

Supporting Information

Pyrazole derivatives as selective Orexin-2 Receptor Antagonists (2-SORA): Synthesis, Structure-Activity-Relationship, and Sleep-Promoting Properties in Rats.

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A Chemistry.

Commercially available starting materials were used as received without further purification. All reactions were carried out under an atmosphere of nitrogen or argon. Compounds were purified by flash chromatography on silica gel, or by preparative HPLC. Compounds described below are characterized by LC-MS data (retention time t_R is given in min, molecular weight obtained from the mass spectrum is given in g/mol using the conditions below. In cases where compounds appeared as a mixture of conformational isomers, as visible in their LC-MS spectra, the retention time of the most abundant conformer was given.

Mass spectrometry:

Mass spectrometry data were recorded by one of the following methods:

LC-MS under acidic conditions

Method A: Agilent 1100 series with mass spectrometry detection (MS: Finnigan single quadrupole). Column: Zorbax SB-aq (3.5 μm , 4.6 x 50 mm). Conditions: MeCN [eluent A]; H₂O + 0.04% TFA [eluent B]. Gradient: 95% B \rightarrow 5% B over 1.5 min (flow: 4.5 mL/min). Detection: UV/Vis + MS.

Method B: Agilent 1100 series with mass spectrometry detection (MS: Finnigan single quadrupole). Column: Waters XBridge C18 (2.5 μm , 4.6 x 30 mm). Conditions: MeCN [eluent A]; H₂O + 0.04% TFA [eluent B]. Gradient: 95% B \rightarrow 5% B over 1.5 min (flow: 4.5 mL/min). Detection: UV/Vis + MS.

Method C: Agilent 1100 series with mass spectrometry detection (MS: Finnigan single quadrupole). Column: Atlantis T3 (5 μm , 4.6 x 30 mm). Conditions: MeCN [eluent A]; H₂O + 0.04% TFA [eluent B]. Gradient: 95% B \rightarrow 5% B over 1.5 min (flow: 4.5 mL/min). Detection: UV/Vis + MS.

LC-MS under basic conditions

Method D: Agilent 1100 series with mass spectrometry detection (MS: Finnigan single quadrupole). Column: Waters XBridge C18 (5 μm , 4.6 x 50 mm). Conditions: MeCN [eluent A]; 13 mmol/L NH₃ in H₂O [eluent B]. Gradient: 95% B \rightarrow 5% B over 1.5 min (flow: 4.5 mL/min). Detection: UV/Vis + MS.

LC-HRMS parameters were the following: analytical pump Waters Acquity binary, Solvent Manager, MS, SYNAPT G2 MS, source temperature of 150 °C, desolvation temperature of 400 °C, desolvation gas flow of 400 L/h; cone gas flow of 10 L/h, extraction cone of 4 RF; lens 0.1 V; sampling cone 30; capillary 1.5 kV; high resolution mode; gain of 1.0, MS function of 0.2 s per scan, 120–1000 amu in full scan, centroid mode. Lock spray: keucine enkephalin, 2

ng/mL (556.2771 Da), scan time of 0.2 s with interval of 10 s and average of 5 scans; DAD: Acquity UPLC PDA detector. Column was an Acquity UPLC BEH C18 1.7 μ m, 2.1 mm x 50 mm from Waters, thermostated in the Acquity UPLC column manager at 60 °C. Eluents were the following: H₂O + 0.05% formic acid; B, acetonitrile + 0.05% formic acid. Gradient was 2% to 98% B over 3.0 min. Flow was 0.6 mL/min. Detection was at UV 214 nm. In cases where final compounds appear as a mixture of conformational isomers, visible in their LC-MS spectra, the retention time of the most abundant conformer is given.

Preparative HPLC under acidic conditions

Method E: Column: Waters Atlantis (10 μ m, 75 x 30 mm). Conditions: MeCN [eluent A]; H₂O + 0.5% HCOOH [eluent B]; Gradient: 90% B \rightarrow 5% B over 6.4 min (flow: 75 mL/min).

Detection: UV/Vis + MS.

Method F: Column: Waters XBridge (10 μ m, 75 x 30 mm). Conditions: MeCN [eluent A]; H₂O + 0.5% HCOOH [eluent B]; Gradient: 90% B \rightarrow 5% B over 6.4 min (flow: 75 mL/min).

Detection: UV/Vis + MS.

Preparative HPLC under basic conditions

Method G: Column: Waters XBridge (10 μ m, 75 x 30 mm). Conditions: MeCN [eluent A]; H₂O + 0.5% NH₄OH (25% aq.) [eluent B]; Gradient: 90% B \rightarrow 5% B over 6.5 min (flow: 75 mL/min). Detection: UV/Vis + MS

Chromatography

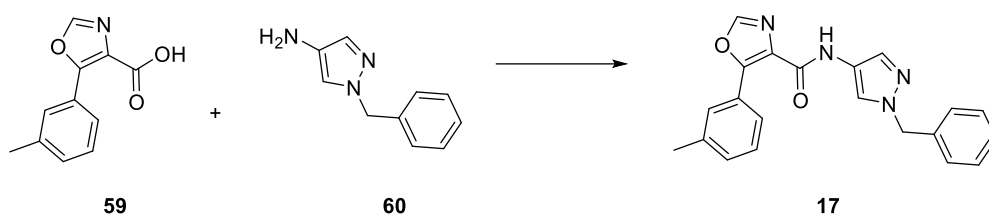
Flash column chromatography (FC) was performed either conventional or by using Biotage SNAP cartridges (10–340 g) and elution was with a Biotage Isolera system. Merck pre-coated thin layer chromatography (TLC) plates were used for TLC analysis.

¹H NMR and ¹³C NMR spectra were recorded on a Bruker (400 or 500 MHz) spectrometer in the indicated deuterated solvent. Chemical shifts are reported in ppm relative to solvent peaks as the internal reference.

Abbreviations used: aq., aqueous; DCM, dichloromethane; DIBAL, diisobutylaluminium hydride; DIPEA, diisopropylethylamine; DMF, dimethylformamide; DMSO, dimethylsulfoxide; EDC, 3-(Ethyliminomethyleneamino)-*N,N*-dimethylpropan-1-amine; EtOAc, ethyl acetate; EtOH, ethanol; HCl, hydrochloric acid; FC, flash chromatography; HATU, (1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate); H₂O, water; HOBt, Hydroxybenzotriazole; hex., hexane; hept., heptane; HPLC, high performance liquid chromatography; inorg., inorganic; MeCN, acetonitrile; MeOH, methanol; min, minutes; MgSO₄, magnesium sulfate; NaHCO₃, sodium bicarbonate; NaOH,

sodium hydroxide; NMP, *N*-Methyl-2-pyrrolidone; org. organic; prep., preparative; rt, room temperature; sat., saturated; TBTU, 2-(1*H*-benzotriazole-1-yl)-1,2,3,3-tetramethyluronium tetrafluoroborate; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TLC, thin layer chromatography; t_R , retention time.

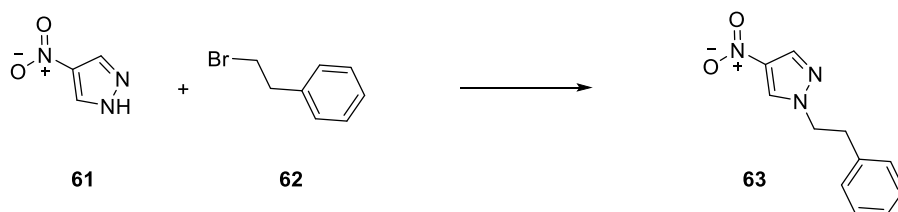
5-*m*-Tolyl-oxazole-4-carboxylic acid (1-benzyl-1*H*-pyrazol-4-yl)-amide (17)



TBTU (118 mg, 0.37 mmol) was added to a rt solution of **59** (50 mg, 0.25 mmol) and DIPEA (0.13 mL, 0.74 mmol) in DMF (0.7 mL), after stirring for 25 min commercially available 1-benzyl-1*H*-pyrazol-4-amine **60** (42.6 mg, 0.25 mmol) was added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was directly purified by prep. HPLC (Method F), followed by a prep. TLC (hept./EtOAc 3:2) to obtain **17** (18 mg, 20%) as a white solid. LC-MS A: t_R = 1.01 min; $[M+H]^+$ = 359.05; LC-HRMS: t_R = 1.10 min; $[M+H]/z$ = 359.1503, found = 359.1509; 1H NMR (400 MHz, DMSO) δ : 2.39 (s, 4 H), 5.31 (s, 2 H), 5.76 (s), 7.23-7.45 (m, 8 H), 7.72 (s, 1 H), 7.99 (s, 1 H), 8.04-8.06 (m, J_1 = 0.3 Hz, J_2 = 7.7 Hz, 1 H), 8.21 (s, 1 H), 8.65 (s, 1 H), 10.52 (s, 1 H).

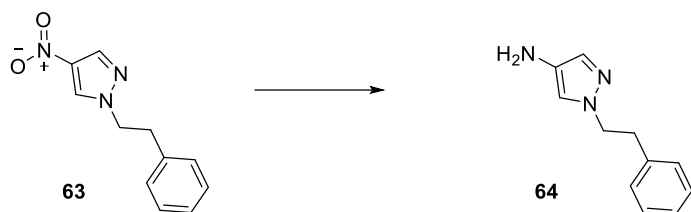
5-*m*-Tolyl-oxazole-4-carboxylic acid (1-phenethyl-1*H*-pyrazol-4-yl)-amide (18)

Step1: 4-Nitro-1-phenethyl-1*H*-pyrazole (63).



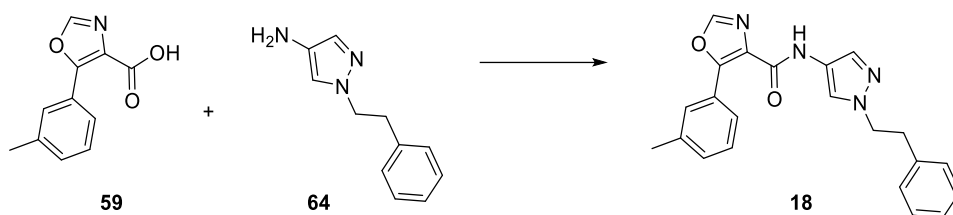
(2-Bromomethyl)-benzene **62** (1.97 mL, 14.15 mmol) was added to a rt solution of 4-nitro-1*H*-pyrazole **61** (1.50 g, 12.87 mmol) and Cs_2CO_3 (4.61 g, 14.15 mmol) in MeCN (30 mL). The resulting mixture was stirred at rt for 35 min then at 80°C for 1.5 h. The reaction mixture was diluted with DCM, the solid filtered off and the filtrate was concentrated *in vacuo* to yield of **63** (2.80 g) as beige solid, which was used in the next step without further purification. LC-MS A: t_R = 0.93 min; $[M+H]^+$ = 217.97.

Step 2: 1-Phenethyl-1*H*-pyrazol-4-ylamine (**64**)



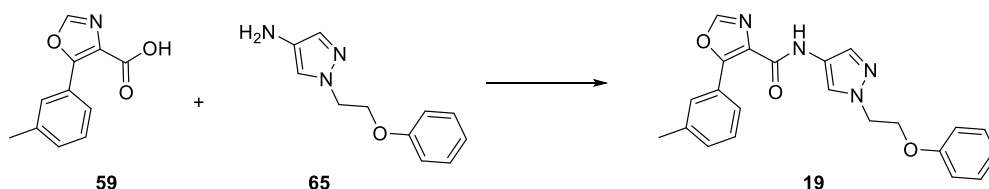
PtO₂ (235 mg, 1.21 mmol) was added to a degassed solution of 4-nitro-1-phenethyl-1*H*-pyrazole **63** (2.88 g, 13.26 mmol) in EtOH/EtOAc (18 mL/ 6 mL). The reaction mixture was stirred at rt under H₂-atmosphere for 4 h, then the mixture was filtered over Celite and the filter cake was rinsed with EtOH. The filtrate was concentrated to obtain 2.44 g of **64** as red solid which was used in the next step without further purification. LC-MS A: t_R = 0.54 min; [M+H]⁺ = 229.04.

Step 3



The title compound was synthesized according to the procedure described for compound **17**, using **59** and 1-phenethyl-1*H*-pyrazol-4-ylamine, and Et₃N instead of DIPEA. Purification by prep. HPLC (Method G) yielded **18** (64 mg, 40%) as a white solid. LC-MS A: t_R = 1.03 min; [M+H]⁺ = 373.11; LC-HRMS: t_R = 1.14 min; [M+H]/z = 373.1659, found = 373.1666; ¹H NMR (400 MHz, DMSO) δ: 2.39 (s, 3 H), 3.10 (t, *J* = 7.5 Hz, 2 H), 4.32 (t, *J* = 7.2 Hz, 2 H), 7.17-7.34 (m, 6 H), 7.41 (t, *J* = 7.7 Hz, 1 H), 7.70 (s, 1 H), 7.99 (s, 1 H), 8.03-8.08 (m, 2 H), 8.65 (s, 1 H), 10.47 (s, 1 H).

5-*m*-Tolyl-oxazole-4-carboxylic acid [1-(2-phenoxy-ethyl)-1*H*-pyrazol-4-yl]-amide (**19**)

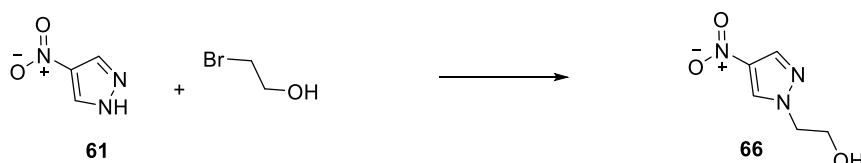


The title compound was synthesized according to the procedure described for compound **18**, using (2-bromoethoxy)benzene in step 1. Purification by prep. HPLC (Method G) yielded **19** (35 mg, 38%) as a colorless oil. LC-MS A: t_R = 0.93 min; [M+H]⁺ = 389.37; LC-HRMS: t_R = 1.12 min; [M+H]/z = 389.1608, found = 389.1612; ¹H NMR (400 MHz, DMSO) δ: 2.39 (s, 3 H),

4.34 (t, $J = 5.2$ Hz, 2 H), 4.48 (t, $J = 5.2$ Hz, 2 H), 6.90-6.99 (m, 3 H), 7.24-7.34 (m, 3 H), 7.42 (t, $J = 7.7$ Hz, 1 H), 7.74 (s, 1 H), 8.00 (s, 1 H), 8.06 (d, $J = 7.8$ Hz, 1 H), 8.21 (s, 1 H), 8.65 (s, 1 H), 10.52 (s, 1 H).

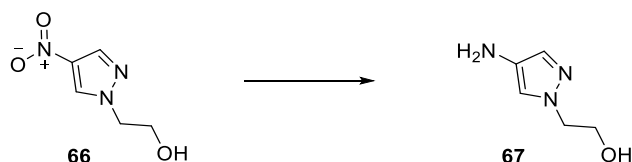
5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(5-fluoro-pyridin-2-yloxy)-ethyl]-1*H*-pyrazol-4-yl}-amide (**20**)

Step 1: 2-(4-Nitro-pyrazol-1-yl)-ethanol (**66**)



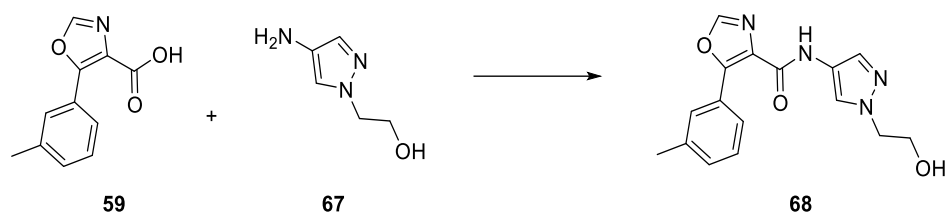
2-Bromoethanol (3.11 mL, 42.4 mmol) was added to a rt solution of 4-nitro-1*H*-pyrazole **61** (4.0 g, 35.4 mmol) and Cs₂CO₃ (12.68 g, 38.9 mmol) in MeCN (50 mL). The resulting mixture was heated to 80°C for 4 h. The mixture was filtered, the filter cake washed with DCM, and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc and water. The org. layer was separated and the aqueous layer was extracted with EtOAc (1x). The combined org. layers were washed with brine, dried (MgSO₄), filtered, and concentrated *in vacuo* to afford 2-(4-nitro-pyrazol-1-yl)-ethanol **66** (5.73 g, 103%) as a white solid. LC-MS A: $t_R = 0.27$ min; [M+H]⁺ = no ionization; ¹H NMR (400 MHz, DMSO) δ : 3.77 (q, $J = 5.4$ Hz, 2 H), 4.22 (t, $J = 5.3$ Hz, 2 H), 4.98 (t, $J = 5.4$ Hz, 1 H), 8.27 (d, $J = 0.3$ Hz, 1 H), 8.82 (s, 1 H).

Step 2: 2-(4-Amino-pyrazol-1-yl)-ethanol (**67**)



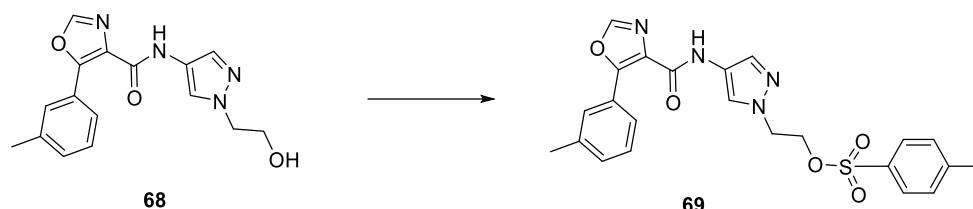
PtO₂ (307 mg, 1.58 mmol) was added to a degassed solution of **66** (2.75 g, 17.50 mmol) in EtOAc (6 mL) and EtOH (18 mL). The reaction mixture was stirred under H₂-atmosphere at rt for 3.5 h. The mixture was diluted with EtOH, filtered over Celite, and the filter cake was rinsed with EtOH. The filtrate was concentrated to obtain **67** as a light red oil (2.26 g) which was used as such in the next step. LC-MS A: $t_R = 0.14$ min; [M+H]⁺ = 128.24.

Step 3: 5-*m*-Tolyl-oxazole-4-carboxylic acid [1-(2-hydroxy-ethyl)-1*H*-pyrazol-4-yl]-amide (68)



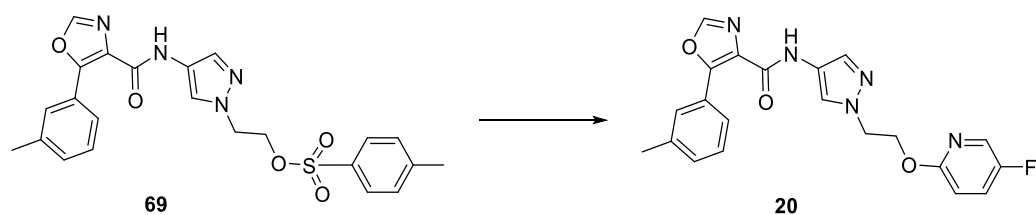
TBTU (8.43 g, 26.26 mmol) was added to a rt solution of **59** (3.56 g, 17.50 mmol) and DIPEA (9.0 mL, 52.57 mmol) in DCM (60 mL), after stirring for 30 min 2-(4-amino-pyrazol-1-yl)-ethanol **67** (2.23 g, 17.50 mmol) dissolved in a mixture of DCM/DMF (10 mL/6mL) was added and the resulting mixture was stirred at rt for 50 min. The reaction mixture was diluted with DCM and washed with water. The org. layer was separated and the inorg. layer was extracted with DCM (2x). The combined org. layers were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The product was purified by FC (EtOAc/MeOH, 98:2 until EtOAc/MeOH, 95:5) to obtain **68** (2.6 g, 47%) as a white solid. LC-MS A: $t_R = 0.70$ min; $[M+H]^+ = 313.18$; ¹H NMR (400 MHz, DMSO) δ : 2.39 (s, 3 H), 3.73 (q, $J = 5.5$ Hz, 2 H), 4.12 (t, $J = 5.6$ Hz, 2 H), 4.87 (t, $J = 5.3$ Hz, 1 H), 7.31 (d, $J = 7.6$ Hz, 1 H), 7.42 (t, $J = 7.7$ Hz, 1 H), 7.70 (s, 1 H), 7.96-8.00 (m, 1 H), 8.06 (d, $J = 7.9$ Hz, 1 H), 8.12 (s, 1 H), 8.64 (s, 1 H), 10.48 (s, 1 H).

Step 4: Toluene-4-sulfonic acid 2-{4-[(5-*m*-tolyl-oxazole-4-carbonyl)-amino]-pyrazol-1-yl}-ethylester (69)



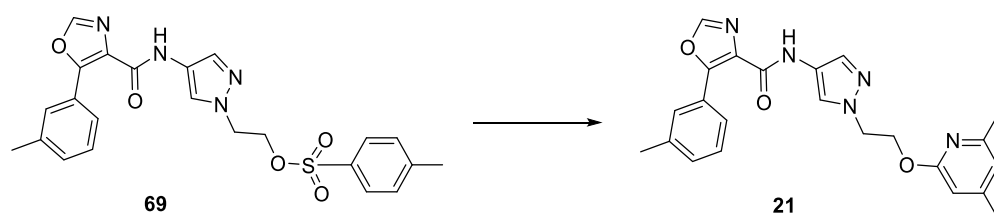
Et₃N (3.70 mL, 26.59 mmol) was added to a 0°C solution of **68** (2.60 g, 8.31 mmol) in DCM (80 mL). After 15 min, *p*-toluenesulfonyl chloride (1.90 g, 9.97 mmol) was added portionwise and the resulting suspension was stirred at 0°C for 1.5 h, then allowed to reach rt overnight. The mixture was diluted with DCM and quenched with water. The org. layer was separated, and the aqueous layer was extracted with DCM (1x). The combined org. layers were washed with brine, dried (MgSO₄), filtered, and concentrated *in vacuo* to yield **69** (4.1 g, 107%) as a light brown paste which was used as such in the next step. LC-MS A: $t_R = 0.93$ min; $[M+H]^+ = 467.43$; ¹H NMR (400 MHz, CDCl₃) δ : 2.42 (s, 3 H), 2.48 (s, 3 H), 4.36 (t, $J = 4.9$ Hz, 2 H), 4.42 (t, $J = 5.3$ Hz, 2 H), 7.30 (d, $J = 8.2$ Hz, 2 H), 7.42 (t, $J = 7.8$ Hz, 1 H), 7.54 (s, 1 H), 7.71 (d, $J = 8.3$ Hz, 2 H), 7.91 (s, 1 H), 8.01 (s, 1 H), 8.12 (s, 1 H), 8.19 (d, $J = 7.9$ Hz, 1 H), 8.91 (s, 1 H).

Step 5



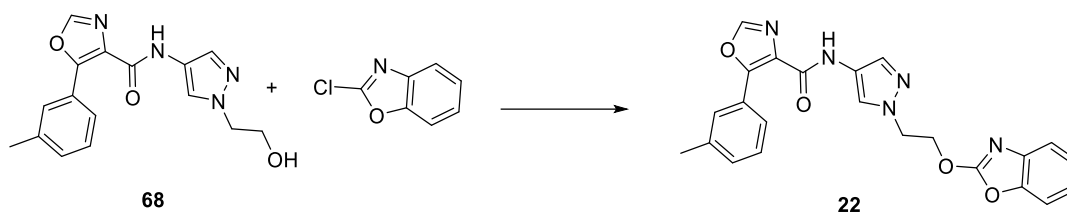
Cs_2CO_3 (302 mg, 0.93 mmol) was added to a rt solution of 5-fluoro-2-hydroxypyridine (49 mg, 0.44 mmol) and **69** (160 mg, 0.34 mmol) in NMP (2.6 mL). The resulting mixture was heated to 60°C for 2 h. The mixture was quenched with water and extracted with EtOAc (2x). The combined org. layers were washed with a 10% aq. LiCl solution and brine, dried (MgSO_4), filtered, and concentrated in *vacuo*. The product was purified by prep. HPLC (Method G) to obtain **20** (29 mg, 21%) as a white solid. LC-MS A: $t_R = 0.92$ min; $[\text{M}+\text{H}]^+ = 408.41$. LC-HRMS: $t_R = 1.08$ min; $[\text{M}+\text{H}]/z = 408.1467$, found = 408.1472; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 2.47 (s, 3 H), 4.51 (t, $J = 5.5$ Hz, 2 H), 4.69 (t, $J = 5.3$ Hz, 2 H), 6.75 (dd, $J_1 = 3.6$ Hz, $J_2 = 9.0$ Hz, 1 H), 7.29-7.38 (m, 2 H), 7.41 (t, $J = 7.7$ Hz, 1 H), 7.61 (s, 1 H), 7.90 (s, 1 H), 7.98 (d, $J = 3.0$ Hz, 1 H), 8.08 (s, 1 H), 8.17 (m, 2 H), 8.97 (s, 1 H).

5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(4,6-dimethylpyridin-2-yloxy)-ethyl]-1H-pyrazol-4-yl}-amide (**21**)



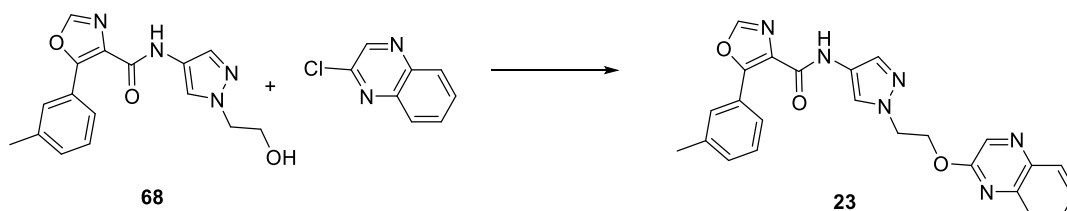
The title compound was synthesized according to the procedure described for compound **20**, using in step 5, 4,6-dimethylpyridin-2-ol instead of 5-fluoro-2-hydroxypyridine. The product was purified by prep. TLC (DCM/MeOH 9:1) to obtain **21** (20 mg, 14%) as a white solid. LC-MS A: $t_R = 0.74$ min; $[\text{M}+\text{H}]^+ = 418.43$. LC-HRMS: $t_R = 1.07$ min; $[\text{M}+\text{H}]/z = 418.1874$, found = 418.1884; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 2.25 (s, 3 H), 2.40 (s, 3 H), 2.47 (s, 3 H), 4.51 (t, $J = 5.5$ Hz, 2 H), 4.69 (t, $J = 5.5$ Hz, 2 H), 6.39 (s, 1 H), 6.58 (s, 1 H), 7.30 (s, 1 H), 7.41 (t, $J = 7.7$ Hz, 1 H), 7.62 (s, 1 H), 7.90 (s, 1 H), 8.09 (s, 1 H), 8.15 (s, 1 H), 8.17 (d, $J = 8.0$ Hz, 1 H), 8.96 (s, 1 H).

5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(benzoxazol-2-yl)oxy]-ethyl}-1*H*-pyrazol-4-yl}-amide (22)



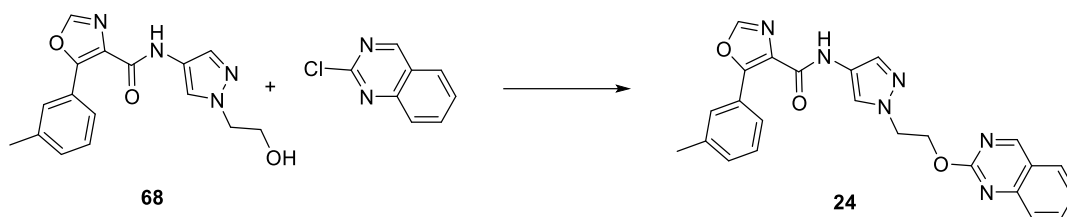
NaH (10 mg, 0.26 mmol) was added to a rt solution of **68** (50 mg, 0.16 mmol) in THF (1 mL). After stirring for 30 min, a solution of commercially available 2-chlorobenzoxazole (20 μ L, 0.18 mmol) in DMF (1 mL) was added and the resulting mixture was stirred at rt for 1 h before the mixture was quenched with water and the solvent was removed *in vacuo*. The inorg. layer was extracted with DCM (2x), the combined org. layers were washed with brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The product was purified by prep. HPLC (Method G) to obtain **22** (3.5 mg, 5%) as a white solid. LC-MS A: t_R = 1.01; [M+H]⁺ = 430.01. LC-HRMS: t_R = 1.10 min; [M+H]/z = 430.1510, found = 430.1528, ¹H NMR (400 MHz, DMSO) δ : 2.39 (s, 3 H), 4.61 (t, J = 5.0 Hz, 2 H), 4.89 (t, J = 4.8 Hz, 2 H), 7.19-7.34 (m, 3 H), 7.42 (t, J = 7.7 Hz, 1 H), 7.52 (dd, J_1 = 1.2 Hz, J_2 = 7.9 Hz, 2 H), 7.74 (s, 1 H), 8.00 (s, 1 H), 8.06 (d, J = 7.9 Hz, 1 H), 8.25 (s, 1 H), 8.65 (s, 1 H), 10.53 (s, 1 H).

5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(quinoxalin-2-yl)oxy]-ethyl}-1*H*-pyrazol-4-yl}-amide (23)



The title compound was synthesized according to the procedure described for compound **22**, using 2-chloroquinoxaline instead of 2-chlorobenzoxazole. The product was purified by prep. HPLC (Method E) to obtain **23** (24 mg, 28%) as a beige solid. LC-MS A: t_R = 1.03; [M+H]⁺ = 441.42. LC-HRMS: t_R = 1.11 min; [M+H]/z = 441.1670, found = 441.1681; ¹H NMR (400 MHz, DMSO) δ : 2.39 (s, 3 H), 4.60 (t, J = 5.2 Hz, 2 H), 4.83 (t, J = 5.2 Hz, 2 H), 7.31 (d, J = 7.6 Hz, 1 H), 7.41 (t, J = 7.7 Hz, 1 H), 7.65 (t, J = 7.2 Hz, 1 H), 7.73 (s, 1 H), 7.76 (t, J = 7.1 Hz, 1 H), 7.86 (d, J = 8.2 Hz, 1 H), 7.98-8.03 (m, 2 H), 8.05 (d, J = 7.8 Hz, 1 H), 8.25 (s, 1 H), 8.57 (s, 1 H), 8.65 (s, 1 H), 10.50 (s, 1 H).

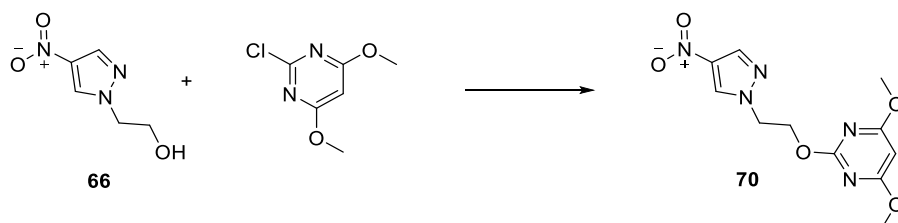
5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(quinazolin-2-yloxy)-ethyl]-1*H*-pyrazol-4-yl}-amide (24)



The title compound was synthesized according to the procedure described for compound **22**, using 2-chloroquinazoline instead of 2-chlorobenzoxazole. The product was purified by prep. HPLC (Method E) to obtain **24** (78 mg, 14%) as a beige foam. LC-MS A: $t_R = 0.98$; $[M+H]^+ = 440.99$. LC-HRMS: $t_R = 1.05$ min; $[M+H]/z = 441.1670$, found = 441.1677; 1H NMR (400 MHz, $CDCl_3$) δ : 2.46 (s, 3 H), 4.64 (t, $J = 5.7$ Hz, 2 H), 4.92 (t, $J = 5.8$ Hz, 2 H), 7.26-7.30 (m, 1 H), 7.40 (t, $J = 7.7$ Hz, 1 H), 7.47-7.52 (m, 1 H), 7.67 (s, 1 H), 7.82-7.87 (m, 2 H), 7.87-7.90 (m, 1 H), 8.10 (s, 1 H), 8.16 (d, $J = 7.9$ Hz, 1 H), 8.20 (s, 1 H), 8.96 (s, 1 H), 9.24 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 21.6, 51.5, 65.9, 120.8, 122.1, 125.3, 125.6, 126.7, 126.8, 127.4, 128.3, 128.4, 128.7, 131.1, 131.3, 134.6, 138.1, 147.8, 151.7, 153.5, 158.0, 161.9, 163.8.

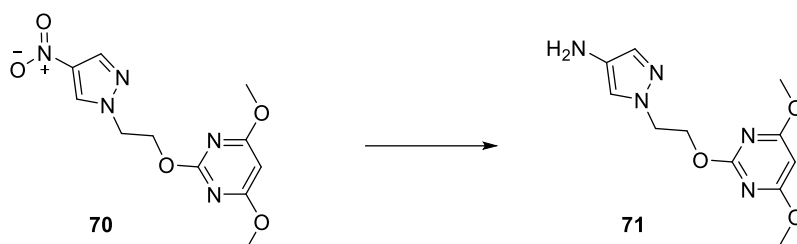
5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(4,6-dimethoxy-pyrimidin-2-yloxy)-ethyl]-1*H*-pyrazol-4-yl}-amide (25)

Step 1: 4,6-Dimethoxy-2-[2-(4-nitro-pyrazol-1-yl)-ethoxy]-pyrimidine



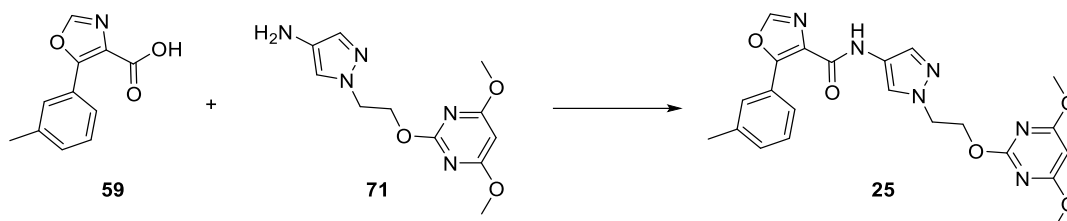
NaH (673 mg, 16.82 mmol) was added to a 0°C solution of 2-(4-nitro-pyrazol-1-yl)-ethanol **66** (1.90 g, 12.02 mmol) in THF (60 mL). The ice bath was removed and the reaction mixture was stirred at rt for 30 min, before commercially available 2-chloro-4,6-dimethoxypyrimidine (2.31 g, 13.22 mmol) was added and stirring was continued at rt for 40 min. The reaction mixture was quenched with H_2O and the org. solvent was removed *in vacuo*. The inorg. layer was extracted with DCM (1x), acidified with aq. 1N HCl until pH = 1, and re-extracted with DCM (2x). The combined org. layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The product was purified by dissolving the crude in minimal amount of DCM, and then adding heptane until the product precipitates to give 4,6-dimethoxy-2-[2-(4-nitro-pyrazol-1-yl)-ethoxy]-pyrimidine **70** (2.34 g, 66%) as a white solid, which was used as such in the next step. LC-MS A: $t_R = 0.88$; $[M+H]^+ = 295.98$.

Step 2: 1-[2-(4,6-Dimethoxy-pyrimidin-2-yloxy)-ethyl]-1H-pyrazol-4-ylamine (71)



PtO₂ (135 mg, 0.69 mmol) was added to a rt solution of **70** (2.05 g, 6.93 mmol) in degassed EtOAc (3 mL) and EtOAc (9 mL), and the resulting mixture was stirred under H₂-atmosphere for 3 h. The mixture was diluted with EtOH, filtered over Celite, and the filter cake rinsed with EtOH. The filtrate was concentrated to obtain 1-[2-(4,6-dimethoxy-pyrimidin-2-yloxy)-ethyl]-1H-pyrazol-4-ylamine **71** (1.88 g, 100%) as crude red oil which was used as such in the next step. LC-MS A: t_R = 0.58 min; [M+H]⁺ = 266.04; ¹H NMR (400 MHz, DMSO) δ: 3.85 (s, 6 H), 3.88 (s br, 2 H), 4.31 (t, J = 5.5 Hz, 2 H), 4.55 (t, J = 5.3 Hz, 2 H), 5.87 (s, 1 H), 6.93 (d, J = 0.7 Hz, 1 H), 7.09 (d, J = 0.7 Hz, 1 H).

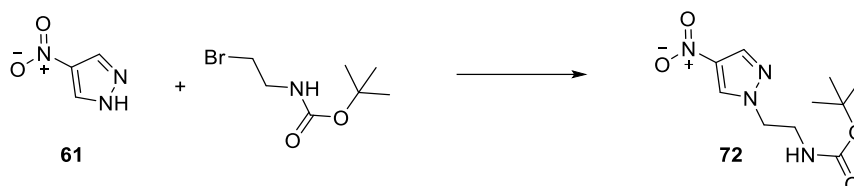
Step 3



The title compound was synthesized according to the procedure described for compound **17**, using **71** and **59**. The product was purified by FC (DCM/MeOH 20:1) to yield **25** (188 mg, 33%) as a yellowish solid. ¹H NMR (400 MHz, DMSO) δ: 10.52 (s, 1H), 8.65 (s, 1H), 8.20 (s, 1H), 8.06 (d, J = 7.9 Hz, 1H), 8.00 (s, 1H), 7.72 (d, J = 0.4 Hz, 1H), 7.42 (t, J = 7.7 Hz, 1H), 7.32 (m, 1H), 5.87 (s, 1H), 4.64 (t, J = 5.1 Hz, 2H), 4.49 (t, J = 5.3 Hz, 2H), 3.85 (s, 6H), 2.39 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 172.8 (2), 164.1, 158.2, 152.1, 150.7, 138.1, 131.5, 131.1, 129.0, 128.9, 128.6, 127.3, 125.7, 122.2, 121.7, 83.5, 66.1, 54.5 (2), 50.9, 21.5. LC-MS A: t_R = 1.00 min; [M+H]⁺ = 451.06; LC-HRMS: t_R = 1.08 min; [M+H]/z = 451.1725, found = 451.1736; ¹H NMR (400 MHz, DMSO) δ: 2.39 (s, 3 H), 3.85 (s, 6 H), 4.49 (t, J = 5.2 Hz, 2 H), 4.64 (t, J = 5.1 Hz, 2 H), 5.86 (s, 1 H), 7.32 (d, J = 7.6 Hz, 1 H), 7.41 (t, J = 7.7 Hz, 1 H), 7.72 (s, 1 H), 8.00 (s, 1 H), 8.06 (d, J = 7.9 Hz, 1 H), 8.20 (s, 1 H), 8.65 (s, 1 H), 10.52 (s, 1 H).

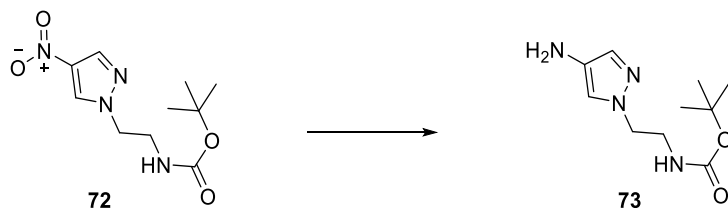
5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(4,6-dimethoxy-pyrimidin-2-ylamino)-ethyl]-1*H*-pyrazol-4-yl}-amide (26)

Step 1: [2-(4-Nitro-pyrazol-1-yl)-ethyl]-carbamic acid *tert*-butyl ester (72)



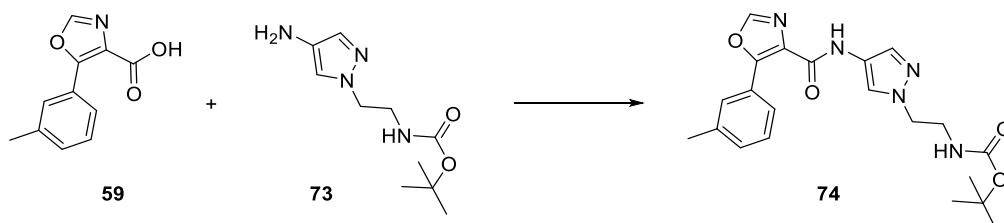
2-(Boc-amino)ethylbromide (3.47 g, 15.01 mmol) was added to a rt solution of 4-nitro-1*H*-pyrazole **61** (1.75 g, 15.01 mmol) and Cs₂CO₃ (5.38 g, 16.51 mmol) in MeCN (35 mL) and the resulting mixture was stirred at 80°C for 2 h. The mixture was filtered, the filter cake washed with DCM, and the filtrate concentrated *in vacuo* to obtain [2-(4-nitro-pyrazol-1-yl)-ethyl]-carbamic acid *tert*-butyl ester **72** (4.1 g, 107 %) as an orange oil which was used as such in the next step. LC-MS B: *t*_R = 0.62 min; [M+H]⁺ = 257.10.

Step 2: [2-(4-Amino-pyrazol-1-yl)-ethyl]-carbamic acid *tert*-butyl ester (73)



Pd/C 10% (788 mg) was added to a rt solution **72** (7.88 g, 30.75 mmol) in degassed MeOH (130 mL). The suspension was stirred at rt under H₂-atmosphere overnight, then filtered over Celite, washed with MeOH, and concentrated *in vacuo* to yield [2-(4-amino-pyrazol-1-yl)-ethyl]-carbamic acid *tert*-butyl ester **73** (6.97 g, 100%) as a violet oil which was used as such in the next step. LC-MS B: *t*_R = 0.35 min; [M+H]⁺ = 227.49.

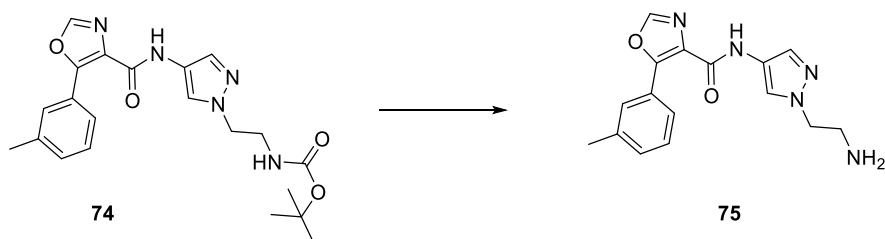
Step 3: (2-{4-[(5-*m*-Tolyl-oxazole-4-carbonyl)-amino]-pyrazol-1-yl}-ethyl)-carbamic acid *tert*-butyl ester (74)



HATU (7.58 g, 19.93 mmol) was added to a rt solution of **73** (3.0 g, 13.3 mmol), carboxylic acid **59** (2.70 g, 13.29 mmol), and DIPEA (6.8 mL, 39.86 mmol) in DCM (30.0 mL). The reaction mixture was stirred at rt for 18 h, then the mixture was diluted with DCM and water.

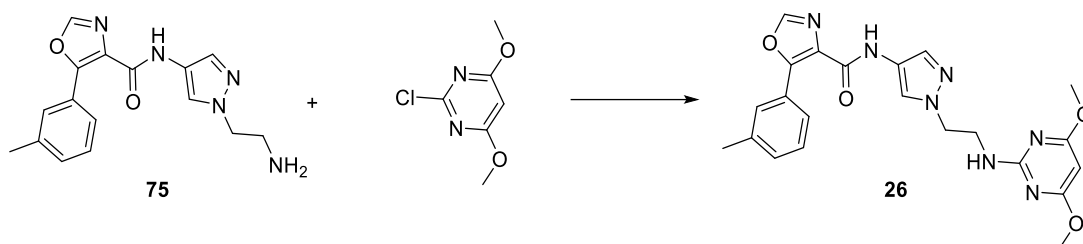
The layers were separated and the inorg. layer was extracted with DCM (3x). The combined org. layers were dried (MgSO₄), filtered, and concentrated *in vacuo*. The product was purified by FC (EtOAc/hex. with R_f = 0.61 in 100% EtOAc) to yield (2-{4-[(5-*m*-tolyl-oxazole-4-carbonyl)-amino]-pyrazol-1-yl}-ethyl)-carbamic acid *tert*-butyl ester **74** (4.30 g, 79%) as a white solid. LC-MS B: t_R = 0.80 min; [M+H]⁺ = 412.46.

Step 4: 5-*m*-Tolyl-oxazole-4-carboxylic acid [1-(2-amino-ethyl)-1*H*-pyrazol-4-yl]-amide (**75**)



TFA (12 mL, 156 mmol) was added to a 0°C suspension of (2-{4-[(5-*m*-tolyl-oxazole-4-carbonyl)-amino]-pyrazol-1-yl}-ethyl)-carbamic acid *tert*-butyl ester **74** (4.29 g, 10.4 mmol) in DCM (60 mL). The resulting solution was stirred at rt for 1 h., before the excess TFA was removed under reduced pressure. The residue was dissolved in DCM and 2N aq. NaOH solution (40 mL) was added. The inorg. layer was extracted with DCM (2x) and the org. layer was concentrated *in vacuo* to obtain **75** (3.07 g, 94%) as a white solid which was used as such in the next step. LC-MS B: t_R = 0.54 min; [M+H]⁺ = 312.31.

Step 5

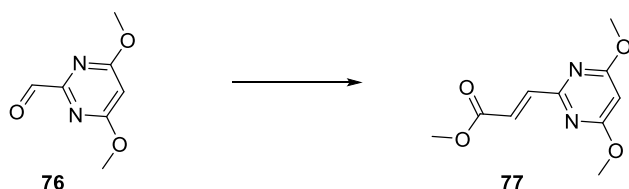


K₂CO₃ (1.07 g, 7.71 mmol) was added to a rt suspension of **75** (800 mg, 2.57 mmol), 2-chloro-4,6-dimethoxypyrimidine (449 mg, 2.57 mmol) and DIPEA (1.32 mL, 7.71 mmol) in *o*-xylol (10 mL). The suspension was stirred at 145°C for 18 h, then the reaction mixture was diluted with EtOAc and water. The layers were separated and the inorg. layer extracted with EtOAc (2x). The combined org. layers were dried (MgSO₄), filtered, and concentrated. The product was purified by prep. HPLC (Method G) to obtain **26** (86 mg, 74%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.97 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 8.09 (s, 2H), 7.90 (s, 1H), 7.63 (s, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.29 (m, 1H), 5.45 (s, 1H), 5.29-5.26 (bs, 1H), 4.36 (t, J = 5.7 Hz, 2H), 3.89 (m, 8H), 2.46 (s, 3H). ¹³C NMR (126 MHz, DMSO) δ 171.9 (2), 161.9, 158.2, 152.1, 150.7, 138.1, 131.3, 131.1, 129.1, 128.9, 128.6, 127.3, 125.7, 121.8, 121.6, 78.6, 53.6 (2), 51.0, 41.9,

21.5. LC-MS B: $t_R = 0.72$ min; $[M+H]^+ = 449.87$. LC-HRMS: $t_R = 1.06$ min; $[M+H]/z = 450.1885$, found = 450.1901.

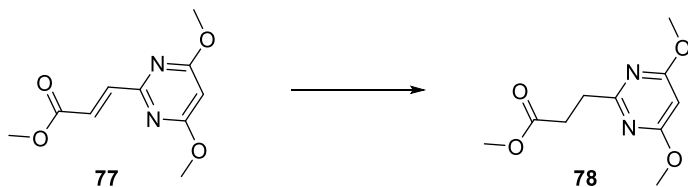
5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[3-(4,6-dimethoxy-pyrimidin-2-yl)-propyl]-1*H*-pyrazol-4-yl}-amide (27)

Step 1: (E,Z)-3-(4,6-Dimethoxy-pyrimidin-2-yl)-acrylic acid methyl ester (77)



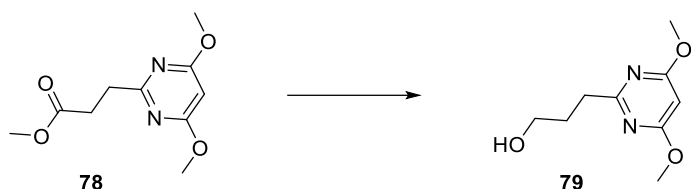
Methyl(triphenylphosphoranylidene)-acetate (3.00 g, 8.92 mmol) was added to a rt solution of 4,6-dimethoxypyrimidine-2-yl-carbaldehyde **76** (1.50 g, 8.9 mmol) in THF (90.0 mL) and the resulting reaction mixture was stirred at rt overnight. The reaction mixture was concentrated *in vacuo* and the product was purified by FC (EtOAc/ hept. 1:1, $R_f = 0.77$) to give (E,Z)-3-(4,6-dimethoxy-pyrimidin-2-yl)-acrylic acid methyl ester **77** (1.81 g, 90 %) as a yellow solid. LC-MS B: $t_R = 0.75$ min; $[M+H]^+ = 225.05$; 1H NMR (400 MHz, $CDCl_3$) δ : 3.85 (s, 3 H), 3.98 (s, 6 H), 5.98 (s, 0.25 H), 6.00 (s, 0.75 H), 7.14 (d, $J = 15.8$ Hz, 0.25 H), 7.16 (d, $J = 15.7$ Hz, 0.75 H), 7.51 (d, $J = 15.6$ Hz, 0.25 H), 7.53 (d, $J = 15.7$ Hz, 0.75 H).

Step 2: 3-(4,6-Dimethoxy-pyrimidin-2-yl)-propionic acid methyl ester (78)



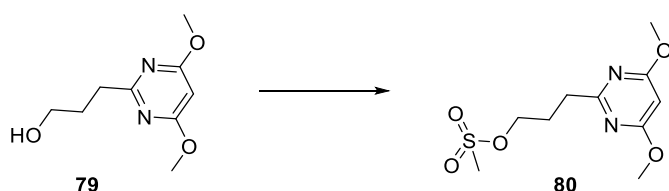
Pd/C (10 %, 180 mg) was added to a rt solution of **77** (1.80 g, 8.03 mmol) in MeOH (60 mL). The reaction mixture was stirred under H_2 -atmosphere for 2 h. The mixture was filtered over Celite and the filtrate concentrated *in vacuo* to yield 3-(4,6-dimethoxy-pyrimidin-2-yl)-propionic acid methyl ester **78** (1.76g, 97%) as a yellow oil which was used as such in the next step. LC-MS B: $t_R = 0.61$ min; $[M+H]^+ = 227.04$; 1H NMR (400 MHz, $CDCl_3$) δ : 2.79-2.90 (m, 2 H), 3.10-3.19 (m, 2 H), 3.71 (s, 3 H), 3.92 (s, 6 H), 5.88 (s, 1 H).

Step 3: 3-(4,6-Dimethoxy-pyrimidin-2-yl)-propan-1-ol (79)



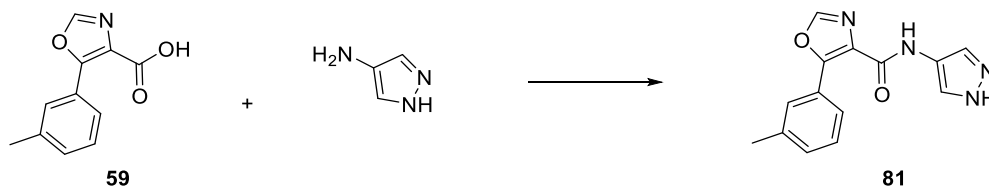
DIBAL (1M in THF; 23.0 mL, 23.0 mmol) was added to a 0°C solution of **78** (1.71 g, 7.56 mmol) in THF (25.0 mL). The resulting mixture was stirred at 0°C for 30 min and then allowed to warm to rt overnight. The mixture was diluted with DCM and acidified with 2N aq. HCl solution (50 mL) until pH 1. The layers were separated, the inorg. layer extracted with DCM (2x) and the combined org. layers were concentrated *in vacuo*. The product was purified by prep. HPLC (Method G) to obtain **79** as a yellow oil (952 mg, 64%). LC-MS B: $t_R = 0.43$ min; $[M+H]^+ = 199.1$; 1H NMR (400 MHz, $CDCl_3$) δ : 2.03-2.10 (m, 2 H), 2.96 (m, 2 H), 3.74-3.78 (m, 2 H), 3.94 (s, 6 H), 5.90 (s, 1 H).

Step 4: Methanesulfonic acid 3-(4,6-dimethoxy-pyrimidin-2-yl)-propyl ester (**80**)



TEA (0.21 mL, 1.51 mmol) was added to a 0°C solution of **79** (100 mg, 0.50 mmol) in DCM (1.0 mL). After stirring for 10 min methanesulfonylchloride (50 μ L, 0.61 mmol) was added at 0°C and the reaction mixture was stirred at this temperature for 1 h, followed by 1 h at rt. The mixture was poured into ice water and extracted with DCM. The org. layer was washed with 1 N aq. HCl solution, followed by sat. aq. $NaHCO_3$ solution, and brine. The org. layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield **80** as an orange oil (107 mg, 73%) which was used as such in the next step. LC-MS B: $t_R = 0.6$ min; $[M+H]^+ = 277.24$.

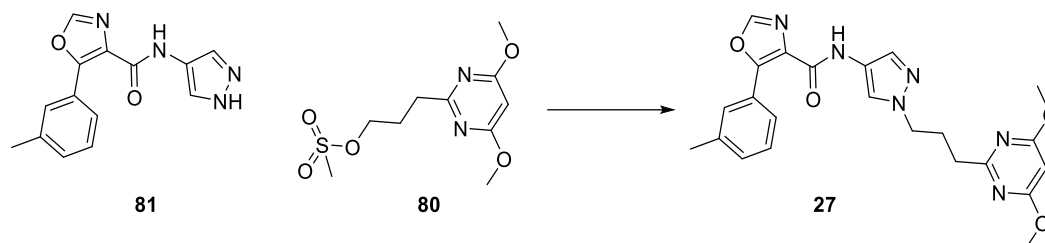
Step 5: 5-*m*-Tolyl-oxazole-4-carboxylic acid (1*H*-pyrazol-4-yl)-amide (**81**)



HOBT (11.15 g, 0.083 mol) was added to a 0°C solution of **59** (11.17 g, 0.06 mol) and EDC HCl (15.8 g, 0.083 mol) in DCM (65 mL). After stirring for 10 min at 0°C, a solution of 1*H*-pyrazol-4-ylamine (5.5 g, 0.07 mol) and DIPEA (17.7 mL, 0.103 mol) in DCM (50 mL) was added and the suspension was allowed to reach rt overnight. By adding water to the reaction mixture, the product precipitated out and was filtered off to yield **81** (10.7 g, 73%) as a light

violet solid. LC-MS B: $t_R = 0.62$ min; $[M+H]^+ = 269.15$; 1H NMR (400 MHz, DMSO) δ : 2.39 (s, 3 H), 7.25-7.35 (m, 1 H), 7.41 (t, $J = 7.7$ Hz, 1 H), 7.79 (s), 7.99 (s, 1 H), 8.02-8.10 (m, 2 H), 8.64 (s, 1 H), 10.46 (s, 1 H), 12.63 (s, 1 H).

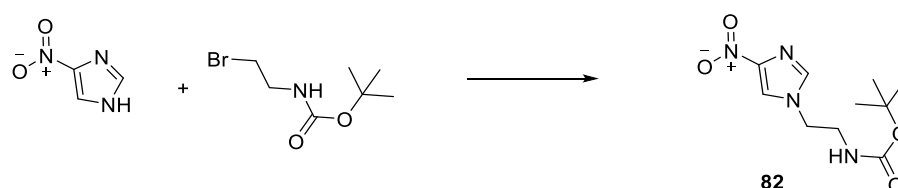
Step 6



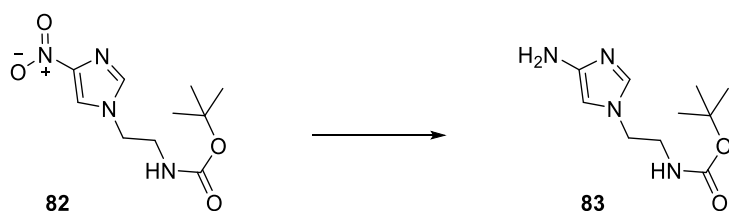
Cs_2CO_3 (252 mg, 0.77 mmol) was added to a rt solution of **81** (104 mg, 0.39 mmol) and **80** (107 mg, 0.387 mmol) in DMF (2.0 mL) and the resulting mixture was stirred at 65°C overnight. The title compound **27** was purified by prep. HPLC (Method G) to yield a brownish oil (37 mg, 21%). LC-MS B: $t_R = 0.84$ min; $[M+H]^+ = 449.1$; LC-HRMS: $t_R = 1.11$ min; $[M+H]/z = 449.1932$, found = 449.1938; 1H NMR (400 MHz, MeOD) δ : 2.35 (quint, $J = 7.1$ Hz, 2 H), 2.41 (s, 3 H), 2.74 (t, $J = 7.2$ Hz, 2 H), 3.91 (s, 6 H), 4.23 (t, $J = 6.8$ Hz, 2 H), 4.83 (s, 2 H), 5.93 (s, 1 H), 7.24-7.30 (m, 1 H), 7.35 (t, $J = 7.7$ Hz, 1 H), 7.68 (s, 1 H), 8.00 (d, $J = 7.8$ Hz, 1 H), 8.04 (s, 1 H), 8.10 (s, 1 H), 8.20 (s, 1 H); ^{13}C NMR (126 MHz, DMSO) δ 171.5 (2), 169.5, 158.2, 152.1, 150.7, 138.1, 131.2, 131.1, 129.1, 128.9, 128.6, 127.3, 125.7, 121.7, 121.4, 87.2, 54.3 (2), 51.2, 35.6, 28.5, 21.6.

5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(4,6-dimethoxy-pyrimidin-2-ylamino)-ethyl]-1*H*-imidazol-4-yl}-amide (**28**)

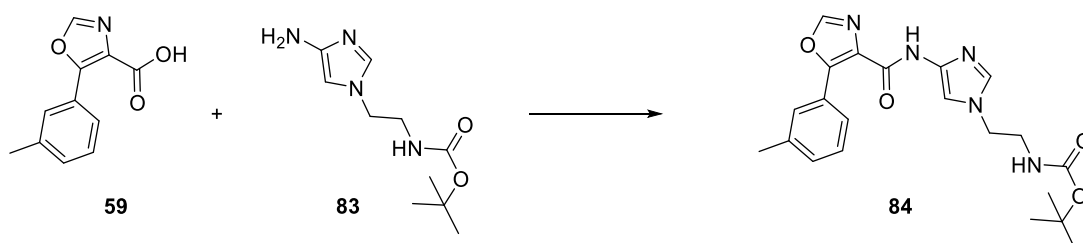
Step 1: [2-(4-Nitro-imidazol-1-yl)-ethyl]-carbamic acid *tert*-butyl ester (**82**)



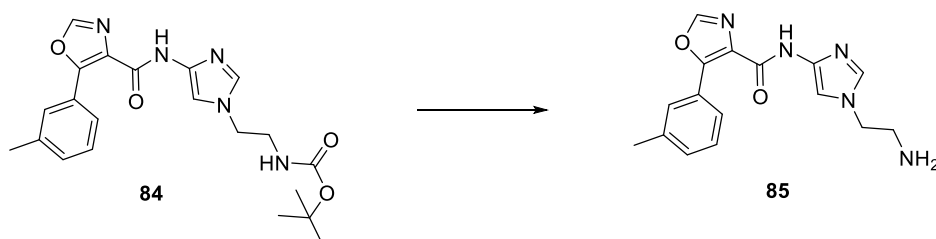
2-(Boc-amino)ethylbromide (3.10 g, 13.47 mmol) was added to a rt solution of commercially available 4-nitroimidazole (1.50 g, 13.46 mmol) and Cs_2CO_3 (4.82 g, 14.80 mmol) in MeCN (30 mL) and the resulting mixture was stirred at 80°C for 4 h. The mixture was filtered, the filter cake washed with DCM, and the filtrate concentrated *in vacuo* to obtain **82** as a yellow oil (3.87 g, 112 %) which was used as such in the next step. LC-MS B: $t_R = 0.53$ min; $[M+H]^+ = 257.37$; 1H NMR (400 MHz, DMSO) δ : 1.33 (s, 9 H), 3.28-3.36 (m, 2 H), 4.10 (t, $J = 5.6$ Hz, 2 H), 6.99 (t, $J = 4.8$ Hz, 1 H), 7.77 (s, 1 H), 8.32 (s, 1 H).

Step 2: [2-(4-Amino-imidazol-1-yl)-ethyl]-carbamic acid *tert*-butyl ester (83)

Pd/C 10% (332 mg) was added to a rt solution of **82** (3.32 g, 12.96 mmol) in degassed MeOH (60.0 mL). The suspension was stirred at rt under H₂-atmosphere overnight, then filtered over Celite, washed with MeOH, and concentrated *in vacuo* to yield **83** as a black solid (3.36 g, 115%) which was used as such in the next step. LC-MS B: t_R = 0.35 min; [M+H]⁺ = 227.44.

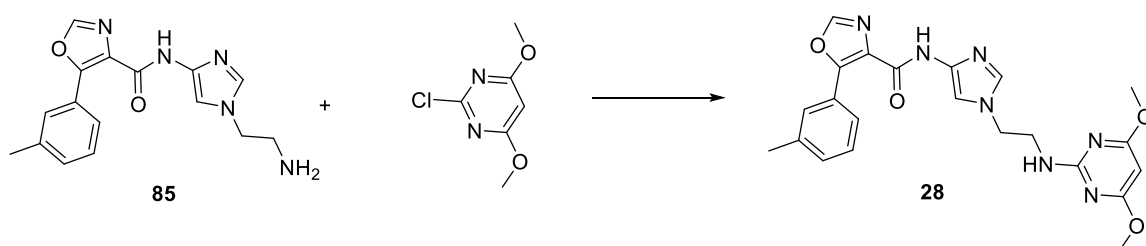
Step 3: (2-{4-[(5-*m*-Tolyl-oxazole-4-carbonyl)-amino]-imidazol-1-yl}-ethyl)-carbamic acid *tert*-butyl ester (84)

TBTU (6.2 g, 19.3 mmol) was added to a rt solution of **59** (3.02 g, 14.85 mmol) and DIPEA (7.63 mL, 44.50 mmol) in DCM (40.0 mL) and after stirring for 15 min, a solution of **83** (3.36 g, 14.85 mmol) in DCM (20 mL) was added. The resulting mixture was stirred at rt for 45 min, then the mixture was diluted with DCM and water. The layers were separated and the inorg. layer was extracted with DCM (3x). The combined org. layers were dried (MgSO₄), filtered, and concentrated *in vacuo*. The product was purified by FC (100% EtOAc, followed by DCM/MeOH 97/3) to yield **84** (2.12 g, 35%) as a brownish solid. LC-MS B: t_R = 0.68 min; [M+H]⁺ = 412.00; ¹H NMR (400 MHz, DMSO) δ: 1.37 (s, 9 H), 2.40 (s, 3 H), 3.23-3.30 (m, 2 H), 4.02 (t, *J* = 5.7 Hz, 2 H), 6.98 (t, *J* = 5.3 Hz, 1 H), 7.30-7.36 (m, 1 H), 7.39-7.48 (m, 3 H), 8.02-8.07 (m, 2 H), 8.63 (s, 1 H), 9.73 (s, 1 H).

Step 4: 5-*m*-Tolyl-oxazole-4-carboxylic acid [1-(2-amino-ethyl)-1*H*-imidazol-4-yl]-amide (85)

TFA (5.9 mL, 77.29 mmol) was added to a 0°C suspension of **84** (2.12 g, 5.15 mmol) in DCM (60.0 mL). The resulting solution was stirred at rt for 3 h, before the excess TFA was removed under reduced pressure. The residue was dissolved in DCM and 4 N aq. NaOH solution (80 mL) was added. The inorg. layer was extracted with DCM (2x) and the org. layer was concentrated *in vacuo* to yield **85** (1.63 g, 102%) as a brownish solid which was used as such in the next step. LC-MS B: $t_R = 0.47$ min; $[M+H]^+ = 312.89$; 1H NMR (400 MHz, $CDCl_3$) δ : 2.45 (s, 3 H), 3.09 (t, $J = 5.9$ Hz, 2 H), 3.98 (t, $J = 5.8$ Hz, 2 H), 7.24-7.30 (m, 1 H), 7.38 (t, $J = 7.7$ Hz, 1 H), 7.53 (s, 1 H), 7.88 (s, 1 H), 8.07 (s, 1 H), 8.15 (d, $J = 7.9$ Hz, 1 H), 9.54 (s, 1 H).

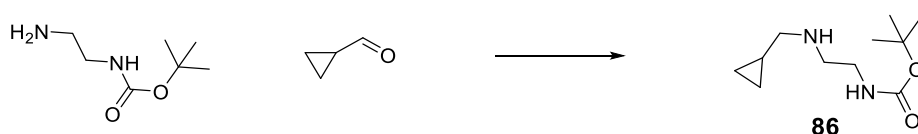
Step 5



K_2CO_3 (97 mg, 0.70 mmol) was added to a rt suspension of **85** (70 mg, 2.35 mmol), 2-chloro-4,6-dimethoxypyrimidine (70 mg, 0.40 mmol) and DIPEA (0.13 mL, 0.7 mmol) in NMP (1.5 mL). The suspension was irradiated in the microwave to 150°C for 25 min, then the reaction mixture was diluted with DCM and water. The layers were separated and the inorg. layer extracted with DCM (2x). The combined org. layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The product was purified by prep. HPLC (Method G) to obtain the title compound **28** (31 mg, 30%) as an off-white solid. LC-MS B: $t_R = 0.68$ min; $[M+H]^+ = 450.04$. LC-HRMS: $t_R = 0.94$ min; $[M+H]/z = 450.1885$, found = 450.1891; 1H NMR (400 MHz, $CDCl_3$) δ : 2.47 (s, 3 H), 3.79 (q, $J = 6.1$ Hz, 2 H), 3.88 (s, 6 H), 4.19 (t, $J = 5.8$ Hz, 2 H), 5.07 (t, $J = 6.0$ Hz, 1 H), 5.48 (s, 1 H), 7.26-7.32 (m, 3 H), 7.40 (t, $J = 7.7$ Hz, 1 H), 7.55 (d, $J = 1.5$ Hz, 1 H), 7.89 (s, 1 H), 8.09 (s, 1 H), 8.17 (d, $J = 7.8$ Hz, 1 H), 9.48 (s, 1 H).

2-Cyclopropyl-5-*m*-tolyl-oxazole-4-carboxylic acid cyclopropylmethyl-[2-(4,6-dimethoxy-pyrimidin-2-ylamino)-ethyl]-amide (**29**)

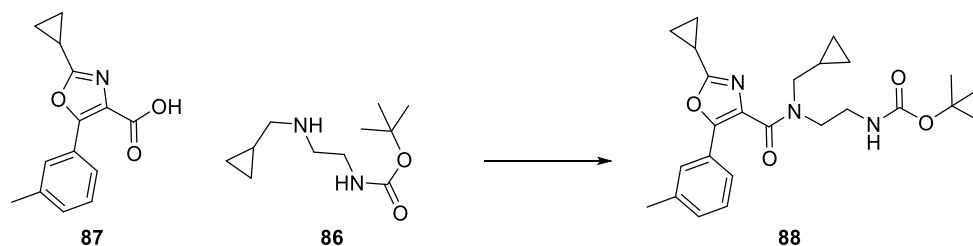
Step 1: [2-(Cyclopropylmethyl-amino)-ethyl]-carbamic acid tert-butyl ester (**86**)



Cyclopropanecarboxaldehyde (0.17 mL, 2.28 mmol) was added to a rt solution of *N*-boc-ethylendiamine (2.47 mL, 15.60 mmol) and TEA (0.38 mL, 2.73 mmol) in MeOH (35.0 mL) and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with DCM and water,

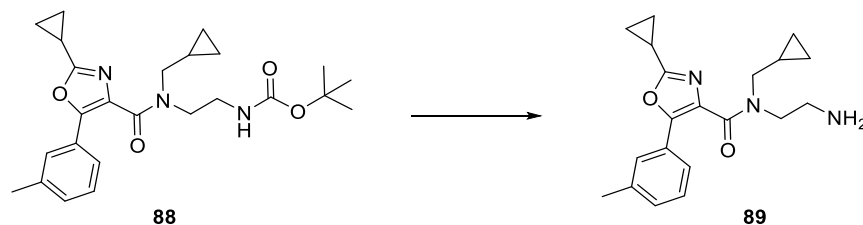
the layers separated, and the inorg. layer extracted with DCM (2x). The combined org. layers were dried (MgSO₄), filtered, and concentrated to yield **86** (2.93 g, 100%) as a yellow oil which was used as such in the next step. LC-MS B: t_R = 0.63 min; [M+H]⁺ = 340.29; ¹H NMR (400 MHz, CDCl₃) δ: 0.07-0.16 (m, 2 H), 0.44-0.54 (m, 2 H), 0.89-1.00 (m, 1 H), 1.46 (s, 9 H), 2.48 (d, J = 6.8 Hz, 2 H), 2.77 (t, J = 6.0 Hz, 2 H), 3.20-3.28 (m, 2 H), 4.96 (s br, 1 H).

Step 2: {2-[Cyclopropylmethyl-(2-cyclopropyl-5-*m*-tolyl-oxazole-4-carbonyl)-amino]-ethyl}-carbamic acid *tert*-butyl ester (88**)**



HATU (7.98 g, 21.0 mmol) was added to a rt solution of **87** (3.4 g, 14.0 mmol), **86** (3.0, 14.0 mmol) and DIPEA (7.18 mL, 42.0 mmol) in DCM (20.0 mL). The reaction mixture was stirred at rt for 18 h, then the mixture was diluted with DCM and water. The layers were separated, and the aqueous layer was extracted with DCM (3x). The combined org. layers were dried (MgSO₄), filtered, and concentrated *in vacuo*. The product was purified by FC (EtOAc/ hex. 1:1, R_f = 0.42) to yield **88** (5.11 g, 83%) a yellow oil. LC-MS B: t_R = 0.94 min; [M+H]⁺ = 440.12; ¹H NMR (400 MHz, CDCl₃) δ: 0.12-0.16 (m, 1 H), 0.37-0.42 (m, 1 H), 0.46-0.53 (m, 1 H), 0.54-0.62 (m, 1 H), 1.07-1.25 (m, 5 H), 1.46 (s, 9 H), 2.08-2.17 (m, 1 H), 2.39 (s, 3 H), 3.21-3.25 (m, 1 H), 3.31-3.38 (m, 1 H), 3.45-3.52 (m, 2 H), 3.55-3.62 (m, 1 H), 3.75-3.81 (m, 1 H), 7.14-7.19 (m, 1 H), 7.28-7.35 (m, 1 H), 7.43-7.52 (m, 1 H), 7.57-7.64 (m, 1 H).

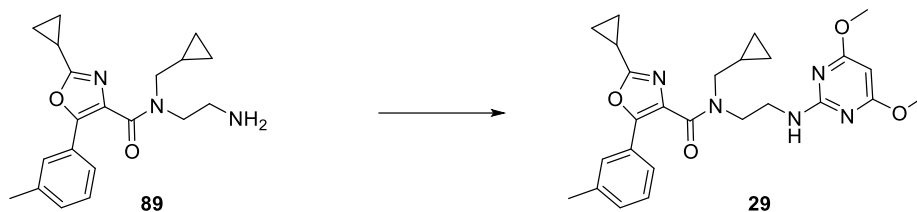
Step 3: 2-Cyclopropyl-5-*m*-tolyl-oxazole-4-carboxylic acid (2-amino-ethyl)-cyclopropylmethyl-amide (89**)**



TFA (13.33 mL, 174.0 mmol) was added to a 0°C suspension of **88** (5.10 g, 11.60 mmol) in DCM (50.0 mL). The resulting solution was stirred at rt for 1 h, before the excess TFA was removed *in vacuo*. The residue was dissolved in DCM, then 2 N aq. NaOH solution (40.0 mL) was added. The aqueous layer was extracted with DCM (2x) and the combined org. layers

were concentrated *in vacuo* to yield **89** (3.93 g, 100%) as a yellow oil which was used as such in the next step. LC-MS B: $t_R = 0.63$ min; $[M+H]^+ = 340.29$.

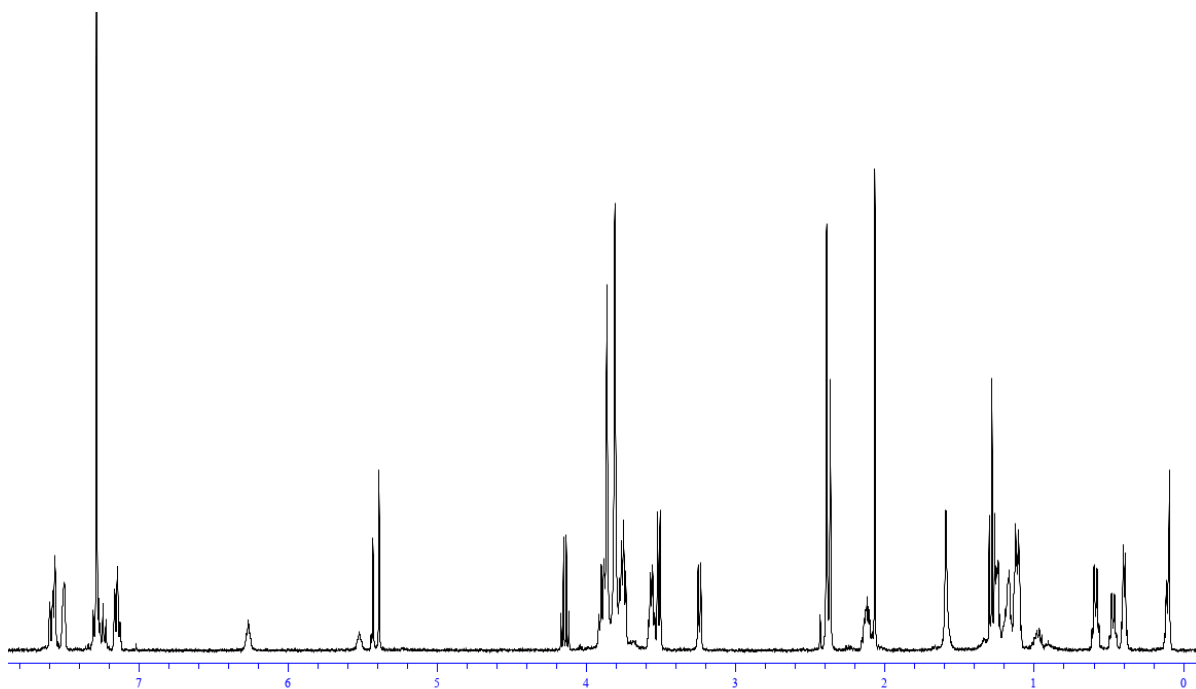
Step 4



The title compound was synthesized according to the procedure described for compound **26** (step 5) using **89** instead of compound **75**. The product was purified by prep. HPLC (Method G) to yield **29** (271 mg, 43%) as a yellow oil. LC-MS A: $t_R = 0.86$ min; $[M+H]^+ = 477.56$; LC-HRMS: $t_R = 1.21$ min; $[M+H]/z = 478.2449$, found = 478.2455.

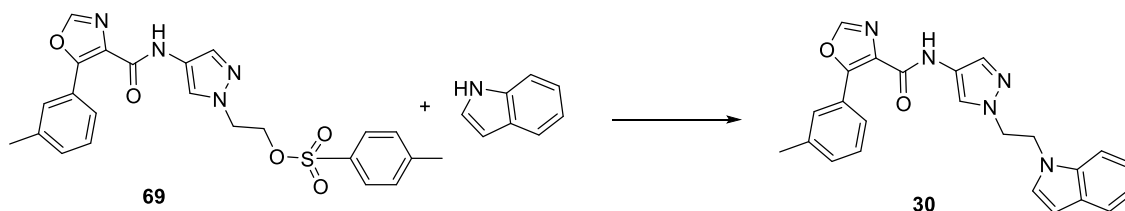
Compound **29** exists in multiple conformations on the NMR timescale, therefore full ^1H -NMR spectrum is depicted.

^1H -NMR (400 MHz, CDCl_3):



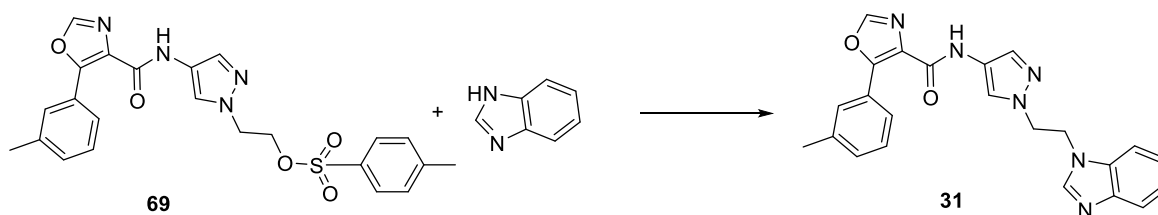
^{13}C NMR (126 MHz, DMSO) δ 172.0, 171.5, 164.6, 164.4, 164.0, 162.1, 161.6, 147.0, 146.8, 138.6, 138.3, 130.4, 130.2, 129.9, 129.6, 129.3, 129.0, 127.4, 125.8, 125.7, 122.8, 78.5, 53.6, 53.2, 48.5, 46.7, 44.7, 38.8, 21.5, 10.7, 9.8, 8.8, 3.9.

5-*m*-Tolyl-oxazole-4-carboxylic acid [1-(2-indol-1-yl-ethyl)-1*H*-pyrazol-4-yl]-amide (**30**)



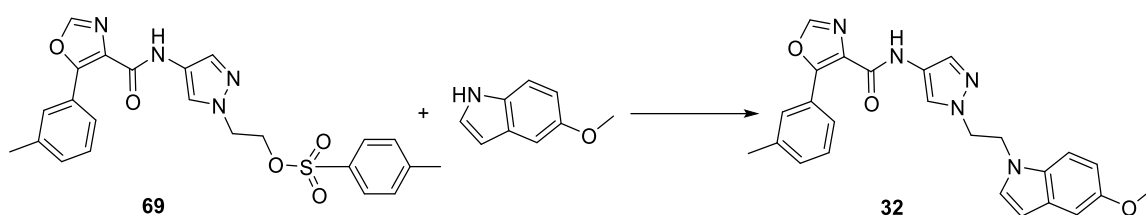
NaH (18 mg, 0.41 mmol) was added to a rt solution of indole (30 mg, 0.26 mmol) in DMF (1.2 mL) and the suspension was stirred at rt for 50 min, before a solution of **69** (120 mg, 0.26 mmol) in DMF (1 mL) was added and stirring continued overnight. The reaction mixture was quenched with water and extracted with DCM (1x). The inorg. layer was acidified with 1N HCl and the inorg. layer was extracted with DCM (1x). The combined org. layers were washed with brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The product was purified by prep. HPLC (Method G) to yield **30** (25 mg, 23%) as a yellowish solid. LC-MS A: $t_R = 1.03$ min; $[M+H]^+ = 412.07$; LC-HRMS: $t_R = 1.14$ min; $[M+H]/z = 412.1768$, found = 412.1782; ¹H NMR (400 MHz, DMSO) δ : 2.39 (s, 3 H), 4.48 (t, $J = 5.9$ Hz, 2 H), 4.61 (t, $J = 6.0$ Hz, 2 H), 6.37 (d, $J = 3.1$ Hz, 1 H), 7.01 (t, $J = 7.4$ Hz, 1 H), 7.07 (d, $J = 3.1$ Hz, 1 H), 7.12 (t, $J = 7.3$ Hz, 1 H), 7.31 (d, $J = 7.6$ Hz, 1 H), 7.41 (t, $J = 8.0$ Hz, 1 H), 7.44 (d, $J = 8.2$ Hz, 1 H), 7.51 (d, $J = 7.8$ Hz, 1 H), 7.73 (s, 1 H), 7.97 (s, 1 H), 7.98 (s, 1 H), 8.04 (d, $J = 7.8$ Hz, 1 H), 8.64 (s, 1 H), 10.46 (s, 1 H).

5-*m*-Tolyl-oxazole-4-carboxylic acid [1-(2-benzimidazol-1-yl-ethyl)-1*H*-pyrazol-4-yl]-amide (**31**)



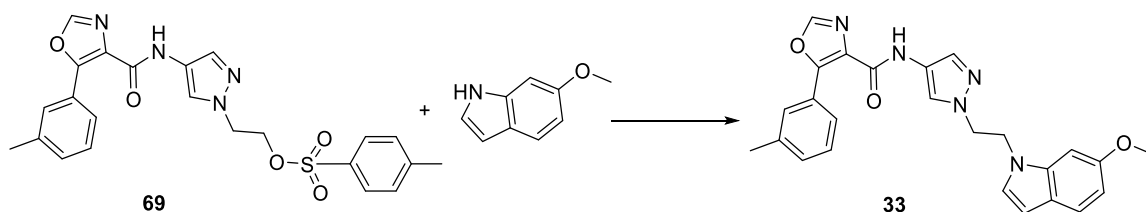
The title compound was synthesized according to the procedure described for compound **30** using benzimidazole instead of indole. The product was purified by FC (DCM/MeOH 9:1) to yield **31** (81 mg, 46%) as a white solid. LC-MS A: $t_R = 0.69$ min; $[M+H]^+ = 413.04$; LC-HRMS: $t_R = 0.73$ min; $[M+H]/z = 413.1721$, found = 413.1727; ¹H NMR (400 MHz, CDCl₃) δ : 2.45 (s, 3 H), 4.50 (t, $J = 6.0$ Hz, 2 H), 4.72 (t, $J = 5.8$ Hz, 2 H), 7.26-7.28 (m, 1 H), 7.30-7.41 (m, 4 H), 7.56 (s, 1 H), 7.70 (s, 1 H), 7.74 (s, 1 H), 7.80-7.82 (m, 1 H), 7.88 (s, 1 H), 8.05 (s, 1 H), 8.12 (d, $J = 7.9$ Hz, 1 H), 8.90 (s, 1 H).

5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(5-methoxy-indol-1-yl)-ethyl]-1*H*-pyrazol-4-yl}-amide (32)



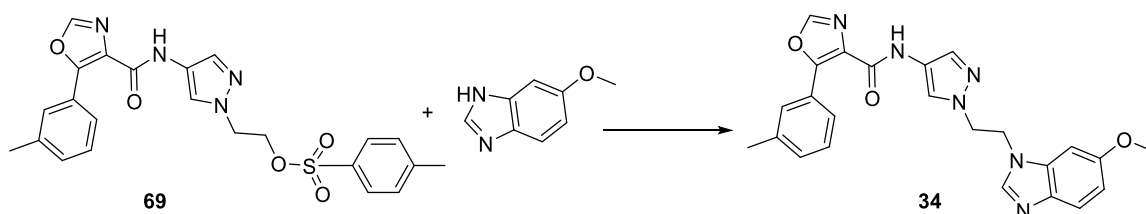
The title compound was synthesized according to the procedure described for compound **30** using 5-methoxyindol instead of indole. The product was purified by prep. HPLC (Method G) to yield **32** (18 mg, 16%) as a beige solid. LC-MS A: $t_R = 0.93$ min; $[M+H]^+ = 442.09$; LC-HRMS: $t_R = 1.12$ min; $[M+H]/z = 442.1874$, found = 442.1882; 1H NMR (400 MHz, $CDCl_3$) δ : 2.46 (s, 3 H), 3.86 (s, 3 H), 4.43 (t, $J = 6.1$ Hz, 2 H), 4.58 (t, $J = 6.1$ Hz, 2 H), 6.38 (d, $J = 3.1$ Hz, 1 H), 6.80 (d, $J = 3.1$ Hz, 1 H), 6.90 (dd, $J_1 = 2.3$ Hz, $J_2 = 8.8$ Hz, 1 H), 7.09 (d, $J = 2.3$ Hz, 1 H), 7.19 (d, $J = 8.9$ Hz, 1 H), 7.26-7.32 (m, 2 H), 7.39 (t, $J = 7.7$ Hz, 1 H), 7.69 (s, 1 H), 7.70 (s, 1 H), 7.87 (s, 1 H), 8.07 (s, 1 H), 8.14 (d, $J = 7.9$ Hz, 1 H), 8.90 (s, 1 H).

5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(6-methoxy-indol-1-yl)-ethyl]-1*H*-pyrazol-4-yl}-amide (33)



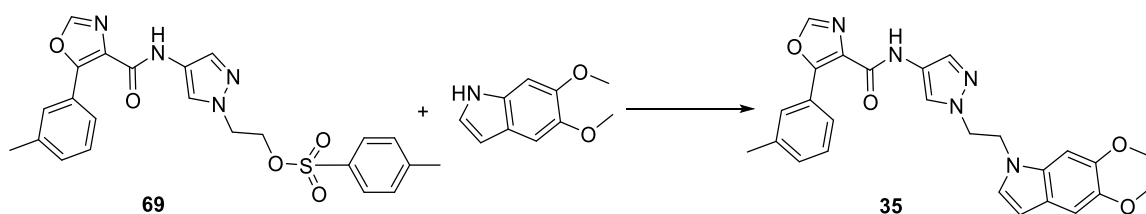
The title compound was synthesized according to the procedure described for compound **30** using 6-methoxyindol instead of indole. The product was purified by prep. HPLC (Method G) to yield **33** (10 mg, 10%) as an orange solid. LC-MS A: $t_R = 0.94$ min; $[M+H]^+ = 442.06$; LC-HRMS: $t_R = 1.13$ min; $[M+H]/z = 442.1874$, found = 442.1880; 1H NMR (400 MHz, $CDCl_3$) δ : 2.46 (s, 3 H), 3.88 (s, 3 H), 4.45 (t, $J = 6.0$ Hz, 2 H), 4.57 (t, $J = 6.1$ Hz, 2 H), 6.40 (d, $J = 3.2$ Hz, 1 H), 6.72 (d, $J = 1.5$ Hz, 1 H), 6.76 (d, $J = 3.2$ Hz, 1 H), 6.79 (dd, $J_1 = 2.0$ Hz, $J_2 = 8.6$ Hz, 1 H), 7.26-7.31 (m, 3 H), 7.39 (t, $J = 7.7$ Hz, 1 H), 7.48 (d, $J = 8.6$ Hz, 1 H), 7.71 (s, 2 H), 7.88 (s, 1 H), 8.07 (s, 1 H), 8.14 (d, $J = 7.9$ Hz, 1 H), 8.88 (s, 1 H).

5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(6-methoxy-benzimidazol-1-yl)-ethyl]-1*H*-pyrazol-4-yl}-amide (34)



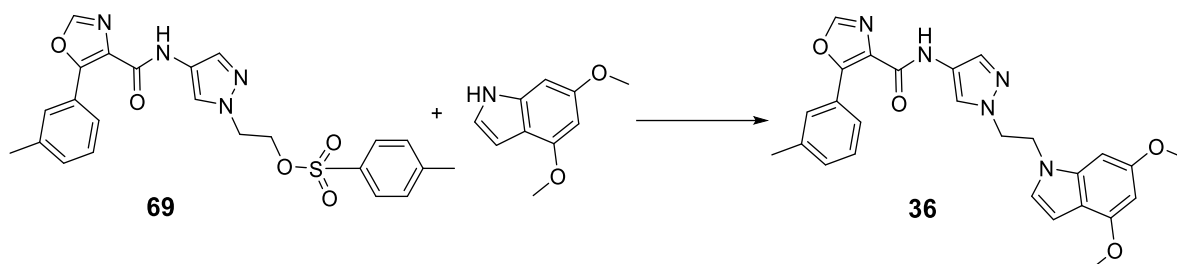
The title compound was synthesized according to the procedure described for compound **30** using 5-methoxy-benzimidazole instead of indole. The product was purified by prep. HPLC (Method G) to yield **34** (81 mg, 86%) as an off-white solid. ^1H NMR (500 MHz, DMSO) δ 10.51 (s, 1H), 8.64 (s, 1H), 8.03 (d, $J = 7.9$ Hz, 1H), 7.99 (d, $J = 13.0$ Hz, 2H), 7.72 (s, 1H), 7.46 (d, $J = 8.8$ Hz, 1H), 7.40 (t, $J = 7.7$ Hz, 1H), 7.30 (d, $J = 7.6$ Hz, 1H), 6.98 (s, 1H), 6.78 (dd, $J = 8.7, 2.5$ Hz, 1H), 4.66 (t, $J = 5.5$ Hz, 2H), 4.52 (t, $J = 5.6$ Hz, 2H), 3.78 (s, 3H), 3.19 – 3.12 (m, 1H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 158.1, 156.5, 152.2, 150.7, 138.14, 131.7, 131.1, 129.0, 128.9, 128.6, 127.3, 125.6, 122.1, 121.8, 120.1, 111.7, 93.8, 55.9, 51.4, 44.7, 23.5, 21.6, 19.7, 14.0. LC-MS A: $t_{\text{R}} = 0.70$ min; $[\text{M}+\text{H}]^+ = 443.02$; LC-HRMS: $t_{\text{R}} = 0.72$ min; $[\text{M}+\text{H}]/z = 443.1826$, found = 443.1835.

5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(5,6-dimethoxy-indol-1-yl)-ethyl]-1*H*-pyrazol-4-yl}-amide (35)



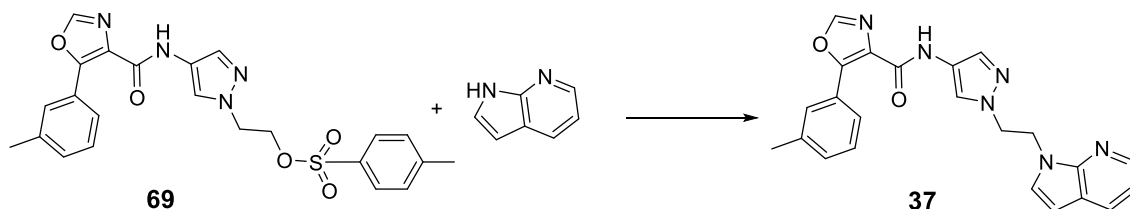
The title compound was synthesized according to the procedure described for compound **30** using 5,6-dimethoxyindole instead of indole. The product was purified by prep. HPLC (Method E) to yield **35** (6 mg, 6%) as a red solid LC-MS A: $t_{\text{R}} = 0.90$ min; $[\text{M}+\text{H}]^+ = 472.51$; LC-HRMS: $t_{\text{R}} = 1.07$ min; $[\text{M}+\text{H}]/z = 472.1980$, found = 472.1985; ^1H NMR (400 MHz, CDCl_3) δ : 2.46 (s, 3 H), 3.91 (s, 3 H), 3.94 (s, 3 H), 4.45 (t, $J = 5.9$ Hz, 2 H), 4.56 (t, $J = 6.0$ Hz, 2 H), 6.37 (d, $J = 3.1$ Hz, 1 H), 6.66 (s, 1 H), 6.78 (d, $J = 3.1$ Hz, 1 H), 7.06 (s, 1 H), 7.26-7.32 (m, 2 H), 7.39 (t, $J = 7.7$ Hz, 1 H), 7.70 (s, 2 H), 7.88 (s, 1 H), 8.06 (s, 1 H), 8.13 (d, $J = 7.8$ Hz, 1 H), 8.88 (s, 1 H).

5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(4,6-dimethoxy-indol-1-yl)-ethyl]-1*H*-pyrazol-4-yl]-amide (36)



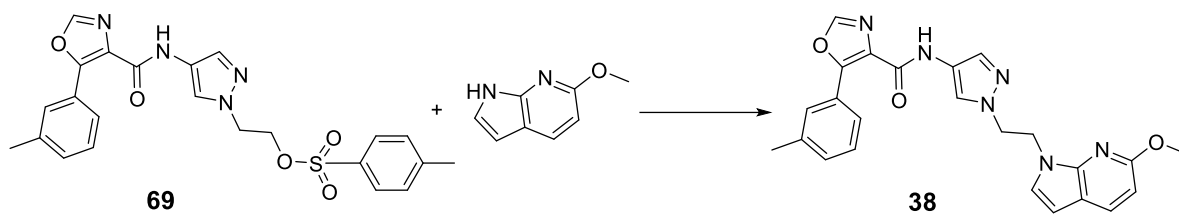
The title compound was synthesized according to the procedure described for compound **30** using 4,6-dimethoxyindole instead of indole. The product was purified by prep. HPLC (Method G) to yield **36** (5 mg, 5%) as a white solid. LC-MS A: $t_R = 0.95$ min; $[M+H]^+ = 472.26$; LC-HRMS: $t_R = 1.12$ min; $[M+H]/z = 472.1980$, found = 472.1986; 1H NMR (400 MHz, $CDCl_3$) δ : 2.46 (s, 3 H), 3.87 (s, 3 H), 3.91 (s, 3 H), 4.44 (t, $J = 5.9$ Hz, 2 H), 4.53 (t, $J = 6.2$ Hz, 2 H), 6.23 (d, $J = 1.1$ Hz, 1 H), 6.31 (s, 1 H), 6.48 (d, $J = 3.2$ Hz, 1 H), 6.66 (d, $J = 3.1$ Hz, 1 H), 7.25-7.30 (m, 1 H), 7.39 (t, $J = 7.7$ Hz, 1 H), 7.68 (s, 1 H), 7.72 (s, 1 H), 7.88 (s, 1 H), 8.06 (s, 1 H), 8.13 (d, $J = 7.9$ Hz, 1 H), 8.88 (s, 1 H).

5-*m*-Tolyl-oxazole-4-carboxylic acid [1-(2-pyrrolo[2,3-*b*]pyridin-1-yl-ethyl)-1*H*-pyrazol-4-yl]-amide (37)



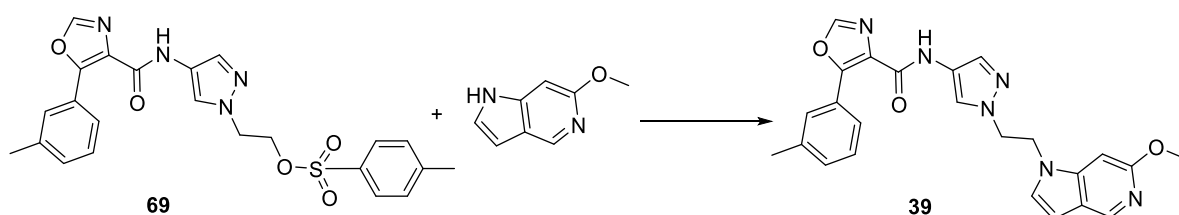
The title compound was synthesized according to the procedure described for compound **30** using 7-azaindole instead of indole. The product was purified by prep. HPLC (Method G) to yield **37** (3 mg, 4%) as a white solid. LC-MS C: $t_R = 0.79$ min; $[M+H]^+ = 413.43$; LC-HRMS: $t_R = 1.04$ min; $[M+H]/z = 413.1721$, found = 413.1729; 1H NMR (400 MHz, $CDCl_3$) δ : 2.45 (s, 3 H), 4.56 (t, $J = 6.1$ Hz, 3 H), 4.80 (t, $J = 5.6$ Hz, 3 H), 6.34 (d, $J = 3.5$ Hz, 1 H), 6.78 (d, $J = 3.5$ Hz, 1 H), 7.10 (dd, $J_1 = 4.7$ Hz, $J_2 = 7.8$ Hz, 1 H), 7.25-7.29 (m, 1 H), 7.39 (t, $J = 7.7$ Hz, 1 H), 7.70 (s, 1 H), 7.70 (s, 1 H), 7.88 (s, 1 H), 7.90 (dd, $J_1 = 1.5$ Hz, $J_2 = 7.8$ Hz, 1 H), 8.06 (s, 1 H), 8.14 (d, $J = 7.8$ Hz, 1 H), 8.35 (dd, $J_1 = 1.4$ Hz, $J_2 = 4.7$ Hz, 1 H), 8.90 (s, 1 H).

5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(6-methoxy-pyrrolo[2,3-*b*]pyridin-1-yl)-ethyl]-1*H*-pyrazol-4-yl}-amide (38)



The title compound was synthesized according to the procedure described for compound **21** using 6-methoxy-7-azaindole instead of indole. The product was purified by prep. HPLC (Method G) to yield **38** (10 mg, 15%) as a yellow solid. LC-MS A: $t_R = 1.04$ min; $[M+H]^+ = 442.75$; LC-HRMS: $t_R = 1.16$ min; $[M+H]/z = 4343.1826$, found = 443.1835; $^1\text{H NMR}$ (400 MHz, DMSO) δ : 2.39 (s, 3 H), 3.91 (s, 3 H), 4.51-4.57 (m, 2 H), 4.57-4.62 (m, 2 H), 6.30 (d, $J = 3.5$ Hz, 1 H), 6.52 (d, $J = 8.4$ Hz, 1 H), 6.99 (d, $J = 3.5$ Hz, 1 H), 7.31 (d, $J = 7.6$ Hz, 1 H), 7.41 (t, $J = 7.7$ Hz, 1 H), 7.68 (s, 1 H), 7.82 (d, $J = 8.4$ Hz, 1 H), 7.98 (s, 2 H), 8.04 (d, $J = 7.9$ Hz, 1 H), 8.64 (s, 1 H), 10.46 (s, 1 H).

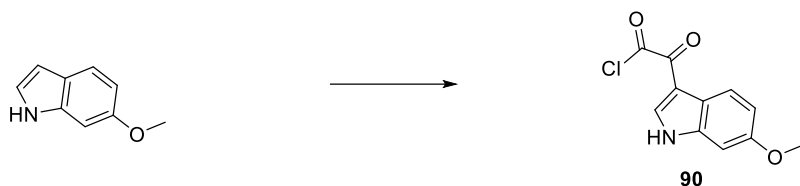
5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(6-methoxy-pyrrolo[3,2-*c*]pyridin-1-yl)-ethyl]-1*H*-pyrazol-4-yl}-amide (39)



The title compound was synthesized according to the procedure described for compound **21** using 6-methoxy-5-azaindole instead of indole. The product was purified by prep. HPLC (Method G) to yield **39** as a white solid (4 mg, 3%). LC-MS C: $t_R = 0.62$ min; $[M+H]^+ = 443.54$. LC-HRMS: $t_R = 0.65$ min; $[M+H]/z = 443.1826$, found = 443.1844; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 2.46 (s, 3 H), 4.00 (s, 3 H), 4.42 (t, $J = 5.9$ Hz, 2 H), 4.52 (d, $J = 5.9$ Hz, 2 H), 6.43 (d, $J = 3.3$ Hz, 1 H), 6.52 (s, 1 H), 6.68 (d, $J = 3.3$ Hz, 1 H), 7.26-7.29 (m, 1 H), 7.39 (t, $J = 7.7$ Hz, 1 H), 7.68 (s, 1 H), 7.70 (s, 1 H), 7.88 (s, 1 H), 8.06 (s, 1 H), 8.13 (d, $J = 7.8$ Hz, 1 H), 8.46 (s, 1 H), 8.89 (s, 1 H).

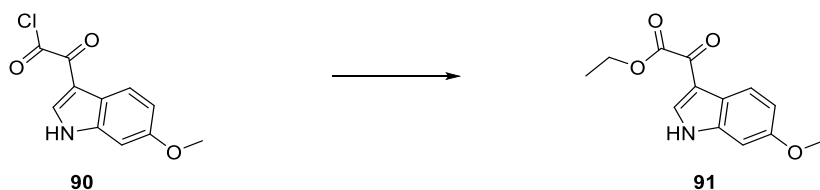
5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(6-methoxy-1*H*-indol-3-yl)-ethyl]-1*H*-pyrazol-4-yl}-amide (40)

Step 1: (6-Methoxy-1*H*-indol-3-yl)-oxo-acetyl chloride (90)



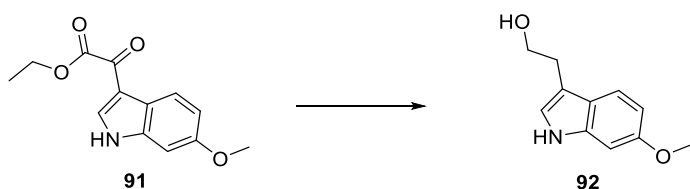
Oxalyl chloride (1.5 mL, 17.7 mmol) was added to a 0°C solution of 6-methoxyindole (2.0 g, 13.59 mmol) in diethylether (50.0 mL) and the reaction mixture was stirred at rt for 1.5 h. The desired product crushed out and was filtered off (wash with cold diethylether) to yield **90** as a red solid (2.83 g, 88%). LC-MS B: $t_R = 0.48$ min; $[M+H]^+ = 220.16$; 1H NMR (400 MHz, DMSO) δ : 3.81 (s, 3 H), 6.91 (s, 1 H), 7.04 (s, 1 H), 8.03 (s, 1 H), 8.30 (s, 1 H), 12.16 (s, 1 H).

Step 2: (6-Methoxy-1*H*-indol-3-yl)-oxo-acetic acid ethyl ester (91)



NEt_3 (1.5 mL, 10.8 mmol) was added to a 0°C suspension of **90** (2.14 g, 9.02 mmol) in EtOH (22.0 mL) and the resulting rxn mixture was stirred at 0°C for 10 min, then at rt for 1 h. The filtrate was filtered off and washed with cold EtOH and Et₂O. The solid was dried *in vacuo* to yield 6-methoxy-1*H*-indol-3-yl)-oxo-acetic acid ethyl ester **91** as a yellow solid (2.1 g, 94%). LC-MS B: $t_R = 0.65$ min; $[M+H]^+ = 248.20$; 1H NMR (400 MHz, DMSO) δ : 1.34 (t, $J = 7.1$ Hz, 3 H), 3.81 (s, 3 H), 4.36 (q, $J = 7.1$ Hz, 2 H), 6.92 (dd, $J_1 = 2.3$ Hz, $J_2 = 8.7$ Hz, 1 H), 7.04 (d, $J = 2.2$ Hz, 1 H), 8.01 (d, $J = 8.7$ Hz, 1 H), 8.29 (d, $J = 3.2$ Hz, 1 H), 12.19 (s, 1 H).

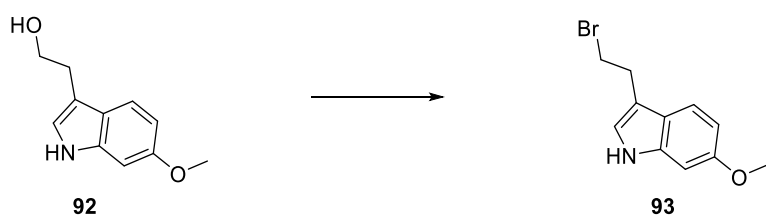
Step 3: 2-(6-Methoxy-1*H*-indol-3-yl)-ethanol (92)



$LiAlH_4$ (1 M in THF, 25.0 mL, 25.0 mmol) was carefully added (exothermic) to a 0°C suspension of **91** (2.06 g, 8.35 mmol) in THF (25.0 mL). The reaction mixture was allowed to reach rt, then heated to 60°C for 1 h. The reaction mixture was cooled to 0°C, diluted with THF and EtOAc and quenched with H₂O. The solid was filtered off and rinsed with MeOH. The

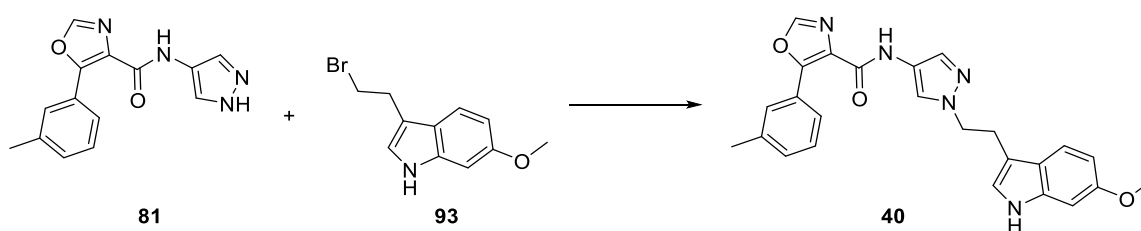
filtrate was concentrated *in vacuo*, redissolved in EtOAc and washed with 0.1 M aq. HCl and brine. The org. layer was dried (MgSO₄), filtered, and concentrated *in vacuo* to yield 2-(6-methoxy-1H-indol-3-yl)-ethanol **92** as a red solid (1.5 g, 89%) which was use as such in the next step. LC-MS B: $t_R = 0.51$ min; $[M+H]^+ = 192.30$; ¹H NMR (400 MHz, DMSO) δ : 2.80 (t, $J = 7.4$ Hz, 2 H), 3.59-3.66 (m, 2 H), 3.75 (s, 3 H), 4.57 (t, $J = 5.3$ Hz, 1 H), 6.63 (dd, $J_1 = 2.2$ Hz, $J_2 = 8.6$ Hz, 1 H), 6.83 (d, $J = 2.2$ Hz, 1 H), 6.98 (d, $J = 1.9$ Hz, 1 H), 7.37 (d, $J = 8.6$ Hz, 1 H), 10.55 (s, 1 H).

Step 4: 3-(2-Bromo-ethyl)-6-methoxy-1H-indole (**93**)



Tetrabromomethane (1.20 g, 3.59 mmol) was added to a 0°C solution of **92** (500 mg, 2.62 mmol) and triphenylphosphine (1.08 g, 4.13 mmol) in DCM (21.0 mL). The reaction mixture was stirred at 0°C for 1.5 h before concentrated *in vacuo*. The product was purified by FC (EtOAc/hex. 1:9, $R_f = 0.73$ (EtOAc/ hept. 1:1)) to yield **93** as an off-white solid (346 mg, 39%) which was used as such in the next step. LC-MS B: $t_R = 0.81$ min; $[M+H]^+ = 254.13$; ¹H NMR (400 MHz, CDCl₃) δ : 3.33 (t, $J = 7.7$ Hz, 4 H), 3.65 (t, $J = 7.6$ Hz, 4 H), 3.87 (s, 7 H), 6.84 (dd, $J_1 = 2.2$ Hz, $J_2 = 8.6$ Hz, 2 H), 6.89 (d, $J = 2.1$ Hz, 2 H), 7.00 (d, $J = 1.1$ Hz, 2 H), 7.48 (d, $J = 8.6$ Hz, 2 H), 7.90 (s, 1 H).

Step 5

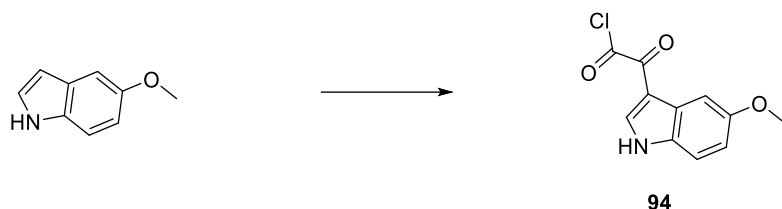


Cs₂CO₃ (128 mg, 0.37 mmol) was added to a rt solution of **81** (50 mg, 0.19 mmol) and **93** (42 mg, 0.19 mmol) in MeCN (1.0 mL) and the resulting reaction mixture was stirred in the microwave at 100°C for 1.5 h. The reaction mixture was filtered and directly purified by prep. HPLC (Method F) to yield **40** (30 mg, 35%) as a yellowish foam. LC-MS B: $t_R = 0.84$ min; $[M+H]^+ = 442.13$. LC-HRMS: $t_R = 1.08$ min; $[M+H]/z = 442.1874$, found = 442.1881; ¹H NMR (400 MHz, CDCl₃) δ : 2.47 (s, 3 H), 3.33 (t, $J = 7.5$ Hz, 2 H), 3.87 (s, 3 H), 4.41 (t, $J = 7.3$ Hz, 2 H), 6.81-6.88 (m, 3 H), 7.29-7.31 (m, 1 H), 7.40 (t, $J = 7.7$ Hz, 1 H), 7.47 (d, $J = 8.6$ Hz, 1

H), 7.63 (s, 1 H), 7.88 (s br, 1 H), 7.89 (s, 1 H), 7.99 (s, 1 H), 8.09 (s, 1 H), 8.17 (d, $J = 7.9$ Hz, 1 H), 8.95 (s, 1 H).

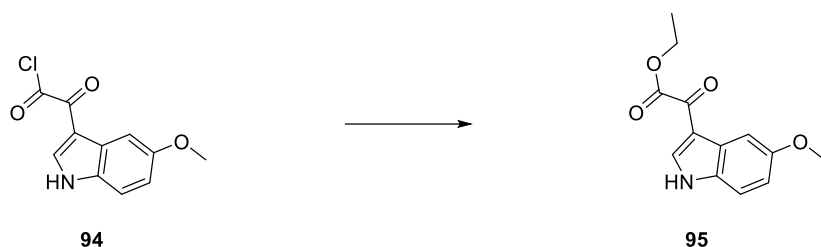
5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(5-methoxy-1*H*-indol-3-yl)-ethyl]-1*H*-pyrazol-4-yl}-amide (41)

Step 1: (5-Methoxy-1*H*-indol-3-yl)-oxo-acetyl chloride (94)



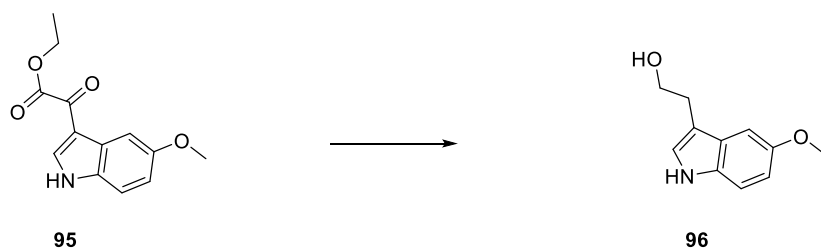
Oxalyl chloride (17.1 mL, 194 mmol) was added to a 0°C solution of 5-methoxyindole (22.0 g, 149 mmol) in Et₂O (440 mL) and the reaction mixture was stirred at rt for 15 min. The desired product crushed out and was filtered off (wash with cold Et₂O) to yield 5-methoxy-1*H*-indol-3-yl)-oxo-acetyl chloride **94** as an orange solid (33.53 g, 94%). LC-MS B: $t_R = 0.46$ min; $[M+H]^+ = 220.09$.

Step 2: (5-Methoxy-1*H*-indol-3-yl)-oxo-acetic acid ethyl ester (95)



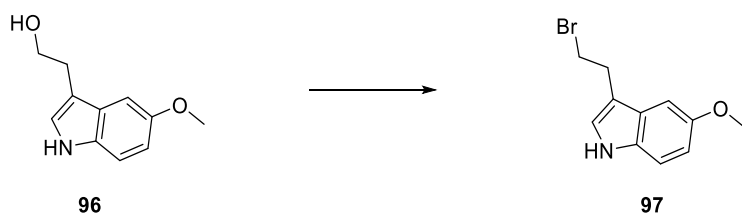
NEt₃ (23.6 mL, 169 mmol) was added to a 0°C suspension of **94** (33.50 g, 141 mmol) in EtOH (300 mL) and the resulting rxn mixture was stirred at 0°C for further 10 min, then at rt for 1 h. The filtrate was filtered off and washed with cold EtOH and Et₂O. The solid was dried *in vacuo* to yield (5-methoxy-1*H*-indol-3-yl)-oxo-acetic acid ethyl ester **95** as a yellow solid (33.17 g, 95%). LC-MS C: $t_R = 0.71$ min; $[M+H]^+ = 248.25$.

Step 3: 2-(5-Methoxy-1*H*-indol-3-yl)-ethanol (96)



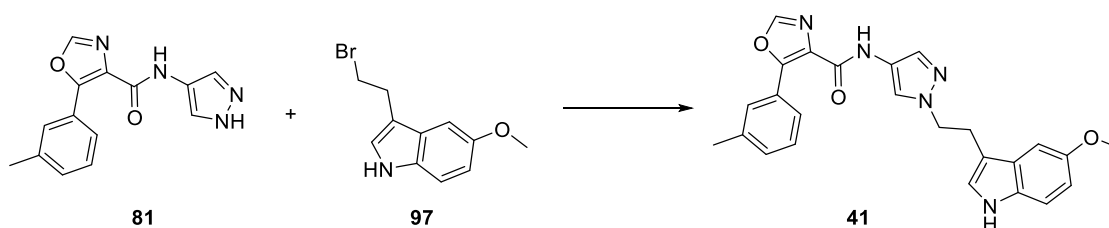
LiAlH₄ (2.4 M in THF, 74.3 mL, 178.4 mmol) was carefully added (exothermic) to a 0°C suspension of **95** (14.70 g, 59.5 mmol) in THF (160.0 mL). The reaction mixture was allowed to reach rt, then heated to 60°C for 20 min. The reaction mixture was cooled to 0°C, diluted with EtOAc (10.0 mL) and quenched with H₂O (10.0 mL). The solid was filtered off and rinsed with THF. The filtrate was concentrated *in vacuo*, redissolved in EtOAc and washed with 0.1 M aq. HCl and brine. The org. layer was dried (MgSO₄), filtered, and concentrated *in vacuo* to yield 2-(5-methoxy-1*H*-indol-3-yl)-ethanol **96** as a brownish oil (9.68 g, 85%) which was used as such in the next step. LC-MS B: t_R = 0.49 min; [M+H]⁺ = 192.24; ¹H NMR (400 MHz, CDCl₃) δ: 3.03 (t, *J* = 6.3 Hz, 2 H), 3.89 (s, 3 H), 3.93 (t, *J* = 6.4 Hz, 2 H), 6.91 (dd, *J*₁ = 2.4 Hz, *J*₂ = 8.8 Hz, 1 H), 7.07 (s, 1 H), 7.09 (d, *J* = 2.4 Hz, 1 H), 7.28 (d, *J* = 8.7 Hz, 1 H), 8.04 (s, 1 H).

Step 4: 3-(2-Bromo-ethyl)-5-methoxy-1*H*-indole (**97**)



Tetrabromomethane (19.31 g, 58.23 mmol) was added to a 0°C solution **96** (9.68 g mg, 50.63 mmol) and triphenylphosphine (15.27 g, 58.23 mmol) in DCM (70.0 mL). The reaction mixture was stirred at rt for 1 h before concentrated *in vacuo*. The product was purified by FC (EtOAc/hex. 1:9 to 3:7) to give **97** as a beige solid (9.58 g, 74%). LC-MS B: t_R = 0.78 min; [M+H]⁺ = 254.10; ¹H NMR (400 MHz, DMSO) δ: 3.22 (t, *J* = 7.6 Hz, 2 H), 3.73 (t, *J* = 7.5 Hz, 2 H), 3.77 (s, 3 H), 6.72 (dd, *J*₁ = 2.4 Hz, *J*₂ = 8.7 Hz, 1 H), 7.05 (d, *J* = 2.3 Hz, 1 H), 7.21 (d, *J* = 2.3 Hz, 1 H), 7.24 (d, *J* = 8.7 Hz, 1 H), 10.75 (s, 1 H).

Step 5

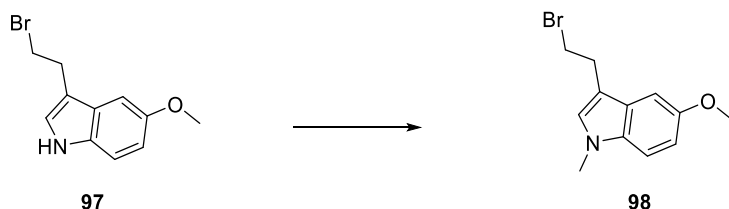


A solution of **97** (284 mg, 1.12 mmol) in DMF (1.0 mL) was added to a rt solution of **81** (250 mg, 0.93 mmol) and Cs₂CO₃ (607 mg, 1.86 mmol) in MeCN (3.5 mL). The resulting reaction mixture was stirred in the microwave at 100°C for 40 min (with cooling). The reaction mixture was diluted with 1N aq. HCl and DCM. The org. layer was separated and the inorg. layer extracted with DCM (2x). The combined org. layers were washed with brine, dried (MgSO₄), filtered, and concentrated. The product was purified by FC (hex./EtOAc 2:7; R_f = 0.4) followed

by crystallization in a mixture of hex., DCM and small amounts of EtOAc at 4°C to yield **41** (242 mg, 59%) as beige crystals. ¹H NMR (400 MHz, DMSO) δ: 2.39 (s, 3 H), 3.17 (t, J = 7.3 Hz, 2 H), 3.76 (s, 3 H), 4.35 (t, J = 7.3 Hz, 2 H), 6.70 (dd, J₁ = 2.1 Hz, J₂ = 8.7 Hz, 1 H), 6.97 (d, J = 1.9 Hz, 1 H), 7.04 (d, J = 1.3 Hz, 1 H), 7.21 (d, J = 8.7 Hz, 1 H), 7.31 (m, 1 H), 7.41 (t, J = 7.7 Hz, 1 H), 7.73 (s, 1 H), 7.99 (s, 1 H), 8.06 (d, J = 7.8 Hz, 1 H), 8.10 (s, 1 H), 8.66 (s, 1 H), 10.51 (s, 1 H), 10.68 (s, 1 H). ¹³C NMR (126 MHz, DMSO) δ 158.1, 153.6, 152.1, 150.7, 138.2, 131.7, 131.1, 131.0, 129.1, 128.9, 128.6, 127.9, 127.3, 127.3, 125.7, 124.1, 121.6, 121.40, 112.5, 111.7, 111.1, 100.4, 55.8, 52.6, 26.6, 21.5. LC-MS A: t_R = 0.91 min; [M+H]⁺ = 442.13. LC-HRMS: t_R = 1.08 min; [M+H]/z = 442.1874, found = 442.1884.

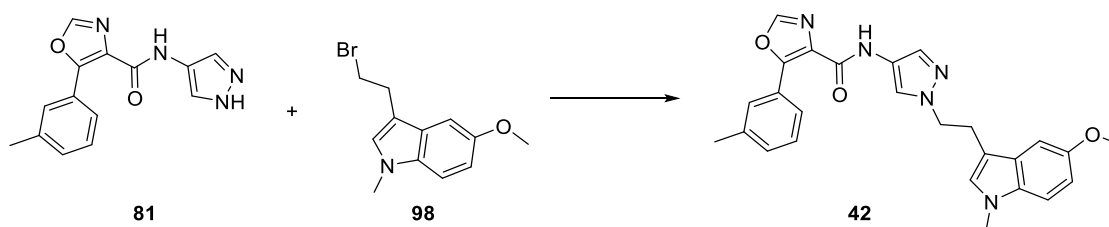
5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(5-methoxy-1-methyl-1*H*-indol-3-yl)-ethyl]-1*H*-pyrazol-4-yl}-amide (**42**)

Step 1: 3-(2-bromoethyl)-5-methoxy-1-methyl-1*H*-indole (**98**)



NaH (145 mg, 3.62 mmol) was added to a 0°C solution of **97** (23 mg, 0.9 mmol) and MeI (0.45 mL, 7.24 mmol) in THF (1.7 mL). The reaction mixture was stirred at rt overnight. The solid was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in DCM and H₂O, the org. layer was separated and the inorg. layer was extracted with DCM. The combined org. layers were dried (MgSO₄) filtered, and concentrated. The product was purified by FC (EtOAc/hex. 1:2, R_f = 0.4) to yield **98** (115 mg, 47%) as a mixture of desired product and side product which was used as such in the next step.

Step 2

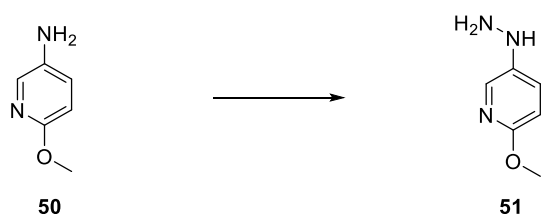


Cs₂CO₃ (115 mg, 0.335 mmol) was added to a rt solution of **81** (50 mg, 0.19 mmol) in MeCN (1.0 mL) and **98** (64 mg, 0.17 mmol) in DMF (0.5 mL). The resulting mixture was irradiated in the microwave for 50 min at 110°C (with cooling). The reaction mixture was diluted with 1N HCl and DCM. The org. layer was separated and the inorg. layer was extracted with DCM (2x). The combined org. layers were washed with brine, dried (MgSO₄), filtered, and

concentrated. The product was purified prep HPLC (Method F) to yield **42** (13 mg, 17%) as a yellowish solid LC-MS C: $t_R = 0.96$ min; $[M+H]^+ = 456.07$. LC-HRMS: $t_R = 1.15$ min; $[M+H]/z = 456.2030$, found = 456.2031; 1H NMR (400 MHz, $CDCl_3$) δ : 2.47 (s, 3 H), 3.32 (t, $J = 7.6$ Hz, 2 H), 3.73 (s, 3 H), 3.89 (s, 3 H), 4.39 (t, $J = 7.4$ Hz, 2 H), 6.79 (s, 1 H), 6.91 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.8$ Hz, 1 H), 7.00 (d, $J = 2.3$ Hz, 1 H), 7.20 (d, $J = 8.8$ Hz, 1 H), 7.29-7.31 (m, 1 H), 7.41 (t, $J = 7.7$ Hz, 1 H), 7.64 (s, 1 H), 7.90 (s, 1 H), 8.03 (s, 1 H), 8.09 (s, 1 H), 8.17 (d, $J = 7.8$ Hz, 1 H), 8.95 (s, 1 H).

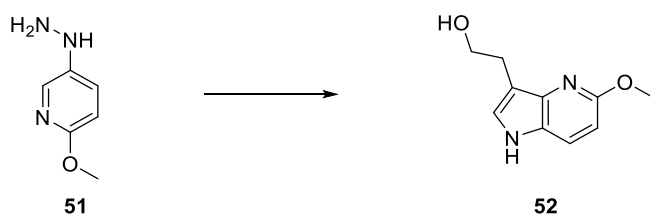
5-*m*-Tolyl-oxazole-4-carboxylic acid {1-[2-(5-methoxy-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)-ethyl]-1*H*-pyrazol-4-yl}-amide (**43**)

Step 1: (6-Methoxy-pyridin-3-yl)-hydrazine (**51**)



A solution of $NaNO_2$ (5.56 g, 80.6 mmol) in H_2O (60.0 mL) was added dropwise to a $-5^\circ C$ solution of 5-amino-2-methoxypyridine (10.0 g, 80.6 mmol) in aq. 6 N HCl (100.0 mL). After 30 min at $0^\circ C$, a solution of tin(II) chloride dihydrate (45.67 g, 202 mmol) in aq. 6 N HCl (100 mL) was added to the reaction mixture and stirring was continued at $0^\circ C$ for 1 h. The mixture was basified at $0^\circ C$ with 40% aq. KOH (300 mL) and the inorg. layer was extracted with EtOAc (5 x 300 mL). The combined org. layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield **51** as a red solid (11.37 g, 101%) which was used as such in the next step. LC-MS A: $t_R = 0.22$ min; $[M+H]^+ = 140.12$. 1H NMR (400 MHz, $CDCl_3$) δ : 3.48-3.76 (m, 2 H), 3.91 (s, 3 H), 4.84-5.14 (m, 1 H), 6.69 (d, $J = 8.8$ Hz, 1 H), 7.23 (dd, $J_1 = 2.9$ Hz, $J_2 = 8.8$ Hz, 1 H), 7.80 (d, $J = 2.9$ Hz, 1 H).

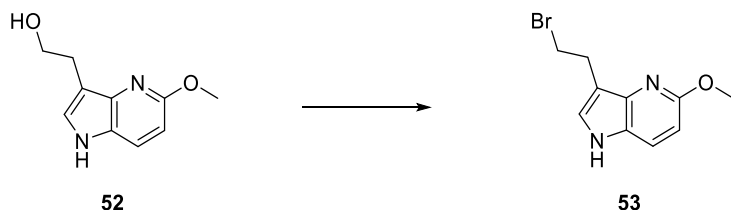
Step 2: 2-(5-Methoxy-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)-ethanol (**52**)



2-(3-Chloropropyl)-1,3-dioxolane (10.75 g, 71.4 mmol) was added to a rt solution of **51** (9.03 g, 64.9 mmol) in an aq. 4% H_2SO_4 solution (281 mL, 64.9 mmol) and the resulting mixture was stirred at $100^\circ C$ for 16 h. The mixture was quenched with aq. sat. Na_2CO_3 (400 mL) and

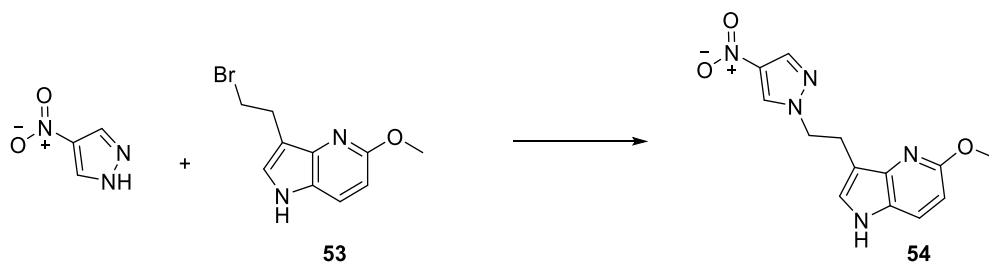
extracted with EtOAc (3x). The combined org layers were dried (MgSO₄), filtered, and concentrated *in vacuo*. The product was purified by FC (EtOAc/hex. 1:9 to 1:1; R_f in EtOAc/hept. 1:1 = 0.23) to yield **52** (9.97 g, 29%) as a yellow solid LC-MS A: t_R = 0.38 min; [M+H]⁺ = 193.2. ¹H NMR (400 MHz, DMSO) δ: 2.85 (t, J = 7.1 Hz, 2 H), 3.68-3.73 (m, 2 H), 3.86 (s, 3 H), 4.86 (t, J = 5.5 Hz, 1 H), 6.52 (d, J = 8.7 Hz, 1 H), 7.30 (d, J = 2.5 Hz, 1 H), 7.65 (d, J = 8.7 Hz, 1 H), 10.88 (s, 1 H).

Step 3: 3-(2-Bromo-ethyl)-5-methoxy-1H-pyrrolo[3,2-b]pyridine (**53**)



A solution of phosphorus tribromide (0.5 mL, 5.32 mmol) in Et₂O (10 mL) was added to a 0°C solution of **52** (1.00 g, 5.2 mmol) in Et₂O (30.0 mL). The resulting pink suspension was allowed to warm up to rt and stirring was continued overnight. The reaction mixture was diluted with EtOAc and aq. sat Na₂CO₃ solution. The org. layer was separated and the inorg. layer was extracted with EtOAc (1x). The combined org. layers were dried (MgSO₄), filtered, and concentrated to yield **53** (1.88 g, 142%) as a red oil which was used as such in the next step. LC-MS A: t_R = 0.53 min; [M+H]⁺ = 256.99. ¹H NMR (400 MHz, DMSO) δ: 3.25 (t, J = 7.5 Hz, 2 H), 3.86 (m, 5 H), 6.54 (d, J = 8.7 Hz, 1 H), 7.40 (d, J = 2.7 Hz, 1 H), 7.67 (d, J = 8.7 Hz, 1 H), 10.97 (s, 1 H).

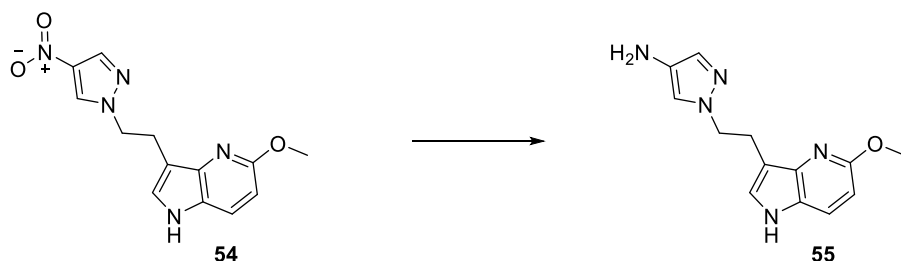
Step 4: 5-Methoxy-3-[2-(4-nitro-pyrazol-1-yl)-ethyl]-1H-pyrrolo[3,2-b]pyridine (**54**)



Cs₂CO₃ (14.34 g, 44 mmol) was added to a rt solution of **53** (18.7 g, 22 mmol) and 4-nitro-1H-pyrazole (2.49 g, 22 mmol) in MeCN (60 mL) and DMF (60 mL) and the resulting yellow suspension was stirred at 110°C for 30 min, followed by rt overnight. Water was added to the reaction mixture and the inorg. layer was extracted with DCM (2x). The combined org. layers were dried (MgSO₄), filtered, and concentrated *in vacuo*. The product was purified by FC (EtOAc/hex. 1:9 to 1:1, R_f in EtOAc/hept. 1:1 = 0.45) to yield **54** (11.1 g, 75%) as a yellow solid. LC-MS A: t_R = 0.55 min; [M+H]⁺ = 288.08. ¹H NMR (400 MHz, DMSO) δ: 3.26 (t, J = 7.0

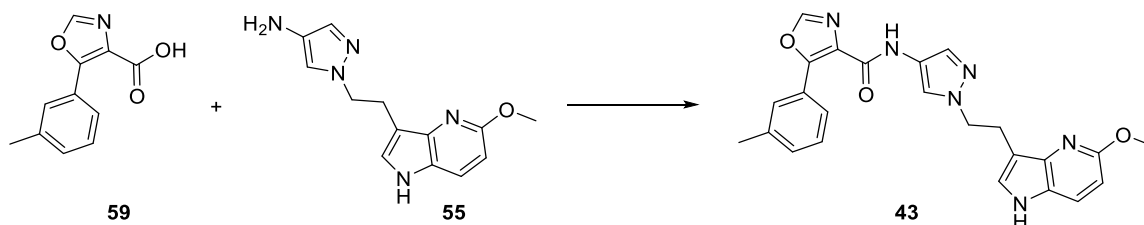
Hz, 2 H), 3.89 (s, 3 H), 4.57 (t, $J = 7.0$ Hz, 2 H), 6.54 (d, $J = 8.7$ Hz, 1 H), 7.22 (d, $J = 1.4$ Hz, 1 H), 7.66 (d, $J = 8.7$ Hz, 1 H), 8.26 (s, 1 H), 8.78 (s, 1 H), 10.93 (s, 1 H).

Step 5: 1-[2-(5-Methoxy-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)-ethyl]-1*H*-pyrazol-4-ylamine (**55**)



Pd/C (1.18 g, 11.2 mmol) was added to a degassed solution of **54** (11.11 g, 34.8 mmol) in EtOH (350.0 mL). The reaction mixture was stirred under H₂-atmosphere at rt overnight. The reaction mixture was filtered over Celite, washed with EtOH, and the filtrate was concentrated *in vacuo* to yield **55** (9.97 g, 111%) as a red oil which was used as such in the next step. LC-MS A: $t_R = 0.35$ min; $[M+H]^+ = 257.92$. ¹H NMR (400 MHz, DMSO) δ : 3.12 (t, $J = 7.5$ Hz, 2 H), 3.77 (s, 2 H), 3.90 (s, 3 H), 4.30 (t, $J = 7.3$ Hz, 2 H), 6.54 (d, $J = 8.7$ Hz, 1 H), 6.91 (d, $J = 0.8$ Hz, 1 H), 6.98 (d, $J = 0.8$ Hz, 1 H), 7.18 (d, $J = 2.7$ Hz, 1 H), 7.65 (d, $J = 8.7$ Hz, 1 H), 10.89 (s, 1 H).

Step 6

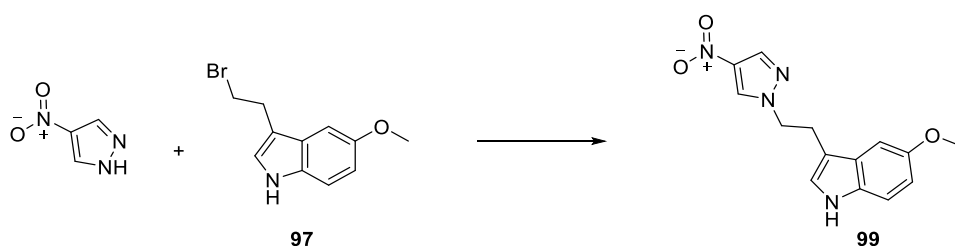


TBTU (11.90 g, 37.1 mmol) was added to a rt solution **59** (7.07 g, 34.8 mmol) and DIPEA (11.9 mL, 69.6 mmol) in DCM (100.0 mL). The reaction mixture was stirred for 10 min, then a solution **55** (10.02 g, 34.8 mmol) in DCM (150.0 mL) was added and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with DCM (200.0 mL) and washed with water (5x). The org. layer was dried (MgSO₄), filtered, and concentrated *in vacuo*. The product was purified by FC (EtOAc/hept. 3:7 to 1:1; R_f in EtOAc/hept. 1:1 = 0.13) to yield **43** (9.1 g, 59%) as a yellow foam. ¹H NMR (400 MHz, DMSO) δ : 2.40 (s, 3H), 3.20 (t, $J = 7.5$ Hz, 2H), 3.91 (s, 3H), 4.47 (t, $J = 7.3$ Hz, 2H), 6.54 (d, $J = 8.7$ Hz, 1H), 7.20 (d, $J = 2.6$ Hz, 1H), 7.32 (d, $J = 7.6$ Hz, 1H), 7.42 (t, $J = 7.7$ Hz, 1H), 7.66 (d, $J = 8.7$ Hz, 1H), 7.72 (s, 1H), 7.99 (s, 1H), 8.06 (m, 2H), 8.66 (s, 1H), 10.50 (s, 1H), 10.90 (d, $J = 2.0$ Hz, 1H). ¹³C NMR (125 MHz, DMSO) δ : 159.1, 158.1, 152.1, 150.7, 141.5, 138.1, 131.12, 131.14, 129.1, 128.8, 128.6, 127.3, 126.1,

125.6, 125.0, 122.8, 121.41, 121.40, 110.7, 104.9, 53.0, 51.9, 25.8, 21.6. LC-MS B: t_R = 0.64 min; $[M+H]^+$ = 443.16. LC-HRMS: t_R = 0.92 min; $[M+H]/z$ = 443.1826, found = 443.1826.

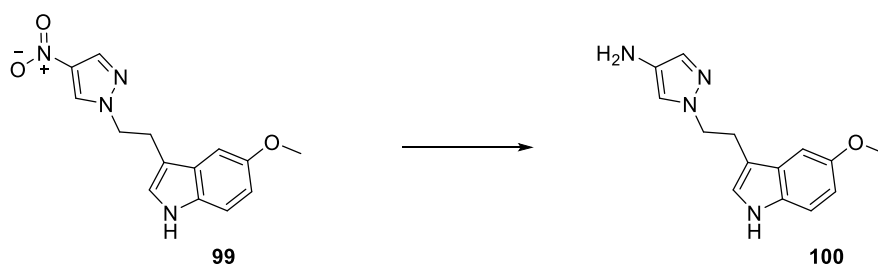
5-Phenyl-oxazole-4-carboxylic acid {1-[2-(5-methoxy-1*H*-indol-3-yl)-ethyl]-1*H*-pyrazol-4-yl}-amide (44)

Step 1: 5-Methoxy-3-[2-(4-nitro-pyrazol-1-yl)-ethyl]-1*H*-indole (99)



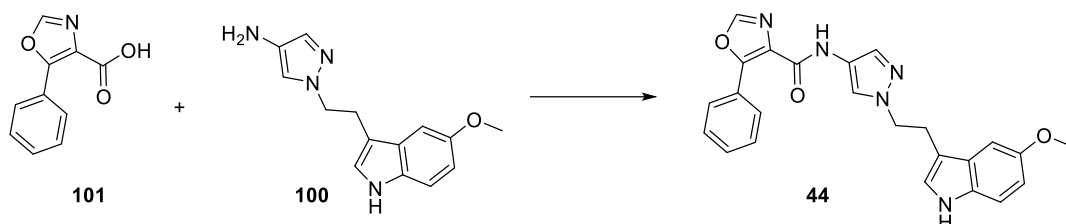
Cs_2CO_3 (2.08 g, 6.38 mmol) was added to a rt solution of 4-nitro-1*H*-pyrazole (361 mg, 3.19 mmol) and **97** (811 mg, 3.19 mmol) in MeCN (15.0 mL) and DMF (5.0 mL). The reaction mixture was irradiated in the microwave for 10 min at 100°C (with cooling). The rxn mixture was diluted with water, the org. layer was separated and the inorg. layer was extracted with DCM (2x). The combined org. layers were dried (MgSO_4), filtered, and concentrated *in vacuo*. The product was purified by FC (EtOAc/hex. 1:4 to 2:4, R_f in EtOAc/hex. 1:1 = 0.48) to yield **99** (446 mg, 53%) as a yellow oil. LC-MS B: t_R = 0.70 min; $[M+H]^+$ = 287.13; ^1H NMR (400 MHz, DMSO) δ : 3.23 (t, J = 7.1 Hz, 2 H), 3.76 (s, 3 H), 4.44 (t, J = 7.1 Hz, 2 H), 6.72 (dd, J_1 = 2.2 Hz, J_2 = 8.7 Hz, 1 H), 6.95 (d, J = 2.0 Hz, 1 H), 7.04 (d, J = 1.8 Hz, 1 H), 7.22 (d, J = 8.7 Hz, 1 H), 8.28 (s, 1 H), 8.79 (s, 1 H), 10.70 (s, 1 H).

Step 2: 1-[2-(5-Methoxy-1*H*-indol-3-yl)-ethyl]-1*H*-pyrazol-4-ylamine (100)



Pd/C (200 mg) was added to a rt solution of **99** (2.11 g, 7.37 mmol) in degassed EtOH (35 mL). The reaction mixture was stirred under H_2 -atmosphere at rt overnight. The reaction mixture was filtered over Celite, washed with EtOH, and the filtrate was concentrated *in vacuo* to yield **100** (1.89 g, 100%) as a red oil, which was used as such in the next step. LC-MS B: t_R = 0.42 min; $[M+H]^+$ = 257.16; ^1H NMR (400 MHz, DMSO) δ : 3.09 (t, J = 7.4 Hz, 2 H), 3.75 (s br, 2 H), 3.76 (s, 3 H), 4.18 (t, J = 7.3 Hz, 2 H), 6.70-6.72 (m, 1 H), 6.91-6.95 (m, 2 H), 7.02 (s, 2 H), 7.22 (d, J = 8.7 Hz, 1 H), 10.64 (s, 1 H).

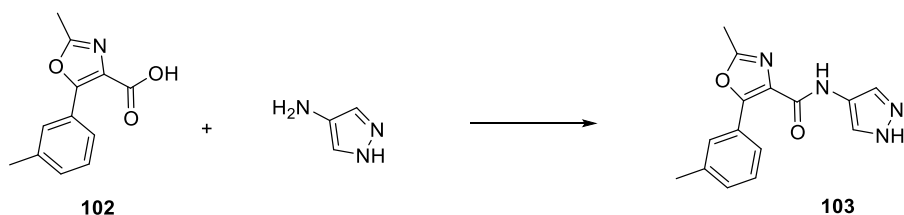
Step 3



The title compound was synthesized according to the procedure described for compound **43** (step 6) using **100** and **101**. Purification by prep. HPLC (Method G) yielded **44** (54 mg, 84%) as an off-white solid. LC-MS C: $t_R = 0.87$ min; $[M+H]^+ = 427.94$; LC-HRMS: $t_R = 1.01$ min; $[M+H]/z = 428.1717$, found = 428.1721; 1H NMR (400 MHz, $CDCl_3$) δ : 2.03 (s, 3 H), 3.34 (t, $J = 7.4$ Hz, 2 H), 3.89 (s, 3 H), 4.41 (t, $J = 7.4$ Hz, 2 H), 6.88 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.8$ Hz, 1 H), 6.91 (d, $J = 2.1$ Hz, 1 H), 7.01 (d, $J = 2.3$ Hz, 1 H), 7.26 (d, $J = 8.8$ Hz, 1 H), 7.29 (s, 1 H), 7.45-7.55 (m, 3 H), 7.65 (s, 1 H), 7.91 (s, 1 H), 7.94 (s, br 1 H), 8.00 (s, 1 H), 8.31-8.34 (m, 2 H), 8.97 (s, 1 H).

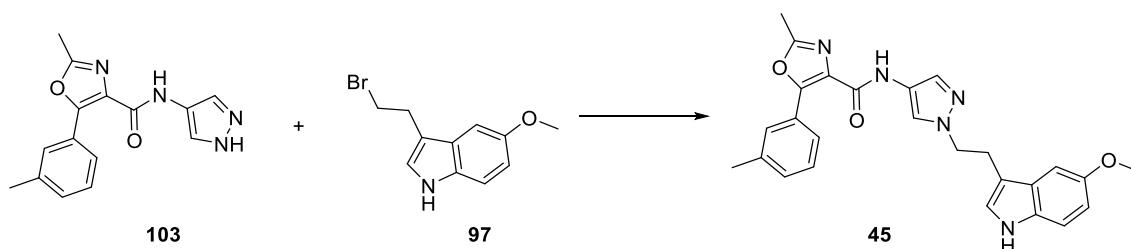
2-Methyl-5-*m*-tolyl-oxazole-4-carboxylic acid {1-[2-(5-methoxy-1*H*-indol-3-yl)-ethyl]-1*H*-pyrazol-4-yl}-amide (**45**)

Step 1: 2-Methyl-5-*m*-tolyl-oxazole-4-carboxylic acid (1*H*-pyrazol-4-yl)-amide (**103**)



The product was synthesized according to the procedure described for compound **81**, using **102** instead of **59**. Purification by FC (EtOAc/ hept. 1:1; $R_f = 0.12$) yielded **103** (3.29 g, 82%) as a white solid. LC-MS B: $t_R = 0.68$ min; $[M+H]^+ = 283.16$; 1H NMR (400 MHz, DMSO) δ : 2.39 (s, 3 H), 2.57 (s, 3 H), 7.29 (d, $J = 7.5$ Hz, 1 H), 7.40 (t, $J = 7.7$ Hz, 1 H), 7.78 (s, 1 H), 7.96 (s, 1 H), 8.01-8.09 (m, 2 H), 10.38 (s, 1 H), 12.60 (s, 1 H)

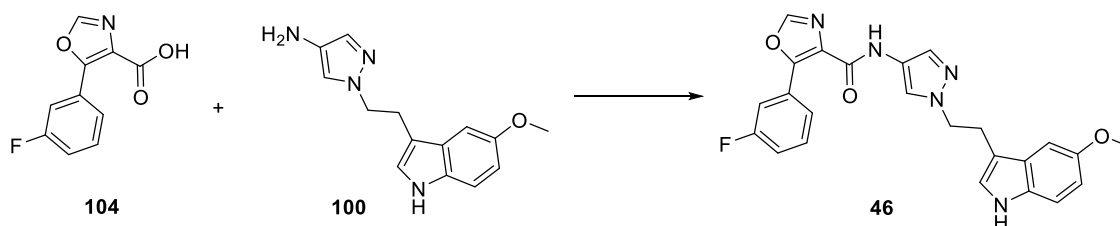
Step 2



The title compound was synthesized according to the procedure described for compound **41** (step 5) using **103** instead of **81**. Purification by prep. HPLC (Method F) yielded **45** (148 mg,

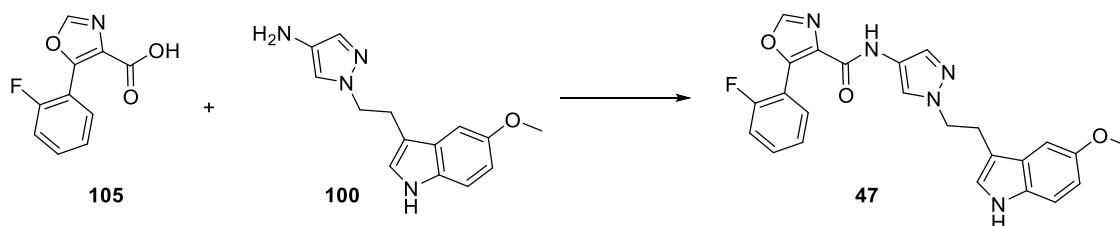
61%) as a white solid. LC-MS B: $t_R = 0.86$ min; $[M+H]^+ = 456.17$; LC-HRMS: $t_R = 1.13$ min; $[M+H]/z = 456.2030$, found = 456.2049; 1H NMR (400 MHz, $CDCl_3$) δ : 2.45 (s, 3 H), 2.57 (s, 3 H), 3.33 (t, $J = 7.4$ Hz, 2 H), 3.90 (s, 3 H), 4.42 (t, $J = 7.4$ Hz, 2 H), 6.88 (dd, $J_1 = 2.3$ Hz, $J_2 = 8.8$ Hz, 1 H), 6.91 (d, $J = 1.4$ Hz, 1 H), 7.01 (d, $J = 2.2$ Hz, 1 H), 7.25 (s, 1 H), 7.27 (s, 1 H), 7.38 (t, $J = 7.7$ Hz, 1 H), 7.66 (s, 1 H), 7.95 (s br, 1 H), 8.01 (s, 1 H), 8.03 (s, 1 H), 8.07 (s, 1 H), 8.12 (d, $J = 7.9$ Hz, 1 H), 8.98 (s, 1 H).

5-(3-Fluoro-phenyl)-oxazole-4-carboxylic acid {1-[2-(5-methoxy-1*H*-indol-3-yl)-ethyl]-1*H*-pyrazol-4-yl}-amide (46**)**



The title compound was synthesized according to the procedure described for compound **44** (step 3) using **104** and **100**. Purification by prep. HPLC (Method G) yielded **46** (54 mg, 84%) as an off-white solid. LC-MS A: $t_R = 0.80$ min; $[M+H]^+ = 446.15$; LC-HRMS: $t_R = 1.05$ min; $[M+H]/z = 446.1623$, found = 446.1633; 1H NMR (400 MHz, $CDCl_3$) δ : 2.03 (s, 3 H), 3.34 (t, $J = 7.4$ Hz, 2 H), 3.90 (s, 3 H), 4.42 (t, $J = 7.3$ Hz, 2 H), 6.88 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.8$ Hz, 1 H), 6.92 (d, $J = 1.4$ Hz, 1 H), 7.01 (d, $J = 2.3$ Hz, 1 H), 7.14-7.20 (m, 1 H), 7.27 (d, $J = 8.8$ Hz, 1 H), 7.45-7.52 (m, 1 H), 7.65 (s, 1 H), 7.92 (s, 1 H), 7.93 (s br, 1 H), 8.00 (s, 1 H), 8.16 (s, 1 H), 8.18 (s, 1 H), 8.97 (s, 1 H).

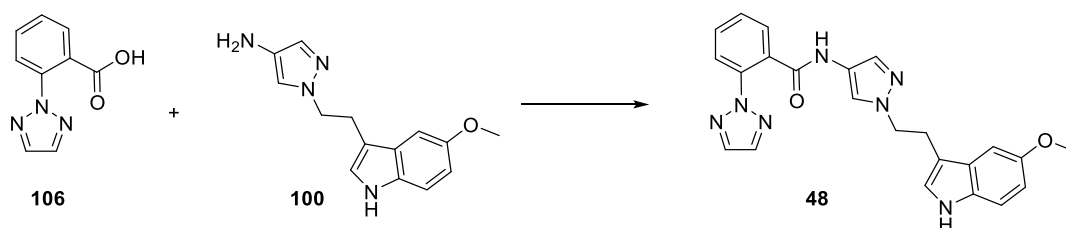
5-(2-Fluoro-phenyl)-oxazole-4-carboxylic acid {1-[2-(5-methoxy-1*H*-indol-3-yl)-ethyl]-1*H*-pyrazol-4-yl}-amide (47**)**



The title compound was synthesized according to the procedure described for compound **43** (step 6) using **105** and **100**. Purification by prep. HPLC (Method D) yielded **47** (47 mg, 71%) as a brownish solid. LC-MS C: $t_R = 0.75$ min; $[M+H]^+ = 446.14$; LC-HRMS: $t_R = 0.98$ min; $[M+H]/z = 446.1623$, found = 446.1631; 1H NMR (400 MHz, DMSO) δ : 3.16 (t, $J = 7.2$ Hz, 2 H), 3.75 (s, 3 H), 4.32 (t, $J = 7.3$ Hz, 2 H), 6.70 (dd, $J_1 = 2.2$ Hz, $J_2 = 8.7$ Hz, 1 H), 6.95 (d, $J = 1.9$ Hz, 1 H), 7.03 (d, $J = 1.3$ Hz, 1 H), 7.21 (d, $J = 8.7$ Hz, 1 H), 7.33-7.41 (m, 2 H), 7.55-7.63

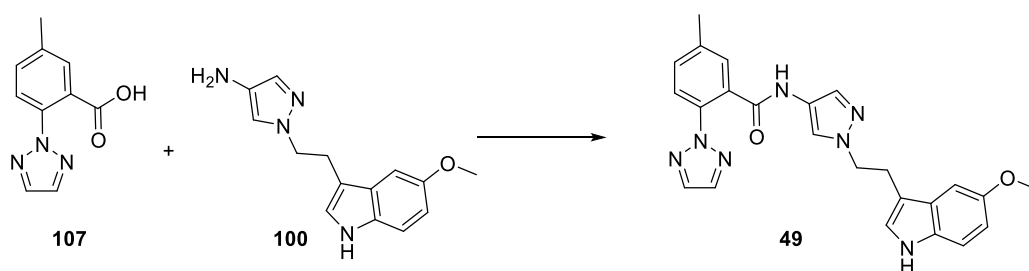
(m, 1 H), 7.68 (s, 1 H), 7.79-7.83 (m, 1 H), 8.03 (s, 1 H), 8.73 (s, 1 H), 10.52 (s, 1 H), 10.65 (s, 1 H).

***N*-{1-[2-(5-Methoxy-1*H*-indol-3-yl)-ethyl]-1*H*-pyrazol-4-yl}-2-[1,2,3]triazol-2-yl-benzamide (48)**



The title compound was synthesized according to the procedure described for compound **43** (step 6) using **106** and **100**. Purification by prep. HPLC (Method D) yielded **48** (51 mg, 79%) as an off-white solid. LC-MS C: $t_R = 0.64$ min; $[M+H]^+ = 428.16$; LC-HRMS: $t_R = 0.85$ min; $[M+H]/z = 428.1830$, found = 428.1827; 1H NMR (400 MHz, $CDCl_3$) δ : 3.30 (t, $J = 7.4$ Hz, 2 H), 3.87 (s, 3 H), 4.36 (t, $J = 7.3$ Hz, 2 H), 6.87 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.8$ Hz, 1 H), 6.91 (d, $J = 1.7$ Hz, 1 H), 6.96 (d, $J = 2.3$ Hz, 1 H), 7.25 (d, $J = 8.8$ Hz, 1 H), 7.41 (s, 1 H), 7.52 (td, $J_1 = 1.0$ Hz, $J_2 = 7.8$ Hz, 1 H), 7.60 (td, $J_1 = 1.3$ Hz, $J_2 = 7.7$ Hz, 1 H), 7.73 (dd, $J_1 = 1.1$ Hz, $J_2 = 7.6$ Hz, 1 H), 7.78-7.83 (m, 4 H), 7.86 (s, 1 H), 8.04 (s, 1 H).

***N*-{1-[2-(5-Methoxy-1*H*-indol-3-yl)-ethyl]-1*H*-pyrazol-4-yl}-5-methyl-2-[1,2,3]triazol-2-yl-benzamide (49)**

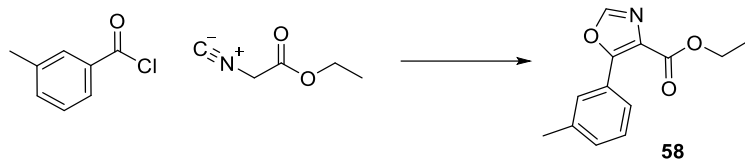


The title compound was synthesized according to the procedure described for compound **43** (step 6) using **107** and **100**. Purification by prep. HPLC (Method D) yielded **49** (36 mg, 54%) as an off-white solid. LC-MS C: $t_R = 0.68$ min; $[M+H]^+ = 442.18$; LC-HRMS: $t_R = 0.91$ min; $[M+H]/z = 442.1986$, found = 442.1989; 1H NMR (400 MHz, $CDCl_3$) δ : 2.47 (s, 3 H), 3.31 (t, $J = 7.4$ Hz, 2 H), 3.88 (s, 3 H), 4.37 (t, $J = 7.3$ Hz, 2 H), 6.88 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.8$ Hz, 1 H), 6.92 (d, $J = 0.4$ Hz, 1 H), 6.97 (d, $J = 2.2$ Hz, 1 H), 7.26 (d, $J = 8.8$ Hz, 1 H), 7.37-7.43 (m, 2 H), 7.57 (s, 1 H), 7.65 (d, $J = 8.2$ Hz, 1 H), 7.75 (s br, 1 H), 7.81 (s, 2 H), 7.86 (s, 1 H), 7.99 (s br, 1 H).

Intermediates

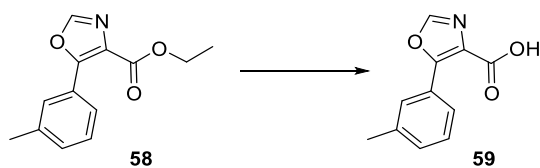
5-(*m*-tolyl)oxazole-4-carboxylic acid (**59**)

Step 1: Ethyl 5-(*m*-tolyl)oxazole-4-carboxylate (**58**)



DMAP (7.56 g, 0.62 mol) and TEA (189 mL, 1.36 mol) were added to a rt solution of ethyl isocyanoacetate (70.0 g, 0.62 mol) in THF (900 mL). The mixture was heated to 75°C, then a solution of *m*-toluylchloride in THF (100 mL) was added dropwise over a period of 1 h (slurry). After 30 min at 75°C, the mixture was allowed to reach rt. A 25 % HCl-solution (100 mL) was added, followed by water (100 mL) and tBME (200 mL). The org. layer was separated, washed with water (200 mL), and concentrated. The crude material was distilled in high vacuum at external temperature of 160°C (Head temperature 120 - 130°C) to yield **58** (120 g, 84%) as a yellow to orange oil; ¹H NMR (400 MHz, CDCl₃) δ: 1.43 (t, *J* = 7.1 Hz, 3 H), 2.45 (s, 3 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 7.31 (d, *J* = 7.6 Hz, 1 H), 7.39 (t, *J* = 7.8 Hz, 1 H), 7.87-7.91 (m, 2 H), 7.92 (s, 1 H).

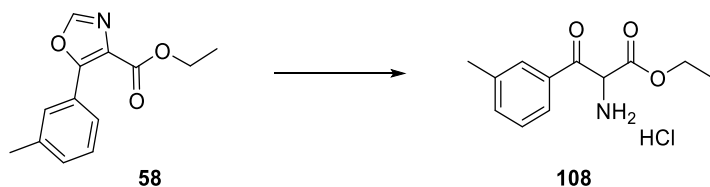
Step 2



4 N NaOH (240 mL) was added to a rt solution of **58** (32.0 g, 0.14 mol) in THF (500 mL). The resulting mixture was stirred at rt for 18 h. The reaction mixture was cooled to 0°C and acidified to pH = 1 with HCl (32%, 100 mL) and extracted with EtOAc (3x). The combined org. layers were dried (MgSO₄), filtered, and concentrated *in vacuo* to yield **59** (28.4 g, 100%) as off white solid, which was used as such in the next step. LC-MS B: *t*_R = 0.59 min; [M+H]⁺ = 204.12; ¹H NMR (400 MHz, DMSO) δ: 2.36 (s, 3 H), 7.31 (d, *J* = 7.6 Hz, 1 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 7.74-7.82 (m, 2 H), 8.51 (s, 1 H).

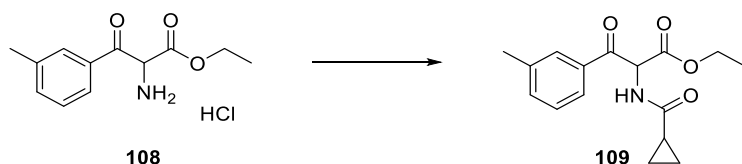
2-Cyclopropyl-5-(m-tolyl)oxazole-4-carboxylic acid (**87**)

Step 1: Ethyl 2-amino-3-oxo-3-(m-tolyl)propanoate HCl (**108**)



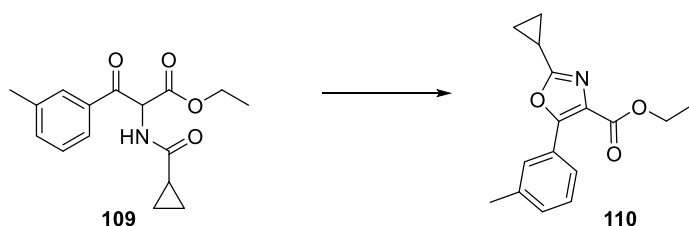
Acetyl chloride (4.65 mL) was added to a rt solution of **58** (15.0 g) in EtOH (160 mL) and the mixture was heated to 75°C overnight. The reaction mixture was concentrated *in vacuo* to yield **108** which was used as such in the next step. LC-MS A: $t_R = 0.40$ min; $[M+H]^+ = 222.32$; 1H NMR (400 MHz, $CDCl_3$) δ : 1.08 (t, $J = 7.1$ Hz, 3 H), 2.37 (s, 3 H), 4.16 (q, $J = 6.5$ Hz, 2 H), 6.34 (s, 1 H), 7.30-7.38 (m, 1 H), 7.39-7.44 (m, 1 H), 7.92-7.97 (m, 2 H), 9.28 (s, 2 H).

Step 2: Ethyl 2-(cyclopropanecarboxamido)-3-oxo-3-(m-tolyl)propanoate (**109**)



Cyclopropanecarbonylchloride (7.0 mL) was added to a 0°C solution of **108** (17.6 g) in DCM (600 mL) and pyridine (14 mL) (slightly exotherm) and the mixture was stirred for 20 min at 0°C, then 16 h at rt. The rxn mixture was diluted with water (400 mL), the two layers were separated and the org. layer washed with brine (400 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by FC (EtOAc/hex. 1:9 to 3:7, R_f in EtOAc/hexane 1:1 = 0.48) to yield **109** (14.47 g, 73%) as a yellow solid. LC-MS A: $t_R = 0.64$ min; $[M+H]^+ = 290.00$; 1H NMR (400 MHz, $CDCl_3$) δ : 0.78-0.90 (m, 2 H), 0.97-1.08 (m, 2 H), 1.18 (t, $J = 7.1$ Hz, 3 H), 1.54-1.62 (m, 1 H), 2.45 (s, 3 H), 4.19 (q, $J = 7.0$ Hz, 2 H), 6.23 (d, $J = 7.4$ Hz, 1 H), 7.01 (d, $J = 6.5$ Hz, 1 H), 7.37-7.44 (m, 1 H), 7.45-7.48 (m, 1 H), 7.91-7.98 (m, 2 H).

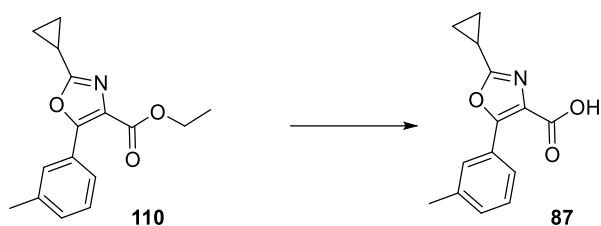
Step 3: Ethyl 2-cyclopropyl-5-(m-tolyl)oxazole-4-carboxylate (**110**)



Concentrated H_2SO_4 (40.1 mL) was added to a 0°C solution of **109** (13.8 g) in DCM (40 mL). The DCM was evaporated, and the mixture stirred at rt for 5 min. The rxn mixture was poured

on ice and then extracted with TBME (2x). The org. layers were evaporated to yield **110** (12.97 g, 98%) as a yellow oil. LC-MS A: $t_R = 0.75$ min; $[M+H]^+ = 272.19$; 1H NMR (400 MHz, $CDCl_3$) δ : 1.12-1.20 (m, 2 H), 1.21-1.27 (m, 2 H), 1.41 (t, $J = 7.1$ Hz, 3 H), 2.21-2.30 (m, 1 H), 2.44 (s, 3 H), 4.42 (q, $J = 7.1$ Hz, 2 H), 7.27 (d, $J = 7.6$ Hz, 1 H), 7.36 (t, $J = 7.6$ Hz, 1 H), 7.77-7.83 (m, 2 H).

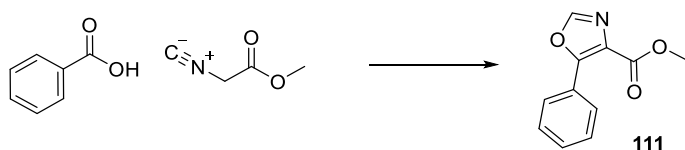
Step 4



1 N NaOH (250 mL) was added to **110** (12.95 g) in THF (450 mL) and the mixture was stirred at rt for 16 h. The reaction mixture was poured in an aq. 4 N HCl (100 mL) and extracted with EtOAc (3x). The org. layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford the title compound **87** (11.83 g, 100%) as a light green solid. LC-MS A: $t_R = 0.62$ min; $[M+H]^+ = 244.19$; 1H NMR (400 MHz, $CDCl_3$) δ : 1.12-1.19 (m, 2 H), 1.20-1.25 (m, 2 H), 2.17-2.25 (m, 1 H), 2.44 (s, 3 H), 7.24-7.28 (m, 1 H), 7.36 (t, $J = 7.7$ Hz, 1 H), 7.90 (s, 1 H), 7.93 (d, $J = 7.8$ Hz, 1 H).

5-Phenyl-oxazole-4-carboxylic acid (**101**)

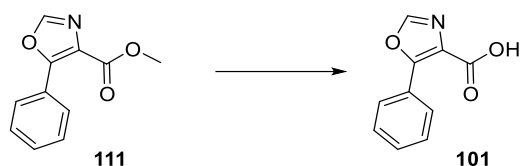
Step 1: Methyl 5-phenyloxazole-4-carboxylate (**111**)



A solution of methyl isocyanoacetate (0.6 mL, 6.4 mmol) in DMF (3.0 mL) was added dropwise to a suspension of benzoic acid (247 mg, 2 mmol) and K_2CO_3 (332 mg, 2.4 mmol) in DMF (4.0 mL). The dark red solution was stirred for 5 min at rt, then the mixture was cooled to $0^\circ C$ and a solution of diphenylphosphoryl azide (0.43 mL, 2 mmol) in DMF (3.0 mL) was added dropwise and stirring was continued at $0^\circ C$ for 2 h, followed by rt overnight. The reaction mixture was diluted with EtOAc and the org layer was washed with 10% citric acid, and sat. $NaHCO_3$ solution. The org. layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The product was purified by FC (EtOAc/hex. 1:1 $R_f = 0.44$) to yield **111** (240 mg, 59%) a yellow solid which was used as such in the next step. LC-MS A: $t_R = 0.89$ min; $[M+H+MeCN]^+ =$

245.35; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 3.97 (s, 3 H), 7.48-7.53 (m, 3 H), 7.94 (s, 1 H), 8.09-8.13 (m, 2 H).

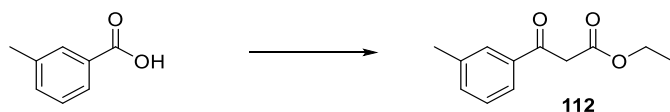
Step 2



NaOH (1N, 6.0 mL) was added to a rt solution of **111** (240 mg, 1.18 mmol) in THF (12.0 mL) and the mixture was stirred at rt overnight. The reaction mixture was poured in 1N HCl (12.0 mL) and extracted with EtOAc (3x). The organic layer was dried (MgSO_4), filtered, and concentrated *in vacuo* to yield **101** (170 mg, 76%) as a white solid. LC-MS A: t_{R} = 0.78 min; $[\text{M}+\text{H}]^+$ = 190.53; $^1\text{H NMR}$ (400 MHz, MeOD) δ : 7.49-7.54 (m, 3 H), 8.06-8.09 (m, 2 H), 8.30 (s, 1 H).

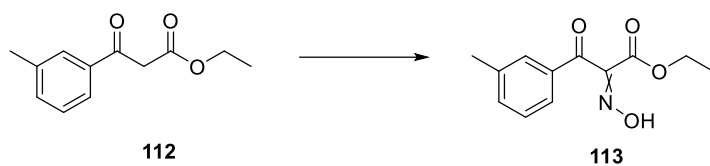
2-Methyl-5-m-tolyl-oxazole-4-carboxylic acid (102)

Step 1: Ethyl 3-oxo-3-(m-tolyl)propanoate (112)



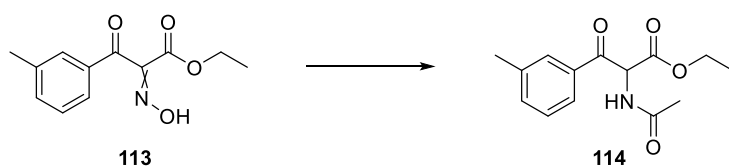
3-Methyl benzoic acid (10.0 g) was diluted with 1,2-dichloroethane (70.0 mL). A few drops of DMF were added, followed by oxalyl chloride (8.4 mL). Gas evolution was observed. The yellow reaction mixture was stirred at rt for 3 h, then at 80°C for 20 min. The reaction mixture was concentrated, then to the residue was added MeCN (190 mL) and cooled to 10°C. Monoethyl malonate potassium salt (25.0 g) and triethylamine (20.4 mL) were added to the cooled mixture, followed by careful addition in portions of MgCl_2 (17.5 g) (exothermic). The suspension was stirred for 30 min at 10-15°C, then for 3 h at rt. The mixture was cooled to 0°C and the crude 3-methyl benzoyl chloride was added dropwise over 30 min, followed by triethylamine (1.7 mL). The suspension was stirred over the weekend at rt. The crude reaction mixture was concentrated, toluene (200 mL) was added, and the crude was cooled to 10°C. 4M HCl (1 L) was added and the layers were separated. The org. layer was washed with 4M HCl (2 x 250 mL), with water (2 x 250 mL), and brine (250 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude was purified by FC (EtOAc/hept, 5/95 to 10/90) to obtain **112** (9.0 g, 59%) as a pale brown oil. LC-MS B: t_{R} = 0.75 min; $[\text{M}+\text{H}]^+$ = 207.21.

Step 2: Ethyl 2-(hydroxyimino)-3-oxo-3-(m-tolyl)propanoate (113)



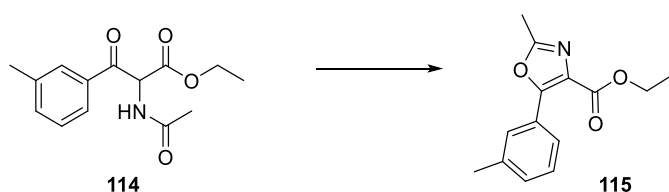
A solution of **112** (9.0 g) in acetic acid 100% (16.0 mL) was cooled to 0°C and maintained below 10°C during the dropwise addition of NaNO₂ (3.6 g) in water (7.0 mL). After the addition was complete, the suspension was allowed to warm to rt and stirring was continued for 30 min. The suspension was poured into water (120 mL) and upon cooling the flask in an ice bath, the product crystallized. The crystals were collected by filtration, the cake was washed with cold water and dried *in vacuo* to yield **113** (10.25 g, 100%) as a white solid. LC-MS B: t_R = 0.69 min; [M+H]⁺ = 236.08; ¹H NMR (400 MHz, CDCl₃) δ: 1.29 (t, *J* = 7.1 Hz, 3 H), 2.45 (s, 3 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 7.40-7.45 (m, 1 H), 7.46-7.50 (m, 1 H), 7.68-7.71 (m, 1 H), 7.73 (s, 1 H), 9.55 (s br, 1 H).

Step 3: Ethyl 2-acetamido-3-oxo-3-(m-tolyl)propanoate (114)



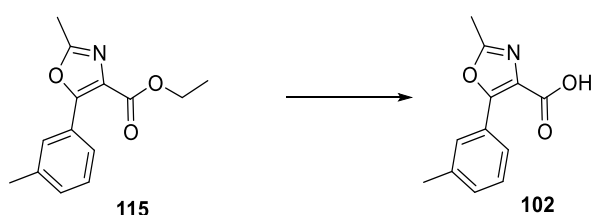
Sodium acetate (218 mg) and zinc chloride (119 mg) were added to a rt suspension of **113** (10.25 g) in acetic anhydride (12.3 mL) and acetic acid (16.6 mL). A condenser was attached to the flask and Zn powder (8.8 g) was added portionwise very carefully (exothermic!) over a time of 30 min. The reaction mixture was then stirred at rt for 2 h. The reaction mixture was filtered and the solid was rinsed with EtOAc. The org. layer was washed with water (2x) and an aq. 2N K₂CO₃-solution, then dried (Na₂SO₄), filtered, and concentrated *in vacuo* to obtain **114** (10.7 g) as a yellow oil. LC-MS B: t_R = 0.64 min; [M+H]⁺ = 264.13; ¹H NMR (400 MHz, CDCl₃) δ: 1.17 (t, *J* = 7.1 Hz, 3 H), 2.13 (s, 3 H), 2.45 (s, 3 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 6.21 (d, *J* = 7.5 Hz, 1 H), 6.85-6.87 (m, 1 H), 7.39-7.44 (m, 1 H), 7.45-7.49 (m, 1 H), 7.93-7.97 (m, 2 H).

Step 4: Ethyl 2-methyl-5-(m-tolyl)oxazole-4-carboxylate (115)



Thionylchloride (6.3 mL) was added to a 0°C solution of **114** (10.7 g) in chloroform (33 mL). The reaction was allowed to reach rt overnight and next morning heated to reflux for 3 h. After cooling to 0°C, excess of thionyl chloride was quenched with 1 M aq. K₂CO₃-solution. The two layers were separated and the aq. layer extracted with DCM (2x). The combined org. layers were dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The crude was purified by FC (EtOAc/hept., 1/9 to 2/, R_f=0.51 in EtOAc/hept. 1:1) to obtain **115** (6.23 g, 58%) as an orange oil which was used as such in the next step. LC-MS B: t_R = 0.79 min; [M+H]⁺ = 246.12; ¹H NMR (400 MHz, CDCl₃) δ: 1.41 (t, J = 7.1 Hz, 3 H), 2.44 (s, 3 H), 2.57 (s, 3 H), 4.43 (q, J = 7.1 Hz, 2 H), 7.27 (d, J = 7.6 Hz, 1 H), 7.36 (t, J = 7.6 Hz, 1 H), 7.84-7.89 (m, 2 H).

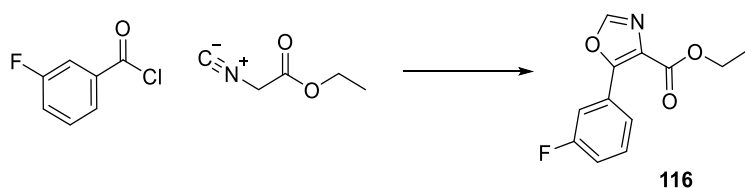
Step 5



1 N NaOH (110 mL) was added to **115** (6.23 g) in THF (220 mL) and the mixture was stirred at rt for 16 h. The reaction mixture was poured in an aq. 1 N HCl (210 mL) and extracted with EtOAc (2x). The org. layer was dried (Na₂SO₄), filtered, and concentrated *in vacuo* to obtain **102** (5.13 g, 93%) as a beige oil. LC-MS B: t_R = 0.62 min; [M+H]⁺ = 218.19; ¹H NMR (300 MHz, CDCl₃) δ: 2.42 (s, 3 H), 2.59 (s, 3 H), 7.26-7.30 (m, 1 H), 7.36 (t, J = 7.6 Hz, 1 H), 7.93-8.01 (m, 2 H).

5-(3-Fluoro-phenyl)-oxazole-4-carboxylic acid (**104**)

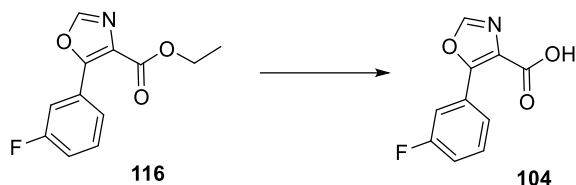
Step 1: Ethyl 5-(3-fluoro-phenyl)-oxazole-4-carboxylate (**116**)



Et₃N (0.66 mL, 4.72 mmol) and DMAP (26 mg, 0.21 mmol) were added to a solution of ethyl isocynoacetate (0.24 mL, 2.14 mmol) and 3-fluorobenzoyl chloride (0.27 mL, 2.23 mmol) in THF (5.0 mL). The reaction mixture was stirred at reflux (75°C) for 17 h. After the reaction mixture reached rt, water was added, and the mixture was extracted with tBME. The org. layer was washed with water, brine, and concentrated *in vacuo*. The residue was purified by FC (EtOAc /hept, 1/9 to 2/8; R_f = 0.26 (EtOAc / hept, 3/7) to obtain **116** as a beige solid (482 mg, 96%). LC-MS A: t_R = 0.81 min; [M+H]⁺ = 236.17; ¹H NMR (400 MHz, CDCl₃) δ: 1.45 (t, J = 7.1

Hz, 3 H), 4.46 (q, $J = 7.1$ Hz, 2 H), 7.19 (tdd, $J_1 = 0.9$ Hz, $J_2 = 2.5$ Hz, $J_3 = 8.3$ Hz, 1 H), 7.44-7.52 (m, 1 H), 7.89-7.94 (m, 2 H), 7.95 (s, 1 H).

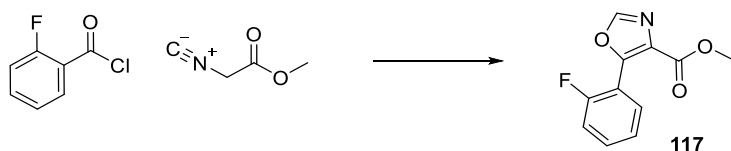
Step 2



A 1 N NaOH -solution (9.0 mL) was added to a rt solution of **116** in THF (16.0 mL) and stirring was continued for 18 h. The mixture was acidified with 1N HCl and extracted with EtOAc (2x). The combined org. layers were washed with brine (50 mL), dried (MgSO_4), filtered, and concentrated *in vacuo* to afford **104** (3.18 g, 97%) as a white solid. LC-MS A: $t_R = 0.81$ min; $[\text{M}+\text{H}+\text{MeCN}]^+ = 249.17$; $^1\text{H NMR}$ (400 MHz, DMSO) δ : 7.37 (td, $J_1 = 2.5$ Hz, $J_2 = 8.3$ Hz, 1 H), 7.55-7.62 (m, 1 H), 7.82 (d, $J = 8.0$ Hz, 1 H), 7.90-7.95 (m, 1 H), 8.58 (s, 1 H), 13.31 (s br, 1 H).

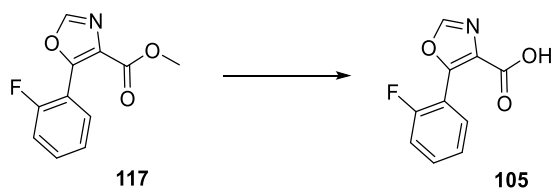
5-(2-Fluoro-phenyl)-oxazole-4-carboxylic acid (**105**)

Step 1: Methyl 5-(2-fluoro-phenyl)-oxazole-4-carboxylate (**117**)



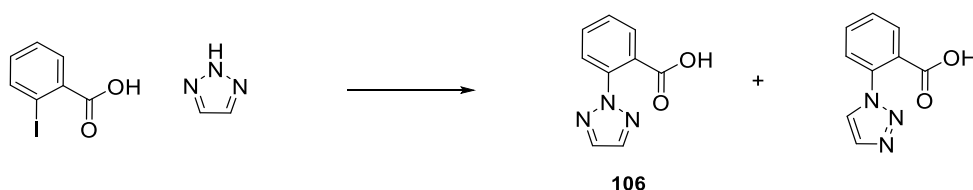
Methyl isocynoacetate (0.14 mL, 1.5 mmol) was added to a rt solution of 2-fluorobenzoic acid (144 mg, 0.99 mmol) and DIPEA (0.26 mL, 1.47 mmol) in DMF (4.0 mL). The resulting yellow solution was stirred at rt for 5 min and cooled to 0 °C before DPPA (0.27 mL, 1.21 mmol) was added and the resulting orange solution was stirred at 0 °C for 15 min and overnight at rt. Sat. aq. NaHCO_3 solution was added, and the mixture extracted with EtOAc (3x). The combined org. extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude was purified by FC (100% hept. to hept./EtOAc 3:1) to yield **117** (89 mg, 40%) as a yellow oil which was used as such in the next step. LC-MS A: $t_R = 0.74$ min; $[\text{M}+\text{H}]^+ = 222.11$.

Step 2



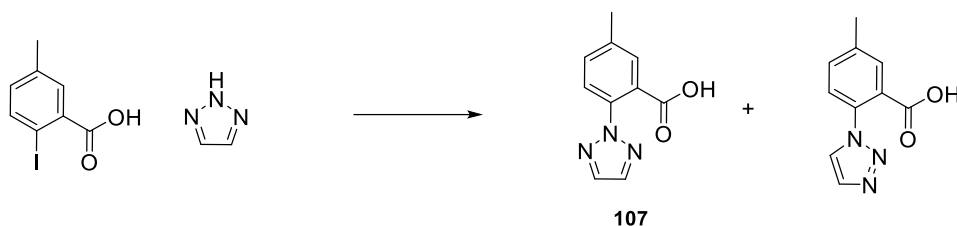
2 N NaOH (1.05 mL, 2.11 mmol) was added to a rt solution of **117** (89 mg, 0.40 mmol) in THF (1.8 mL) and the resulting solution was stirred at rt for 2 h. The reaction mixture was washed with Et₂O, the aqueous layer acidified with 1 N HCl and extracted with EtOAc (3x). The combined organic extracts were dried (MgSO₄), filtered, and concentrated *in vacuo* to yield **105** (61 mg, 73%) as a yellow oil. LC-MS A: $t_R = 0.62$ min; $[M+H]^+ = 208.10$.

2-[1,2,3]Triazol-2-yl-benzoic acid (**106**)



Cs₂CO₃ (13.14 g, 40.30 mmol) was added in portions to a 0°C solution of 1H-1,2,3-triazole (2.34 mL, 40.30 mmol) and 2-iodobenzoic acid (5.00 g, 20.2 mmol) in DMF (13.5 mL). After stirring for 5 min, CuI (192 mg, 1.01 mmol) was added and the resulting blue mixture was stirred for 1.5 h. DCM and water were added to the reaction mixture, the two layers were separated and the org. layer was extracted with water (2 x 30 mL). The combined inorg. layers were acidified with aq. 2 N HCl (40 mL) and the product was extracted with DCM (3 x 100 mL). The combined org. layers were dried (MgSO₄), filtered, and concentrated. Purification by FC (DCM/MeOH 95:5 +0.1% AcOH) yielded **106** (2.26 g, 59 %) as colorless oil. The desired product eluted before the undesired isomer. LC-MS A (of desired isomer): $t_R = 0.45$ min; $[M+H]^+ = 190.16$. ¹H NMR (400 MHz, CDCl₃) δ : 7.93 (d, $J = 7.7$ Hz, 1 H), 7.85 (s, 2 H), 7.78 (m, 1 H), 7.66 (t, $J = 7.6$ Hz, 1 H), 7.53 (t, $J = 7.6$ Hz, 1 H).

5-Methyl-2-[1,2,3]triazol-2-yl-benzoic acid (**107**)



Cs_2CO_3 (17.66 g, 54.190 mmol) was added in portions to a 0°C solution of 1H-1,2,3-triazole (3.14 mL, 54.19 mmol) and 2-iodo-5-methylbenzoic acid (7.10 g, 27.09 mmol) in DMF (19.0 mL). Due to thickening of the reaction mixture, DMF (10 mL) was added and after stirring for another 5 min, CuI (257 mg, 1.35 mmol) was added. To dilute the reaction mixture further, another 10 mL of DMF was added and the blue mixture was stirred for 30 min at rt. To the blue suspension, water (250 mL) and EtOAc (230 mL) was added and the two layers were separated. The inorganic layer was acidified with aq. 2 N HCl (60 mL) and the product was extracted with EtOAc (3x). The combined organic layers were dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification by FC (DCM/MeOH 95:5 +0.1% AcOH) yielded desired product **107** (3.15 g, 57 %) as a yellowish solid. The desired product eluted before the undesired isomer. LC-MS A (of desired isomer): $t_R = 0.62$ min; $[\text{M}+\text{H}]^+ = 204.37$. LC-MS A (of undesired isomer): $t_R = 0.57$ min; $[\text{M}+\text{H}]^+ = 204.39$. ^1H NMR (400 MHz, DMSO) δ : 12.96 (s, 1 H), 8.05 (s, 2 H), 7.63 (m, 1 H), 7.58 (s, 1 H), 7.51 (dd, $J_1 = 1.3$ Hz, $J_2 = 8.1$ Hz, 1 H), 2.51 (s, 3 H).

B Biology.

Intracellular calcium release assays

Chinese hamster ovary (CHO) cells expressing the human, rat or dog orexin-1 receptor or orexin-2 receptor, respectively, were grown in culture medium (Ham F-12 with L-Glutamine) containing 300 $\mu\text{g}/\text{mL}$ G418, 100 U/mL penicillin, 100 $\mu\text{g}/\text{mL}$ streptomycin and 10% heat inactivated fetal calf serum (FCS). The cells were seeded at 20'000 cells / well into 384-well black clear bottom sterile plates (Greiner). The seeded plates were incubated overnight at 37°C in 5% CO_2 .

Orexin-A as an agonist was prepared as 1 mM stock solution in MeOH: water (1:1), diluted in HBSS containing 0.1% bovine serum albumin (BSA), NaHCO_3 : 0.375g/L and 20 mM HEPES for use in the IC_{50} assays (human receptors) at a final concentration of 5 nM ($\sim\text{EC}_{70}$).

Antagonists were prepared as 10 mM stock solution in DMSO, then diluted in 384-well plates using DMSO followed by a transfer of the dilutions into in HBSS containing 0.1% bovine serum albumin (BSA), NaHCO_3 : 0.375g/L and 20 mM HEPES. On the day of the assay, 50 μL of staining buffer (HBSS containing 1% FCS, 20 mM HEPES, NaHCO_3 : 0.375g/L, 5 mM probenecid (Sigma) and 3 μM of the fluorescent calcium indicator fluo-4 AM (1 mM stock

solution in DMSO, containing 10% pluronic) was added to each well. The 384-well cell-plates were incubated for 50 min at 37°C in 5% CO₂ followed by equilibration at RT for 30 - 120 min before compound additions.

Within the Fluorescent Imaging Plate Reader (FLIPR Tetra, Molecular Devices), antagonists were added to the plate in a volume of 10 µL/well, incubated for 120 min, and finally 10 µL/well of agonist was added. Fluorescence was measured for each well at 1 second intervals, and the height of each fluorescence peak was compared to the height of the fluorescence peak induced by an EC₇₀ of orexin A with vehicle in place of antagonist. The IC₅₀ value (the concentration of compound needed to inhibit 50% of the agonistic response) was determined using the proprietary IC₅₀witch software. The K_i values at human, rat and dog receptors were calculated from the antagonist IC₅₀ obtained with ~EC₇₀ of OxA (OxA_{stim} 10 nM; except dog OxA:100 nM) and the corresponding on-day OxA EC₅₀ values via the Cheng-Prusoff equation $K_i = IC_{50} / (1 + [OxA_{stim}] / EC_{50OxA})$.

C PhysChem and DMPK

Aqueous solubility in Fasted and Fed State Simulated Intestinal Fluid (FaSSIF and FeSSIF). The solubility was determined by the miniaturized saturation shake flask method (screening mode). The compound form is an amorphous film, from DMSO evaporation of a 10 mM stock solution, on which FaSSIF (Fasted State Simulated Intestinal Fluid) or Fed State Simulated Intestinal Fluid (FeSSIF) medium was added. After 6 h of equilibration at 25°C, phases are separated by filtration, aqueous phase was diluted with DMSO, and concentration was determined by UV-HPLC.

In vitro Clint determinations.

Intrinsic metabolic clearance (Cl_{int}) was determined by substrate depletion experiments, with a default starting concentration of 1 µM in the presence of 0.5 mg/mL human or rat liver microsomes (HLM or RLM, respectively) in 100 mM sodium phosphate buffer, at pH 7.4. incubations were initiated by the addition of an NADPH regenerating system. All incubations were conducted by shaking reaction mixtures under air, at 37 °C. Aliquots (0.1 ml) were removed at 0, 2.5, 5, 10 and 15 minutes and 0.1 mL of ice-cold methanol was added. After protein precipitation, by centrifugation, the remaining concentrations were analyzed by liquid chromatography coupled to mass spectrometry (LC-MS/MS), Cl_{int} was calculated from the concentration remaining versus time, fitted to a first order decay constant versus time.¹

CYP3A4 inhibition was studied using testosterone to 6β-hydroxy-testosterone hydroxylation as marker reaction. Testosterone was used at a single concentration of 40 µM around its Km (Michaelis-Menten constant) and the test compounds were incubated at eight different concentrations, up to 50 µM. Nicardipine was used as positive control. Microsomal incubations

were initiated by the addition of NADPH-regenerating system and terminated by adding an excess of ice-cold organic solvent. The formation of 6 β -hydroxy-testosterone was measured by liquid chromatography-tandem mass spectrometry (LC/MS-MS) and IC₅₀-values were calculated.

Time dependent CYP3A4 inhibition (TDI)

The effect of a potential metabolic activation on CYP3A4 activity was measured in vitro with human liver microsomes and testosterone 6 β -hydroxylation as the marker reaction. IC₅₀-values were measured at 10 times Km with or without 30 min of preincubation. The difference between the IC₅₀-value with and without preincubation ('IC₅₀-shift') was calculated as a measure of metabolic activation.

MDR1 (P-gp) substrate assessment

To assess whether a compound is a MDR1 transporter substrate, its permeability (P_{app}) across a confluent MDR1-MDCK1 cell monolayer in apical to basolateral (A-B) and basolateral to apical (B-A) direction was determined. Test compound was at 1 μ M, assay was run at pH 7.4 and 37°C.

Pharmacokinetics in the Rat

Male Wistar rats were obtained from Harlan and used for pharmacokinetic experiments after an acclimatization period of at least 7 days. Serial blood samples were taken from each individual rat to obtain a complete concentration vs. time profile per animal. Vials containing the anti-coagulant EDTA were used for collection of the blood samples. Samples of 0.25 mL following oral administration were withdrawn sublingually under short (< 5 minutes) inhalation anesthesia with isoflurane at the nominal sampling times: 0.5, 1, 2, 3, 4, 6, 8, and 24 h after dosing. For brain penetration assessments, samples were taken at 3 h only. Compounds were administered as suspension in PEG400. In the intravenous rat studies, blood samples of 0.2 mL were collected via the surgically implanted jugular vein cannula pre-dose (i.e., before start of infusion), at the end of infusion (5 min) followed by 10, 15, 30 minutes and 1, 2, 3, 4, 6, 8, and 24 h after the end of infusion. Compounds were administered as solutions in 5% DMSO, 95% aq. HPBCD (30%).

D Pharmacology

Pharmacokinetics in the rat

Experiments were conducted on male, adult Wistar (RccHan:WIST; Harlan, Horst, The Netherlands) rats, which were maintained under standard lab conditions (temperature $20 \pm 2^\circ\text{C}$, relative humidity 55–70%, food and water *ad libitum*) under a regular 12 h light–dark cycle (lights on 06:00). After arrival rats were allowed at least one week of habituation to Actelion’s animal facility before experiments commenced. Experimental procedures were approved by the Basel-Landschaft Veterinary Office and strictly adhered to Swiss federal regulations on animal experimentation. Unless noted otherwise, rats were socially housed in groups of four in standard plastic rodent cages, and all tests were conducted during the light phase (08:00 to 18:00) under illumination of > 600 lx, where not otherwise specified.

For telemetric transmitter implantation (EEG/EMG monitoring)

Rats were equipped with telemetric transmitters (TL11M2-F20-EET; Data Science International, St Paul, MN, USA) that allowed the noninvasive detection of electroencephalograms (EEG), electromyograms (EMG) and activity via signal transmission to a receiver. The surgical transmitter implantation was performed under aseptic conditions. The rat was placed and secured in a stereotaxic apparatus. The body of the transmitter was placed subcutaneously along the dorsal flank of the rat with the leads routed subcutaneously to an incision accessing the cranium. For EEG recordings, two trepanations were placed in the skull, 2 mm from either side of the midline and 2 mm anterior to the lambda suture for placement of one differential pair of electrodes. Two other superficial trepanations were drilled for screws as support for cementing the electrodes. The EMG leads were inserted in either side of the muscles of the neck and sutured into place.

Sleep/wake cycle evaluation

Sleep/wake cycles were evaluated via radiotelemetry technology in rats. EEG, EMG and home cage activity were recorded from singly housed Wistar rats while under free moving conditions in their home cages. At the start of the experiment rats were placed together with their home cages in ventilated sound attenuating boxes, on a regular 12 h light/dark cycle for 3 days of acclimation before recordings started. Experiments were done in a crossover design, i.e. animals were alternatively treated with drug and vehicle. Recordings started by 24h baseline (preceding the treatment), the 12h night-period following the treatment, 36h of recovery (wash out period) followed by the crossover. Oral administrations occurred at the transition from the day to the night phase (17:45 – 18:00). Sleep and wake stages were evaluated automatically using the Somnologica Science software (Medcare, Embla, USA). The recording is divided into user definable (10 s) contiguous epochs. The scoring is based on frequency estimation for EEG and amplitude discrimination for the EMG and the locomotor activity. Using these

measurements, the software determines the probabilities that the EEG and EMG components within each epoch best represent waking, quiet waking, non-REM sleeping or REM sleeping. Essentially, wake consists of low-amplitude EEG activity with relatively 11 greater power in the higher frequency bands such as alpha, from (10–13 Hz), accompanied by moderate to high-level EMG activity. The locomotor activity and the amplitude of the EMG allow the differentiation between wake and quiet wake. Non-REM sleep is defined by high amplitude EEG activity with greater power in the delta frequency band (0.5–5 Hz), and by low EMG activity. REM sleep is characterized by low amplitude EEG activity focused in the theta frequency band (6–9 Hz). There is no EMG activity present during REM sleep.

References

- [1] Obach, R. S.; Reed-Hagen, A. E. Measurement of Michaelis constants for cytochrome P450-mediated biotransformation reactions using a substrate depletion approach. *Drug Metab Dispos* **2002**, *30*, 831-837.