 154.6, 149.4, 148.5, 142.6, 135.0, 130.3, 128.8, 128.5, 125.9, 125.6, 125.5, 47.9, 47.7, 44.0, 42.6, 28.5, 28.3, 26.0, 25.7, 22.4, 22.3, 20.3, 19.9; HRMS: (ESI-TOF) $C_{29}H_{37}N_5O_4H^+$ expected: 520.2918. found: 520.2901.

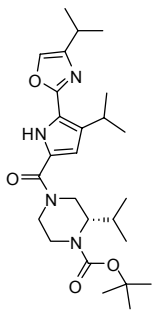


***Tert*-butyl 4-(4-benzyl-5-(4-isopropyloxazol-2-yl)-1H-pyrrole-2-carbonyl)piperazine-1-carboxylate 17a;** Following the typical procedure for the pyridazine to pyrrole reduction described below: Starting from **16a** (68 mg, 0.13 mmol), prep. TLC (CH_2Cl_2/AcOEt 3:1), yield: 8 mg, (12%); ^{1}H NMR: (300 MHz, CD_3COCD_3) δ 10.57 (bs, 1H), 7.65 (s, 1H), 7.34–7.12 (m, 5H), 6.54 (d, *J* = 2.7 Hz, 1H), 4.25 (s, 2H), 3.75–3.72 (m, 4H), 3.49–3.46 (m, 4H), 2.86 (m, 1H), 1.45 (s, 9H), 1.26 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR: (75 MHz, CD_3COCD_3) δ 162.8, 157.6, 156.0, 149.9, 143.5, 133.7, 130.5, 130.0, 128.3, 127.6, 127.4, 121.2, 115.8, 81.00, 34.5, 34.0, 33.0, 29.5, 28.2, 22.8; HRMS: (ESI-TOF) $C_{27}H_{34}N_4O_4H^+$ expected: 478.2653. found: 479.2666.



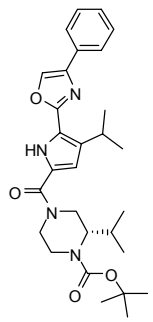
***Tert*-butyl 4-(5-(4-isobutyloxazol-2-yl)-4-(naphthalen-1-ylmethyl)-*1H*-pyrrole-2-carbonyl)piperazine-1-carboxylate 17b;** Following the typical procedure for the pyridazine to pyrrole reduction described below: starting from **16b** (70 mg, 0.12 mmol), prep. TLC (Hexane/AcOEt 7/3), yield: 13 mg, (19%); ^{1}H NMR: (600 MHz, $CDCl_3$) δ 9.86 (bs, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.52-7.36 (m, 5H), 6.05 (d, *J* = 2.7 Hz, 1H), 4.71 (s, 2H), 3.65 (m, 4H), 3.41 (m, 4H), 2.46 (d, *J* = 7.0 Hz, 2H), 2.05 (hept, *J* = 6.7 Hz, 1H), 1.47 (s, 9H), 0.99 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR: (150 MHz, $CDCl_3$) δ 161.1, 155.6, 154.4, 140.9, 136.7, 133.8, 133.6, 132.0, 128.6, 127.0, 126.5, 125.8, 125.5, 125.3, 125.2, 124.3, 119.6, 114.0, 80.2, 44.0, 43.9, 43.8, 43.7, 43.3 (broad), 42.8, 42.7, 35.2, 30.0, 28.3, 27.6, 22.3; HRMS: (ESI-TOF) $C_{32}H_{38}N_4O_4H^+$ expected: 543.2966. found: 543.2976.

<u>Typical procedure for the pyridazine to pyrrole reduction.</u>

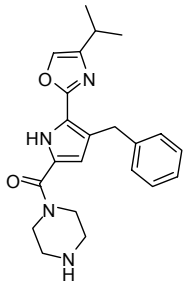


(*S*)-*Tert*-butyl 2-isopropyl-4-(4-isopropyl-5-(4-isopropyloxazol-2-yl)-*1H*-pyrrole-2-carbonyl)piperazine-1-carboxylate 17c; To a stirred solution of the oxazole-pyridazine-piperazine **16c** (101 mg, 0.20 mmol) in CH_3CO_2H (2 mL) was added Zn dust (160 mg, 2.46 mmol). The mixture was stirred at rt for 5 h under nitrogen, and another portion of Zn dust (160 mg, 2.46 mmol) was added. After an additional 18 h under vigorous stirring, the Zn dust was removed by filtering through a plug of cotton and the residue was washed with Et_2O (2x5 mL). The filtrate and washes were combined, made basic (pH 10) with the addition of saturated sodium bicarbonate, and extracted with ether (3x10 mL). The combined ether extracts were dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by preparative thin layer chromatography (Hexane/AcOEt 7/3) to afford the desired oxazole-pyrrole-piperazine **17c** as a pale yellow solid (29 mg, 0.061 mmol, 29%); ^{1}H NMR: (250 MHz, $CDCl_3$) δ 9.86 (bs, 1H), 7.31 (s, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 4.60 (m, 0.5H), 4.42 (m, 0.5H), 4.18-3.44 (m, 5H), 3.30-2.76 (m, 3H), 1.91 (m, 1H), 1.46 (s, 9H), 1.28-1.18 (m, 12H), 0.94 (m, 3H), 0.83 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR: (62.5 MHz, $CDCl_3$) δ 161.8, 155.9, 154.8, 147.9, 134.2, 131.4, 125.2, 118.4, 110.3, 104.1, 80.0, 63.7, 28.3, 26.3, 26.1, 25.3,

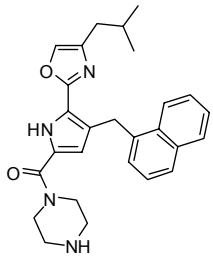
23.8, 21.4, 20.1, 17.9, 15.3; HRMS: (ESI-TOF) $C_{26}H_{40}N_4O_4H^+$ expected: 473.3122. found: 473.3124.



(*S*)-*Tert*-butyl 2-isopropyl-4-(4-isopropyl-5-(4-phenyloxazol-2-yl)-*1H*-pyrrole-2-carbonyl)piperazine-1-carboxylate 17d; Following the typical procedure for the pyridazine to pyrrole reduction described above: starting from **16d** (80 mg, 0.15 mmol), Prep. TLC Hexane/AcOEt 8/2, yield: 23 mg (29%); ^{1}H NMR: (600 MHz, $CDCl_3$) δ 9.86 (bs, 1H), 7.90 (s, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.42 (m, 2H), 7.32 (m, 1H), 6.45 (d, *J* = 2.6 Hz, 1H), 4.63 (m, 1H), 4.44 (m, 1H), 3.93 (m, 2H), 3.65 (hept, *J* = 6.9 Hz, 1H), 3.17 (m, 1H), 2.99 (m, 1H), 1.94 (m, 1H), 1.78 (m, 1H), 1.48 (m, 9H), 1.30 (d, *J* = 6.9 Hz, 3H), 1.29 (d, *J* = 6.9 Hz, 3H), 0.98 (m, 3H), 0.85 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR: (62 MHz, $CDCl_3$) δ 161.6, 156.2, 154.7, 141.4, 134.7, 132.2, 130.8, 128.7, 128.1, 125.5, 125.4, 118.2, 110.3, 80.0, 57.8 (broad), 45.1 (broad), 38.4 (broad), 28.3, 26.2, 25.4, 23.7, 20.1, 18.5; HRMS: (ESI-TOF) $C_{29}H_{38}N_4O_4H^+$ expected: 507.2966. found: 507.2954.



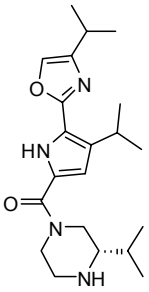
(4-Benzyl-5-(4-isopropyloxazol-2-yl)-*1H*-pyrrol-2-yl)(piperazin-1-yl)methanone 1a; Following the typical procedure for the Boc deprotection described below: starting from **17a** (7 mg, 14.6 μmol), yield: 8 mg, (quant.); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.17 (bs, 1H), 8.10 (bs, 2H), 7.46 (s, 1H), 7.31-7.16 (m, 5H), 6.35 (s, 1H), 4.17 (s, 2H), 3.98 (m, 4H), 3.32 (m, 4H), 3.02 (m, 1H), 1.32 (d, *J* = 6.9 Hz, 6H); HRMS: (ESI-TOF) $C_{22}H_{27}N_4O_2^+$ expected: 379.2128. found: 379.2136.



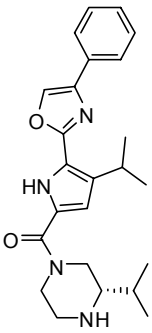
(5-(4-Isobutyloxazol-2-yl)-4-(naphthalen-1-ylmethyl)-*1H*-pyrrol-2-yl)(piperazin-1-yl)methanone 1b; Following the typical procedure for the Boc deprotection described below: starting from **17b** (13 mg, 0.023 mmol), yield: 12 mg, (99%); ^{1}H NMR: (600 MHz, $CDCl_3$) δ 9.86 (bs, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.45-7.28 (m, 5H), 6.02 (s, 1H), 4.65 (s, 2H), 3.82 (m, 4H), 3.02 (m, 4H), 2.40 (d, *J* = 7.0 Hz, 2H), 1.98 (hept, *J* = 6.7 Hz, 1H), 0.94 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR: (150

MHz, $CDCl_3$) δ 161.4, 155.3, 140.9, 136.4, 133.8, 131.9, 128.6, 127.1, 126.5, 125.7, 125.6, 125.5, 124.1, 123.7, 120.6, 114.9, 50.7, 43.0, 41.6 (broad), 35.1, 29.8, 27.5, 22.2; HRMS: (ESI-TOF) $C_{27}H_{30}N_4O_2H^+$ expected: 443.2441. found: 443.2445.

Typical procedure for the Boc deprotection:



(*S*)-(4-Isopropyl-5-(4-isopropyloxazol-2-yl)-*1H*-pyrrol-2-yl)(3-isopropylpiperazin-1-yl)methanone 1c; To a stirred solution of the oxazole-pyrrole-piperazine **17c** (29 mg, 0.061 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added dropwise CF_3CO_2H (1 mL). After 4 h under nitrogen, the mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography (CH_2Cl_2/MeOH 1/0 to 9/1) to afford the trifluoroacetic salt of the desired oxazole-pyrrole-piperazine **1c** as a pale yellow solid (27 mg, 0.056 mmol, 91%); ^{1}H NMR : (250 MHz, $CDCl_3/CD_3OD$: 95/5) δ 7.31 (s, 1H), 6.38 (s, 1H), 4.60 (m, 0.5H), 4.47 (m, 0.5H), 3.70 (m, 3H), 3.48 (hept, *J* = 6.8 Hz, 1H), 3.27 (m, 1H), 3.10-2.74 (m, 2H), 2.66 (m, 1H), 1.81 (m, 1H), 1.26-1.15 (m, 12H), 1.00 (m, 6H); ^{13}C NMR: (62.5 MHz, $CDCl_3/CD_3OD$: 95/5) δ 161.6, 156.1, 147.6, 134.5, 131.7, 124.6, 118.7, 118.5, 110.8, 60.9, 44.7, 29.9, 26.1, 25.2, 23.7, 21.2, 18.5, 18.2; HRMS: (ESI-TOF) $C_{21}H_{32}N_4O_2H^+$ expected: 373.2598. found: 373.2602.



(*S*)-(4-Isopropyl-5-(4-phenyloxazol-2-yl)-*1H*-pyrrol-2-yl)(3-isopropylpiperazin-1-yl)methanone 1d; Following the typical procedure for the Boc deprotection described above: starting from **17d** (23 mg, 0.48 mmol), white foam, yield: 21 mg (91%); ^{1}H NMR: (600 MHz, $CDCl_3$) δ 10.17 (bs, 1H), 7.95 (s, 1H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.46 (t_{app}, *J* = 7.5 Hz, 2H), 7.37 (t_{app}, *J* = 7.2 Hz, 1H), 6.49 (d, *J* = 2.5 Hz, 1H), 4.80 (m, 1H), 4.68 (m, 1H), 3.67 (hept, *J* = 6.8 Hz, 1H), 3.62 (m, 1H), 3.50 (m, 1H), 3.45 (m, 1H), 3.15 (m, 1H), 3.04 (m, 1H), 2.08 (m, 1H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.13 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR: (150 MHz, $CDCl_3$) δ 161.6, 156.0, 141.3, 135.4, 132.5, 130.4, 128.8, 128.3, 125.6, 124.3, 119.0, 111.1, 61.2, 44.0, 29.2, 25.4, 23.7, 18.5, 18.0; HRMS: (ESI-TOF) $C_{24}H_{30}N_4O_2H^+$ expected: 407.2441. found: 407.2426.

Molecular Modeling

Molecular modeling and compound superimposition were carried out using the HyperChem™ 7.51 program. Structures were minimized using the AM1 semi empirical method. Computational modeling shows the superimposition of compound **1** on the *i*, *i*+4 and *i*+7 side chains of a polyalanine α-helix with a root-mean-square deviation (RMSD) value of 0.270 Å, suggesting good stereochemical similarity between the pair (Figure S1). A more accurate minimization using DFT calculations (B3LYP/6-31G*) gave an RMSD of 0.471 Å. The final rendering and stereoview were obtained with WebLabViewerPro 4.0.

Figure S1. Stereoview of an overlay of compound **1** with a polyalanine α-helix.