Supporting Information

Aminopyrazole-phenylalanine Based GPR142 Agonists: Discovery of Tool Compound and In Vivo Efficacy Studies

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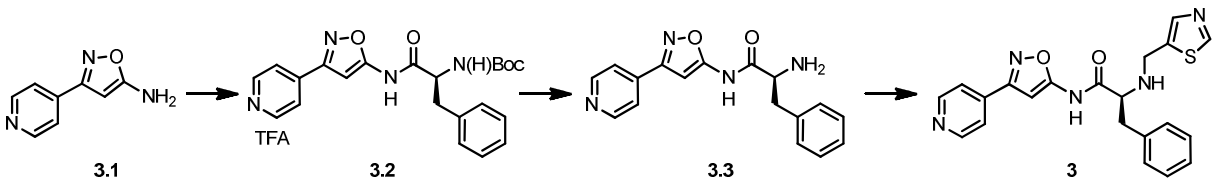
Experimental Section

Unless otherwise noted, all materials were obtained from commercial suppliers and used without purification. Dry organic solvents (DriSolv) were purchased from EMD Chemicals and were packaged under nitrogen in Sure Seal bottles. Reactions were monitered using thin-layer chromatography on 250 μ m plates or using Agilent 1100 series LCMS with UV detection at 254 and/or 220, 280 nm and a low resonance electrospray mode (ES). Purification of the title compounds was accomplished by flash column chromatography using silica gel 60 (particle size 0.04-0.063 mm, 230-400 mesh), or medium pressure liquid chromatography on a CombiFlash Companion (Teledyne Isco) with RediSep normal phase silica gel, or preparative HPLC (system: waters; column: Axia 00D-4454-U0-AX, C18, Gemini NX 5 uM, 100 × 30 mm from Phenomenex). ^{1}H NMR spectra were recorded on a Bruker spectrometer (400 or 500 MHz) at ambient temperature. Chemical shifts are reported in ppm relative to $CDCl_3$, CD_3OD, or DMSO and coupling constants (*J*) are reported in hertz (Hz). Purity of final compounds was ≥95% based on analytical HPLC and NMR analysis.

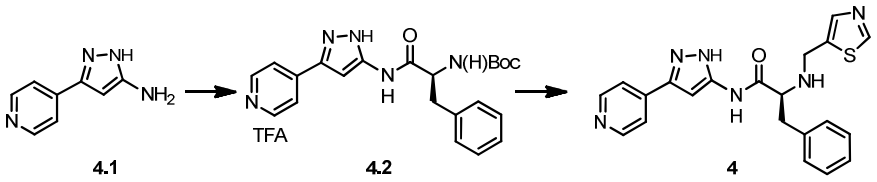


(*S*)-*tert*-Butyl (1-oxo-3-phenyl-1-((3-(pyridin-4-yl)isoxazol-5-yl)amino)propan-2-yl)carbamate (3.2) To a solution of 3-(pyridin-4-yl)isoxazol-5-amine **3.1** (400 mg, 2.48 mmol) in DMF (5.0 mL) and *N,N*-diisopropyl-*N*-ethylamine (1.3 mL, 7.5 mmol) at rt was added 1-H-benzotriazolium,1-[bis(dimethylamino)methylene]-hexafluorophosphate (1-),3-oxide (1.41 g, 3.7 mmol) followed by *N*-(tert-butoxycarbonyl)-L-phenylalanine (790 mg, 2.98 mmoL). The mixture was allowed to stir at 50 °C for 6.0 hr. The resulting mixture was cooled to rt and applied to preparative HPLC (10-90% /0.1%TFA/CH_3CN/water, 45 min) for purification to provide the title intermediate **3.2** as light yellow TFA salt (204 mg, 16%). LCMS (ES) $[M + 1]^+$ m/z 409.1.

(*S*)-2-Amino-3-phenyl-*N*-(3-(pyridin-4-yl)isoxazol-5-yl)propanamide (3.3). To a solution of (*S*)-*tert*-butyl 1-oxo-3-phenyl-1-(3-(pyridin-4-yl)isoxazol-5-ylamino)propan-2-ylcarbamate-TFA salt **3.2** (160 mg, 0.40 mmole) in CH_2Cl_2 (4 mL) at rt was added trifluoroacidic acid (2 mL). After stirring at rt for 3 hr, the solvents was removed under reduced pressure. The residue was redissoved in CH_2Cl_2 (20 mL), and was washed with saturated aqueous $NaHCO_3$ (4 mL), water (5 mL), brine (5 mL), and dried over $MgSO_4$. Removal of organic solvents under reduced pressure provided crude product of (*S*)-2-amino-3-phenyl-*N*-(3-(pyridin-4-yl)isoxazol-5-yl)propanamide **3.3** as a light yellow solid (100 mg, 81% yield). LCMS (ES) $[M + 1]^+$ m/z 309.2.

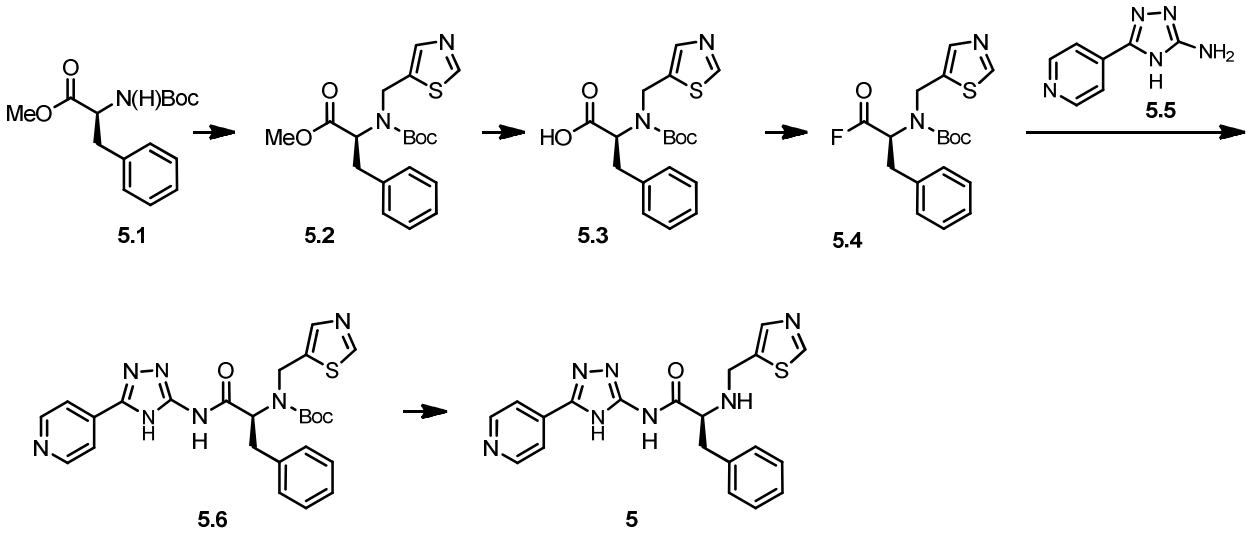
(*S*)-3-Phenyl-*N*-(3-(pyridin-4-yl)isoxazol-5-yl)-2-(thiazol-4-ylmethylamino)propanamide (3). To solution of (*S*)-2-amino-3-phenyl-*N*-(3-(pyridin-4-yl)isoxazol-5-yl)propanamide **3.3** (40 mg, 0.13 mmole) in dichloroethane (10 mL) at rt was added thiazole-4-carbaldehyde (18 mg, 0.16mmole) followed by sodium triacetoxyborohydride (55 mg, 0.26 mmole). The reaction was stirred at 70°C under N_2 for 12 hr, cooled to rt and treated with saturated aqueous NH_4Cl (3 mL) and water (8 mL). The organic layer was separated and the aqueous layer was back extracted with CH_2Cl_2 (2 × 10 mL). Organic layers were combined. After removal of organic solvents

under reduced perssure, the resulting residue was purified by preparative HPLC (10-90% 0.1%TFA/CH_3CN/water, 30 min) to provide the title product **3** as white TFA salt (14.2 mg, 27 % yield). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 9.09 (d, *J* = 1.96 Hz, 1 H), 8.87 (br. s., 2 H), 8.27 (d, *J* = 5.38 Hz, 2 H), 7.77 (d, *J* = 1.96 Hz, 1 H), 7.27 - 7.35 (m, 3 H), 7.20 - 7.25 (m, 2 H) 7.07 (s, 1 H), 4.42 - 4.55 (m, 2 H), 4.35 (dd, *J* = 8.80, 5.87 Hz, 1 H), 3.44 (dd, *J* = 13.57, 5.99 Hz, 1 H), 3.26 (dd, *J* = 13.69, 8.80 Hz, 1 H); HRMS (ESMS) calcd. for $C_{21}H_{19}N_5O_2S$ 406.1329 $(M+H)^+$, found: 406.1334.



(*S*)-*tert*-Butyl 1-oxo-3-phenyl-1-(3-(pyridin-4-yl)-1H-pyrazol-5-ylamino)propan-2-ylcarbamate (4.2) To a solution of 3-(pyridin-4-yl)-1H-pyrazol-5-amine **4.1** (257 mg, 1.6 mmol) and Boc-L-phenylalanine (480 mg, 1.8 mmol) in pyridine (4.5 mL) at rt was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (403 mg, 2.1 mmol). After stirring at rt under N_2 atomosphere for 3.0 hr, the reaction mixture was treated with water (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic solution was washed with water (10 mL), brine (5 mL) and dried over $MgSO_4$. After removal of organic solvents under reduced pressure, purification of the residue by flash chromatography on silica gel using 0-10% MeOH/CH_2Cl_2 for elution gave **4.2** as pale yellow solid (123 mg, 19%). LCMS (ES) $[M + 1]^+$ m/z 408.1.

(*S*)-3-Phenyl-*N*-(3-(pyridin-4-yl)-1H-pyrazol-5-yl)-2-(thiazol-5-ylmethylamino)propanamide (4). This title compound was prepared starting from compound **4.2** according the procedure described above for conversion of **3.2** to **3**. The crude product was purified by preparative HPLC (20-70% 0.1%TFA/CH_3CN/water, 30 min) to provide the title product **4** as white TFA salt (20 mg, 32%). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 3.25 (m, 1 H) 3.36 (dd, *J* = 13.57, 5.75 Hz, 1 H), 4.30 (dd, *J* = 9.05, 5.87 Hz, 1 H), 4.36 - 4.52 (m, 2 H), 6.99 (s, 1 H), 7.17 - 7.33 (m, 5 H), 7.73 (d, *J* = 1.47 Hz, 1 H), 8.26 (d, *J* = 6.60 Hz, 2 H), 8.74 (d, *J* = 6.60 Hz, 2 H), 9.04 (d, *J* = 1.71 Hz, 1 H); HRMS (ESMS) calcd. for $C_{21}H_{20}N_6OS$ 405.1489 $(M+1)^+$, found: 405.1476.



(*S*)-Methyl 2-((*tert*-butoxycarbonyl)(thiazol-4-ylmethyl)amino)-3-phenylpropanoate (5.2). To a solution of (*S*)-methyl 2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanoate **5.1** (627 mg, 2.3 mmol) in THF at 0 °C under N_2 atmosphere was added sodium hydride (88 mg, 60%, 2.3 mmol). When the gas formation ceased, to the mixture was added a solution of 4-(chloromethyl)thiazole (336 mg, 2.5 mmol) in DMF (1.0 mL). The reaction mixture was allowed to warm to rt over 30 min. After stirring at rt for 1.5 hr, the resulting mixture was slowly poured into saturated aqueous NH_4Cl (3.0 mL), diluted with water (15 mL), and extracted with EtOAc (3 × 10 mL). The combined organic solution was washed with water (4 mL), brine (5 mL), and dried over $MgSO_4$. After removal of organic solvent under reduced pressure, purification of the residue by flash chromatography on silica gel using 0-100% EtOAc/Hexanes for elution gave the title intermediate **5.2** as colorless solid (523 mg, 61%). LCMS (ES) $[M + 1]^+$ m/z 377.0.

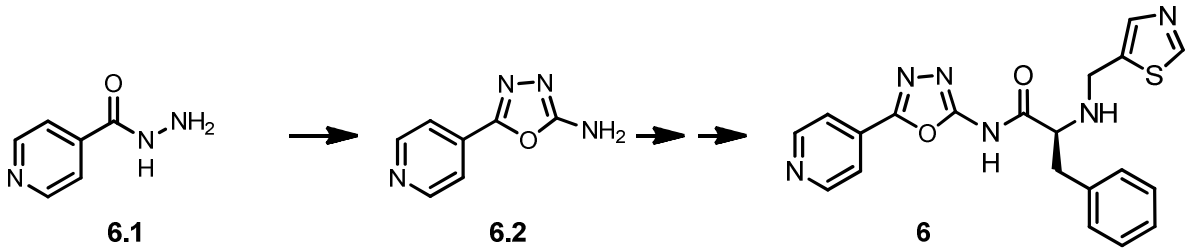
(*S*)-2-((*tert*-Butoxycarbonyl)(thiazol-4-ylmethyl)amino)-3-phenylpropanoic acid (5.3). To a solution of (*S*)-methyl 2-((*tert*-butoxycarbonyl)(thiazol-4-ylmethyl)amino)-3-phenylpropanoate **5.2** (335mg, 0.89 mmol) in dioxane (2.5 mL) and water (1.0 mL) was added lithium hydroxide (56 mg, 1.34 mmol). After stirring at rt for 30min, the reaction mixture was treated with HOAc (43 mg, 3.0 mmol), diluted with water (4 mL) and extracted with 30% *i*-PrOH/chloroform (3 × 5 mL). The combined organic solution was washed with water (8 mL), brine (5 mL) and dried over $MgSO_4$. After removal of organic solvent under reduced pressure, purification of the residue by flash chromatography on silica gel using 0-15% MeOH/CH_2Cl_2 for elution gave the title compound as yellow solid **5.3** (290 mg, 81%). LCMS (ES) $[M - 1]^-$ m/z 361.1.

(*S*)-*tert*-Butyl (1-fluoro-1-oxo-3-phenylpropan-2-yl)(thiazol-4-ylmethyl)carbamate (5.4). To a solution of (*S*)-2-((*tert*-butoxycarbonyl)(thiazol-4-ylmethyl)amino)-3-phenylpropanoic acid **5.3** (290 mg, 0.81 mmol) in CH_2Cl_2 at -20 °C was added pyridine (2.1 mL, 2.1 mmol) followed by cyanuric fluoride (240 mg, 1.8 mmol). The resulting mixture was allowed to stir at < -10 °C for 1.0 hr, quenched with ice-H_2O (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic solution was washed with water (10 mL), brine (6 mL) and dried over $MgSO_4$. After removal of organic solvent under reduced pressure at rt, the residue was left on high vacuum for 3.0 hr to provide the title crude product **5.4** as light purple syrup for direct used in the next step (280 mg, 95%).

(*S*)-*tert*-Butyl (1-oxo-3-phenyl-1-((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)amino)propan-2-yl)(thiazol-5-ylmethyl)carbamate (5.6). To a solution of (*S*)-*tert*-butyl (1-fluoro-1-oxo-3-phenylpropan-2-yl)(thiazol-4-ylmethyl)carbamate **5.4** (267 mg, 0.73 mmol) in DMF (2.5 mL) at rt under N_2 was added 5-(pyridin-3-yl)-1,3,4-oxadiazol-2-amine **5.5** (143 mg, 0.88 mmol) followed by triethylamine (255 μL, 1.82 mmol). After stirring at 45 °C overnight, the reaction mixture was quenched with saturated $NaHCO_3$ (4 mL), diluted with water (5 mL), and extracted with EtOAc (3 × 8 mL). The combined organic solution was washed with water (7 mL), brine (6 mL) and dried over $MgSO_4$. After removal of organic solvent, purification by flash chromatography on silica gel using 0-10% MeOH/CH_2Cl_2 for elution provided the title intermediate **5.6** as pale yellow syrup (159 mg, 43%). LCMS (ES) $[M + 1]^+$ m/z 506.2.

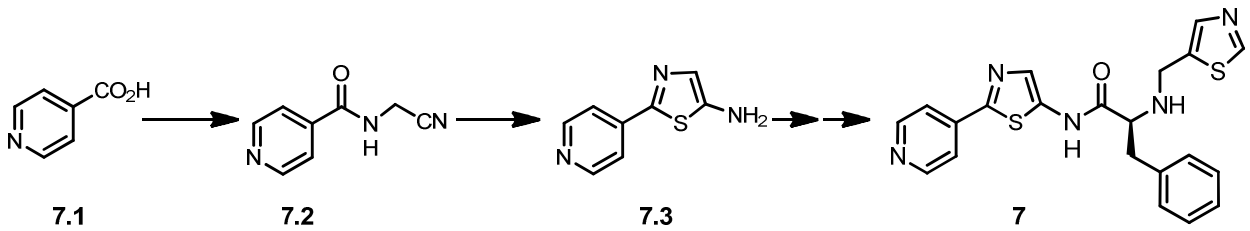
(*S*)-3-Phenyl-*N*-(5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)-2-((thiazol-5-ylmethyl)amino)propanamide (5). To a solution of (*S*)-*tert*-butyl (1-oxo-3-phenyl-1-((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)amino)propan-2-yl)(thiazol-5-ylmethyl)carbamate **5.6** (147 mg, 0.29 mmol) in dioxane (3.0 mL) at rt was added concentrated HCl (0.5 mL). After stirring at rt for 1.5 hr, the reaction mixture was poured into saturated aqeuous $NaHCO_3$ (3 mL), diluted with water (5 mL) and extracted with 30% i-PrOH/chloroform (3 × 5 mL). The combined organic solution was washed with water (5 mL), brine (5 mL) and dried over $MgSO_4$. After removal of solvents under reduced pressure, purification of the residue by preparative HPLC (10-90% 0.1%TFA/CH_3CN/water, 45 min) provided the title product **5** as white solid (48 mg, 35%). ^1H NMR (400 MHz, CD_3OD) δ ppm 3.22 - 3.43 (m, 3H), 3.47- (dd, *J* = 13.50, 6.06 Hz, 1H),

4.40 - 4.63 (m, 3 H), 7.21 - 7.41 (m, 5 H), 7.80 (d, *J* = 1.96 Hz, 1 H), 8.50 (d, *J* = 6.65 Hz, 2 H), 8.86 (d, *J* = 6.65 Hz, 2 H), 9.10 (d, *J* = 1.96 Hz, 1 H); HRMS (ESMS) calcd. for $C_{20}H_{19}N_7OS$ 406.1442 (M+H)+, found: 406.1432.



5-(Pyridin-4-yl)-1,3,4-oxadiazol-2-amine (6.2). To a solution of isonicotinohydrazide **6.1** (3.5 g, 26 mmoL) in MeOH (50 mL) at rt was added cyanogen bromide (1.7 mL, 33 mmoL). After stirring at 50 °C for 12 hr, the reaction solvent was removed under reduced pressure. To the residue was added water (30 mL), and extracted with a solution of 30% *i*-PrOH/$CHCl_3$ (3 × 25 mL). After removal of organic solvents under reduced pressure, purification of the residue by flash chromatography on silica gel using 0-10% MeOH/CH_2Cl_2 for elution provided the title intermediate **6.2** as white solid (0.91 g, 22%). LCMS (ES) $[M + 1]^+$ m/z 163.0.

(*S*)-3-Phenyl-*N*-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)-2-((thiazol-5-ylmethyl)amino)propanamide (6). The title compound was prepared starting with 5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine **6.2** according to the procedure as described above for conversion of **5.5** to **5**. The crude product was purified by preparative HPLC (10-90% 0.1%TFA/CH_3CN/water, 45 min) to provide the title compound **6** as white solid. ^{1}H NMR (400 MHz, MeOH) δ ppm 3.25 (dd, *J* = 14.67, 4.70 Hz, 1H) 3.40 (dd, *J* = 14.67, 4.89Hz, 1H) 4.73 (t, *J* = 4.70Hz, 1H) 4.86 (d, *J* = 16.43Hz, 1H) 5.05 (d, *J* = 16.43Hz, 1H) 7.17 (dd, *J* = 7.43, 1.76Hz, 2H) 7.23 - 7.39 (m, 3H) 7.66 (d, *J* = 1.76Hz, 1H) 8.08 (d, *J* = 5.87Hz, 2H) 8.84 (d, *J* = 6.46Hz, 2H) 9.06 (d, *J* = 1.96Hz, 1H); HRMS (ESMS) calcd. for $C_{20}H_{18}N_6O_2S$ 407.1282 $(M+H)^+$, found: 407.1296.

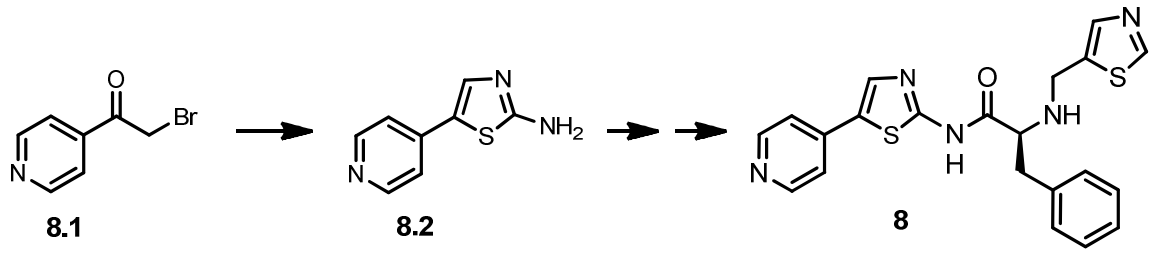


7.1 7.2 7.3 7

***N*- (Cyanomethyl)isonicotinamide (7.2).** A mixture of isonicotinic acid **7.1** (1.00 g, 8.12 mmol), 2-aminoacetonitrile hydrochloride (0.902 g, 9.75 mmol), 1H-benzo[d][1,2,3]triazol-1-ol hydrate (1.24 g, 8.12 mmol), N_1-((ethylimino)methylene)-N_3,N_3-dimethylpropane-1,3-diamine hydrochloride (1.71 g, 8.94 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (4.95 mL, 28.4 mmol) in CH_2Cl_2 (20 mL) was allowed to stir at rt for 24 hr. After removal of organic solvent under reduced pressure, purification of the residue by flash chromatography on silica gel using 0-10% MeOH/CH_2Cl_2 for elution provided the title intermediate **7.2** as white solid (1.31 g, 99%).^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.30 (d, J = 2H), 7.94 (d, J = 8.0 Hz, 2H), 8.87 (d, J = 8.0 Hz, 2H), 9.62 (br s, 1H); LCMS (ES) $[M + 1]^+$ m/z 162.0.

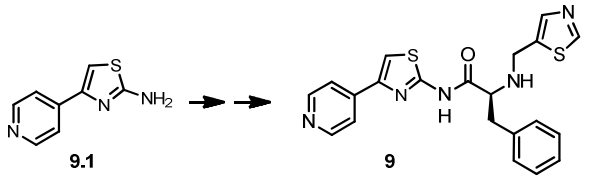
2-(Pyridin-4-yl)thiazol-5-amine (7.3). A solution of *N*-(cyanomethyl)isonicotinamide **7.2** (0.665 g, 4.1 mmol) and phosphorus pentasulfide (1.8 g, 8.3 mmol) in benzene (5.00 mL, 56 mmol) was allowed to refluxed under N_2 for 24 hr. After removal of organic solvent under reduced pressure, purification of the residue by flash chromatography on silica gel using 0-10% MeOH/CH_2Cl_2 for elution provided the title intermediate **7.3** as white solid (730 mg, 49%). ^{1}H NMR (400 MHz, CD_3OD) 7.07 (s, 1H), 7.72 (d, J = 8.0 Hz, 2H), 8.51 (d, J = 8.0 Hz, 2H); LCMS (ES) $[M + 1]^+$ m/z 177.2.

(*S*)-3-Phenyl-*N*-(2-(pyridin-4-yl)thiazol-5-yl)-2-(thiazol-4-ylmethylamino)-propanamide (7). This title compound was prepared starting with 2-(Pyridin-4-yl)thiazol-5-amine **7.3** according to the procedure as described above for conversion of **3.1** to **3**. The crude product was purified by preparative HPLC (10-90% 0.1%TFA/CH_3CN/water, 45 min) to provide the title compound **7** as white solid. ^{1}H NMR (400 MHz, CD_3OD) δ: 3.23 (dd, J = 12, 8.0 Hz, 1H), 3.49 (dd, J = 12, 4.0 Hz, 1H), 4.43 (dd, J = 12, 8.0 Hz, 1H), 4.44 (d, J = 16 Hz, 1H), 4.49 (d, J = 16 Hz, 1H), 7.24 (dd, J = 8.0, 4.0 Hz, 2H), 7.28 – 7.37 (m, 3H), 7.76 (s, 1H), 7.95 (m, 1H), 8.07 (m, 2H), 8.81 (m, 2H), 9.30 (m, 1H); HRMS (ESMS) calcd. for $C_{21}H_{19}N_5OS_2$ 422.1101 $(M+H)^+$, found: 422.1080.

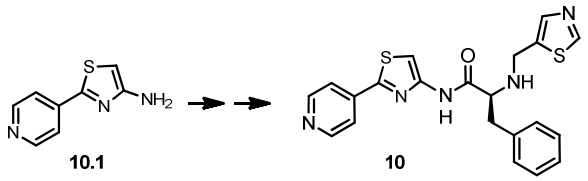


2-(Pyridin-4-yl)thiazol-4-amine (8.2). To a solution of 2-bromo-1-(pyridin-4-yl)ethanone **8.1** (5.00 g, 17.8 mmol) and 2-thiourea (1.25 mL, 23.1 mmol) in EtOH was added triethylamine (2.5 mL, 17.8 mmol). The mixture was heated at 60 °C for 20 hr, and the resulting solution was concentrated under reduced pressure. To the residue was added water (15 mL) and saturated aqueous $NaHCO_3$ (4 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The organic solution was combined, washed with water (15 mL), brine (10 mL) and dried over $MgSO_4$. After removal of organic solvents under reduced pressure, purification of the residue by flash chromatography on silica gel using 0-70% EtOAc/Hexanes for elution provided **8.2** as yellow solid (2.71 g, 86%). ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm 2.80-4.30 (br s, 2H), 7.25-7.60 (br s, 1H), 8.04 (s, 1H); 8.30 (d, J = 8.0 Hz, 2H), 8.85 (d, J = 8.0 Hz, 2H); LCMS (ES) $[M + 1]^+$ m/z 178.0.

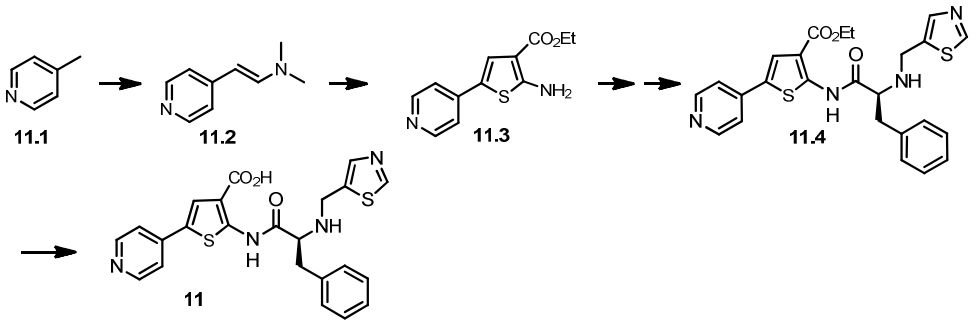
(*S*)-3-Phenyl-*N*-(5-(pyridin-4-yl)thiazol-2-yl)-2-((thiazol-5-ylmethyl)amino)propanamide (8). This title compound was prepared starting with 5-(pyridin-4-yl)thiazol-2-amine **8.2** according to the procedure as described above for conversion of **3.1** to **3**. The crude product was purified by preparative HPLC (10-90% 0.1%TFA/CH_3CN/water, 30 min) to provide **8** as colorless TFA salt. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 3.40-3.25(m, 1H), 3.48 (dt, *J* = 3.42, 1.6 Hz, 1 H), 4.40-4.49(m,3 H), 7.30 (m, 5 H), 7.75 (s, 1H), 8.27 (s, 1 H), 8.34 (d, *J* = 6.65 Hz, 2 H), 8.75 (d, *J* = 6.65 Hz, 2 H), 9.10 (d, *J* = 1.96 Hz, 1 H); HRMS (ESMS) calcd. for $C_{21}H_{19}N_5OS_2$ 422.1101 $(M+H)^+$, found: 422.1092.



(S)-3-Phenyl-*N*-(4-(pyridin-4-yl)thiazol-2-yl)-2-((thiazol-5-ylmethyl)amino)propanamide (9). The title compound was prepared starting with 4-(pyridin-4-yl)thiazol-2-amine 9.1 according to the procedure as described above for conversion of 3.1 to 3. The crude product was purified by preparative HPLC (10-90% 0.1%TFA/CH_3CN/water, 45 min) to provide the title compound **9** as white solid. ^{1}H NMR (400 MHz, DMSO-D_6)δ ppm 3.20 (dd, *J* = 14.67, 12.0, 8.0 Hz, 1H) 3.40 (dd, *J* = 12.0, 8.0 Hz, 1H) 4.73 (m, 3H), 7.17-7.36 (m, 5H) 7.87 (d, *J* = 4.8 Hz, 1H) 8.01 (d, *J* =5.2 Hz, 2H) 8.27 (s, 1H), 8.74 (d, *J* = 7.8 Hz, 2H) 9.22 (d, *J* = 5.2 Hz, 1H); HRMS (ESMS) calcd. for $C_{21}H_{19}N_5OS_2$ 422.1101 $(M+H)^+$, found: 422.1128.



(*S*)-3-Phenyl-*N*-(2-(pyridin-4-yl)thiazol-4-yl)-2-(thiazol-5-ylmethylamino)propanamide (10). This title product was prepared starting from 2-(pyridin-4-yl)thiazol-4-amine **10.1** according to the procedure as described above for conversion of **3.1** to **3**. The final crude product was purified by preparative HPLC (10-90% 0.1%TFA/CH_3CN/water, 30 min) to provide the title product **10** as white TFA salt. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 2.86 - 3.05 (m, 1 H), 3.12 (dd, *J* = 13.30, 6.26 Hz, 1 H), 3.65 (dd, *J* = 7.83, 6.26 Hz, 1 H), 3.79 - 4.03 (m, 2 H), 7.13 - 7.36 (m, 6 H), 7.84 (s, 1 H), 7.89 - 7.99 (m, 2 H), 8.64 (dd, *J* = 4.50, 1.76 Hz, 2 H), 8.90 (d, *J* = 2.35 Hz, 1 H); HRMS (ESMS) calcd. for $C_{21}H_{19}N_5OS_2$ 422.1101 $(M+H)^+$, found: 422.1106.



(*E*)-*N*,*N*-Dimethyl-2-(pyridin-4-yl)ethenamine (11.2). A solution of 4-methylpyridine **11.1** (4.27 g, 45.9 mmol) and *tert*-butoxy-bis(dimethylamino)methaneand (10 g, 57.4 mmol) in DMF (10 mL) was heated at 150 °C for 12 hr. After removal of solvents under reduced pressure, the

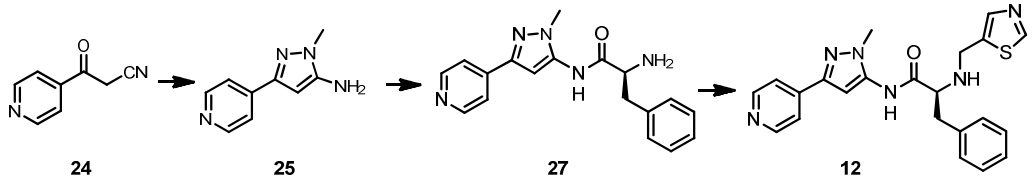
resulting residue solid was recrystalized using cyclohexane (40 mL) to provided the title product **11.2** as crystal solid (4.7 g, 55%).

Ethyl 2-amino-5-(pyridin-4-yl)thiophene-3-carboxylate (11.3). To a solution of (E)-*N,N*-dimethyl-2-(pyridin-4-yl)ethenamine **11.2** (2.55 g, 17 mmol) in EtOH (25) was added ethyl cyanoacetate (1.9 g, 17 mmol), sulfur (0.59 g, 17 mmol) followed by morpholine (0.50 g, 5.7 mmol). The mixture was left stirring at 85 °C for 2.5 hr under N_2 atomosphere. The resulting mixture was placed into ice bath, cooled to 0 °C. The precipitate was filtered, collected and and washed with hexanes to provide the title intermediate **11.3** as a yellow solid (2.8 g, 66%). LCMS (ES) $[M + 1]^+$ m/z 249.1.

(*S*)-Ethyl 2-(3-phenyl-2-((thiazol-5-ylmethyl)amino)propanamido)-5-(pyridin-4-yl)thiophene-3-carboxylate (11.4). This title product was prepared starting from ethyl 2-amino-5-(pyridin-4-yl)thiophene-3-carboxylate **11.3** according to the procedure as described above for conversion of **3.1** to **3**. The final crude product was purified by flash chromatography on silica gel using 0-80% EtOAc/Hexanes for elution to provide **11.4** as yellow solid. ^{1}H NMR (400 MHz, MeOH) δ ppm 1.41 (t, *J* = 7.14 Hz, 3 H), 3.10 - 3.28 (m, 2 H), 4.24 - 4.49 (m, 5 H), 7.12 - 7.38 (m, 5 H), 7.69 (s, 1 H), 8.04 - 8.27 (m, 3 H), 8.60 - 8.75 (m, 2 H), 9.04 (d, *J* = 1.76 Hz, 1 H); LCMS (ES) $[M + 1]^+$ m/z 493.1.

(*S*)-2-(3-Phenyl-2-((thiazol-5-ylmethyl)amino)propanamido)-5-(pyridin-4-yl)thiophene-3-carboxylic acid (11). To a solution of (S)-ethyl 2-(3-phenyl-2-(thiazol-4-ylmethylamino)propanamido)-5-(pyridin-4-yl)thiophene-3-carboxylate **11.4** (56.8 mg, 0.12 mmol) in dioxane (2.0 mL) was added aqueous LiOH (2.0 M, 0.12 mL, 0.24 mmol). After stirring at 70 °C for 2.0 h, the reaction mixture was cooled to rt and treated with AcOH (0.1 mL). The resulting mixture was diluted with water (8 mL), and extracted by 20% *i*-PrOH/$CHCl_3$ (3 × 6 mL). The organic layers were combined and washed with water (3 mL) and brine (3 mL).. After removal organic solvent under reduced pressure, the residue was purified by preparative HPLC (10-70% 0.1%TFA/CH_3CN/water, 30 min) to provide the title product **11** as yellow solid (19.6 mg, 37). ^{1}H NMR (400 MHz, MeOH) δ ppm 3.19 (dd, *J* = 13.30, 9.39 Hz, 1 H), 3.46 (dd, *J* = 13.40, 5.97 Hz, 1 H), 4.44 (s, 2 H), 4.60 (dd, *J* = 9.39, 5.87 Hz, 1 H), 7.12 - 7.42 (m, 5 H),

7.75 (d, *J* = 1.76 Hz, 1 H), 8.10 - 8.28 (m, 3 H), 8.66 (d, *J* = 7.04 Hz, 2 H), 9.06 (d, *J* = 1.76 Hz, 1 H); HRMS (ESMS) calcd. for $C_{23}H_{20}N_4O_3S_2$ 465.1046 $(M+H)^+$, found: 465.1046.

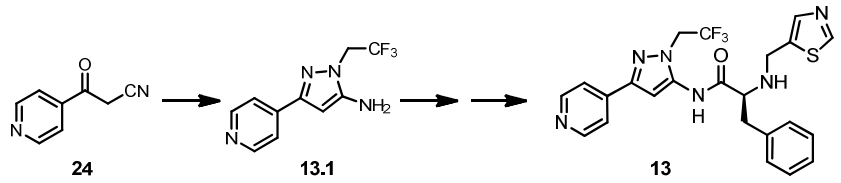


1-Methyl-3-(pyridin-4-yl)-1H-pyrazol-5-amine (25). To a solution of 3-oxo-3-phenylpropanenitrile **24** (400 mg, 2.76 mmol) in MeOH (7 mL) at rt was added methylhydrazine (367 µl, 6.89 µmol) followed by conc. HCl (0.1 mL). The resulting mixture was stirred at 60 °C for 2.5 hr. After removal of organic solvent under reduced pressure, the residue was redissolved in 30% *i*-PrOH/ $CHCl_3$ (20 mL). The solution was washed with brine (5 mL), and dried over $MgSO_4$. After removal of organic solvents under reduced pressure, purification of the residue by flash chromatography on silica gel using 0-20% MeOH/CH_2Cl_2 for elution provided the title product **25** as white solid (341 mg, 71%) . ^{1}H NMR (400 MHz, CD_3OD) δ ppm 3.70 (s, 3 H), 5.97 (s, 1 H), 7.64 - 7.76 (m, 2 H), 8.44 - 8.54 (m, 2 H); LCMS (ES) $[M + 1]^+$ m/z 175.1.

1-Methyl-3-(pyridin-4-yl)-1H-pyrazol-5-amine (27). The title compound was prepared starting with 1-methyl-3-(pyridin-4-yl)-1H-pyrazol-5-amine **25** in 68% yield according to the procedure as described above for conversion of **3.1** to **3.3**. LCMS (ES) $[M + 1]^+$ m/z 322.1.

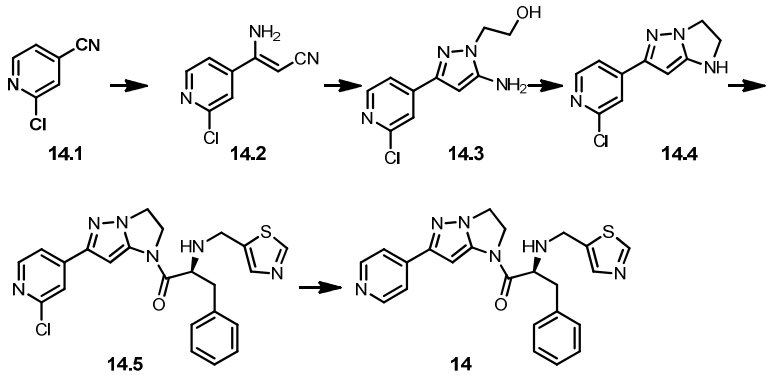
(*S*)-*N*-(1-Methyl-3-(pyridin-4-yl)-1H-pyrazol-5-yl)-3-phenyl-2-((thiazol-5-ylmethyl)amino)propanamide (12). The title compound was prepared starting with (*S*)-2-amino-*N*-(1-methyl-3-(pyridin-4-yl)-1H-pyrazol-5-yl)-3-phenylpropanamide **27** according to the procedure as described above for conversion of **3.3** to **3**. The crude product was purified by preparative HPLC (10-90% 0.1%TFA/CH_3CN/water, 45 min). The combined desired product fractions were treated with saturated aqueous $NaHCO_3$, and extracted with 30% *i*-PrOH /$CHCl_3$. The organic solution was washed with water and brine, and dried over $MgSO_4$. Removal of solvents under reduced pressure provided the title product **12** as white solid (84%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 3.08 (s, 2 H) 3.61 (s, 3 H) 3.68 (s, 1 H), 3.97 (s, 2 H) 6.73 (s, 1 H),

7.28 (m, 6 H), 7.78 (m, 2 H), 8.53 (m, 2 H), 8.97 (s, 1 H); HRMS (ESMS) calcd. for $C_{22}H_{22}N_6OS$ 419.1645 $(M+H)^+$, found: 419.1636.



3-(Pyridin-4-yl)-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-amine (13.1). The title compound was prepared starting with 3-oxo-3-phenylpropanenitrile **24** and 2,2,2-trifluoroethylhydrazine according to the procedure as described above for preparation of **25** (81%). The crude product **13.1** was directly used in the next step without purifcation. LCMS (ES) $[M + 1]^+$ m/z 243.1

(*S*)-*N*-(1-Methyl-3-(pyridin-4-yl)-1H-pyrazol-5-yl)-3-phenyl-2-((thiazol-5-ylmethyl)amino)propanamide (13). This title product was prepared starting from 3-(pyridin-4-yl)-1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-amine **13.1** according to the procedure as described above for conversion of **3.1** to **3**. The final crude product was purified by preparative HPLC (10-90% 0.1%TFA/CH_3CN/water, 30 min). The desired product fractions were combined, treated with saturated aqueous $NaHCO_3$, and extracted with 30% *i*-PrOH/$CHCl_3$. The organic solution was washed with water. Removal of solvents under reduced pressure provided the title product **13** as white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 2.83 - 3.11 (m, 2 H), 3.61 (t, J = 6.94 Hz, 1 H), 3.80 - 3.93 (m, 2 H), 4.55 - 4.83 (m, 2 H), 6.71 - 6.81 (m, 1 H), 7.15 - 7.32 (m, 6 H), 7.55 (s, 1 H), 7.70 - 7.79 (m, 2 H), 8.42 - 8.54 (m, 2 H); HRMS (ESMS) calcd. for $C_{23}F_3H_{21}N_6OS$ 487.1519 $(M+H)^+$, found: 487.1523.



3-(2-Chloropyridin-4-yl)-1H-pyrazol-5-amine (14.2). To a 0 °C solution of 2-chloroisonicotinonitrile **14.1** (25.00 g, 180 mmol) in THF (300 mL) under N_2 atmosphere was added acetonitrile (25 mL, 469 mmol) followed by portionwise addition of potassium *tert*-butoxide (81 g, 722 mmol) over 30 min. The reaction solution was allowed to warm to rt over 30 min, and was then quenched with water (300 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (150 mL). The organic solutions were combined. After removal of organic solvents under reduced pressure, the dark brown solid was collected, washed with pre-cooled $CHCl_3$ (50 mL) and air-dried to provide the crude product **14.2** (28 g, 88%). LCMS (ES) $[M + 1]^+$ 181.0.

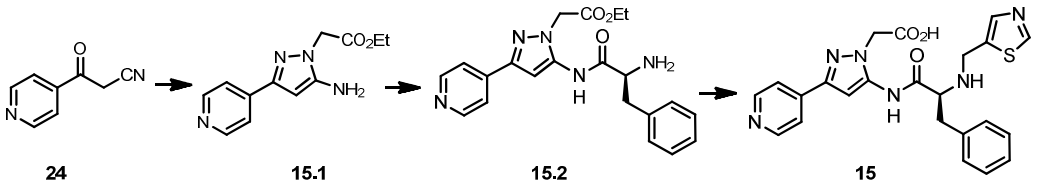
2-(5-Amino-3-(pyridin-4-yl)-1H-pyrazol-1-yl)ethanol (14.3).
To a solution of 3-(2-chloropyridin-4-yl)-1H-pyrazol-5-amine **14.2** (720 mg, 4.0 mmol) in MeOH (20 mL) at rt was added 2-hydrazinylethanol (1.04 mL, 16.0 mmol) followed by concentrated HCl (0.8 mL). After stirring at 80 °C for 1.5 hr, reaction solvents was removed under reduced pressure. The residue was re-dissolved in 30% *i*-PrOH/$CHCl_3$ (30 mL) and washed with saturated $NaHCO_3$ (7 mL), brine, and dried over $MgSO_4$. After removal of organic solvents under reduced pressure, purification of the residue by flash chromatography on silica gel using 0-30% MeOH/CH_2Cl_2 for elution gave title product **14.3** (508 mg, 53%). LCMS (ES) $[M + 1]^+$ m/z 239.1.

6-(2-Chloropyridin-4-yl)-2,3-dihydro-1H-imidazo[1,2-b]pyrazole (14.4)
A mixture of polyphosphoric acid (2.0 mL) and 2-(5-amino-3-(pyridin-4-yl)-1H-pyrazol-1-yl)ethanol **14.3** (500 mg, 2.1 mmol) was allowed to stir at 160 °C for 2 hr. The mixture was treated with aquoues NaOH (6.0 N) to pH~9.0, diluted with water (4 mL) and extracted with 30% *i*-PrOH/$CHCl_3$ (4 × 10 mL). The combined orgnic solution was washed with water (8 mL) and brine (5 mL). After removal of organic solvents under reduced pressure, purification of the residue by flash chromatography on silica gel using 0-10% MeOH/CH_2Cl_2 for elution gave title product **14.4** (357 mg, 77%). LCMS (ES) $[M + 1]^+$ m/z 221.1.

(*S*)-1-(6-(2-Chloropyridin-4-yl)-2,3-dihydro-1H-imidazo[1,2-b]pyrazol-1-yl)-3-phenyl-2-((thiazol-5-ylmethyl)amino)propan-1-one (14.5). This title product was prepared starting from

6-(2-chloropyridin-4-yl)-2,3-dihydro-1H-imidazo[1,2-b]pyrazole **14.4** according to the procedure as described above for conversion of **5.1** to **5**. The final crude product was purified by preparative HPLC (10-60% 0.1%TFA/CH3CN/water, 45 min). The combined desired product fractions were treated with saturated aqueous $NaHCO_3$, and extracted with 30% *i*-PrOH/$CHCl_3$ (10 mL). The organic solution was washed with water and dried over $MgSO_4$. Removal of solvents under reduced pressure provided the title product **14.5** as white solid. LCMS (ES) $[M + 1]^+$ m/z 465.1.

(*S*)-3-Phenyl-1-(6-(pyridin-4-yl)-2,3-dihydro-1H-imidazo[1,2-b]pyrazol-1-yl)-2-((thiazol-5-ylmethyl)amino)propan-1-one (14). To a solution of (*S*)-1-(6-(2-chloropyridin-4-yl)-2,3-dihydro-1H-imidazo[1,2-b]pyrazol-1-yl)-3-phenyl-2-((thiazol-5-ylmethyl)amino)propan-1-one **14.5** (67 mg, 0.13 μmol) in MeOH (5 mL) was added Pd/C. The reaction vessel was purgered with H_2, and the mixture was left stirring under under H_2 atomosphere for 30 min. To the mixture was added aqueous saturated $NaHCO_3$ (1.0 mL) and water (5 mL), organic solvent was removed under reduced pressure. The remaining was extracted with EtOAc (3 × 10 mL). After removal of organic solvents under reduced pressure, purification of the residue by flash chromatography on silica gel using 0-8% MeOH/CH_2Cl_2 for elution gave title product **14** as white solid (18 mg, 31%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 2.93 - 3.21 (m, 2 H), 3.82 - 4.11 (m, 3 H), 4.12 - 4.26 (m, 1 H), 4.26 - 4.49 (m, 2 H), 4.55 (td, *J* = 9.83, 6.16 Hz, 1 H), 6.60 - 6.71 (m, 1 H), 6.91 (t, *J* = 8.80 Hz, 1 H), 6.97 - 7.08 (m, 2 H), 7.20 - 7.36 (m, 2 H), 7.36 - 7.48 (m, 1 H), 7.70 - 7.86 (m, 2 H), 8.48 - 8.62 (m, 2 H), 8.88 - 8.98 (m, 1 H); LCMS (ES) $[M + 1]^+$ m/z calcd. for $C_{19}H_{19}N_5O$ 334.2 $(M+H)^+$, found: 334.3.



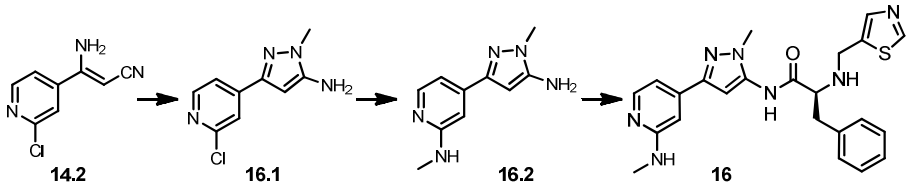
24 15.1 15.2 15

Ethyl 2-(5-amino-3-(pyridin-4-yl)-1H-pyrazol-1-yl)acetate (15.1). The title compound was prepared starting with 3-oxo-3-phenylpropanenitrile **24** and ethyl 2-hydrazinylacetate hydrochloride (1.8 eq.) according to the procedure as described above for preparation of **25**. The

crude product was purified by flash chromatography on silica gel using 0-20% MeOH/CH_2Cl_2 for elution to provide **15.1** as colorless solid (57%).

(*S*)-Ethyl 2-(5-(2-amino-3-phenylpropanamido)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)acetate (15.2). The title compound was prepared starting with ethyl 2-(5-amino-3-(pyridin-4-yl)-1H-pyrazol-1-yl)acetate **15.1** according to the procedure as described above for conversion of **3.1** to **3**. The crude product was purified by flash chromatography on silica gel using 0-10% MeOH/CH_2Cl_2 for elution to provide **15.2** as colorless solid (43%). LCMS (ES) $[M + 1]^+$ m/z 491.1.

(*S*)-2-(5-(3-Phenyl-2-(thiazol-4-ylmethylamino)propanamido)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)acetic acid (15). To a solution of **(***S*)-ethyl 2-(5-(2-amino-3-phenylpropanamido)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)acetate **15.2** (35 mg, 73 μmol) in dioxane (1.0 mL) at rt was added lithium hydroxide monohydrate (6 mg, 147 μmol) followed by water (0.3 mL). After stirring at rt for 1.0 hr, the reaction mixture was diluted with water (2 mL), neutralized by 10% HOAc to pH ~7 and extracted with 30% *i*-PrOH/$CHCl_3$ (3 × 4 mL). The combined organic solution was concentrated under reduced pressure. Purification of the residue by preparative HPLC (10-90% 0.1%TFA/CH_3CN/water, 30 min) provided the title product **15** as white TFA salt (8.5 mg, 21%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 3.26 (dd, *J* = 13.69, 9.00 Hz, 1 H); 3.45 (dd, *J* = 13.69, 5.87 Hz, 1 H), 4.39 - 4.57 (m, 3 H), 4.69 (d, *J* = 18.00 Hz, 1 H), 7.19 (s, 1 H), 7.25 - 7.35 (m, 2 H), 7.35 - 7.44 (m, 3 H), 7.82 (d, *J* = 1.96 Hz, 1 H), 8.44 (d, *J* = 7.04 Hz, 2 H), 8.81 (d, *J* = 6.65 Hz, 2 H), 9.13 (d, *J* = 1.56 Hz, 1 H); HRMS (ESMS) calcd. for $C_{23}H_{20}N_4O_3S_2$ 465.1046 $(M+H)^+$, found: 465.1046.

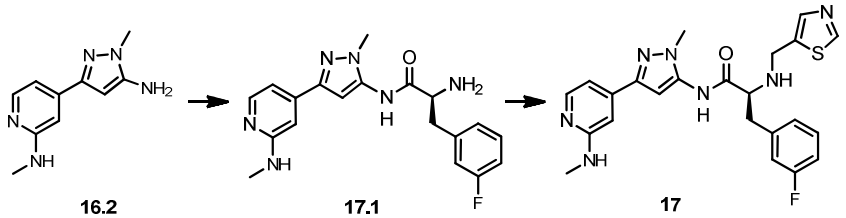


3-(2-Chloropyridin-4-yl)-1-methyl-1H-pyrazol-5-amine (16.1). The title compound was prepared starting with 3-(2-chloropyridin-4-yl)-1H-pyrazol-5-amine **14.2** and methylhydrazine according to the procedure as described above for preparation of **14.3**. The crude product was

purified by flash chromatography on silica gel using 0-8% MeOH/CH_2Cl_2 for elution to provide **16.1** as colorless solid (89%). LCMS (ES) $[M + 1]^+$ m/z 209.1.

4-(5-Amino-1-methyl-1H-pyrazol-3-yl)-*N*-metylpyridin-2-amine (16.2). A mixture of 3-(2-chloropyridin-4-yl)-1-methyl-1H-pyrazol-5-amine **16.1** (3.60 g, 18 mmol) in 40% aqueous $MeNH_2$ solution (25 mL) in sealed tube was heated at 140 °C for 64 hr. The resulting mixture was allowed to cool to rt. After removal of solvents under reduced pressure, purification of the residue by flash chromatography on silica gel using 0-10% MeOH/CH_2Cl_2 for elution gave title product **16.2** as brown solid (3.18 g, 91%). LCMS (ES) $[M + 1]^+$ m/z 204.1.

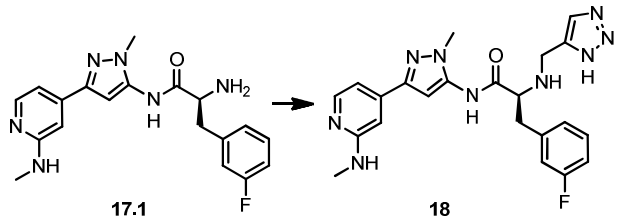
(*S*)-*N*-(1-Methyl-3-(2-(methylamino)pyridin-4-yl)-1H-pyrazol-5-yl)-3-phenyl-2-((thiazol-5-ylmethyl)amino)propanamide (16). This title product was prepared starting from 4-(5-Amino-1-methyl-1H-pyrazol-3-yl)-*N*-metylpyridin-2-amine **16.2** according to the procedure as described above for conversion of **3.1** to **3**. The final crude product was purified by preparative HPLC (10-90% 0.1%TFA/CH_3CN/water, 30 min). The combined desired product fractions were treated with saturated aqueous $NaHCO_3$, and extracted with 30% *i*-PrOH /$CHCl_3$. The organic solution was washed with water. Removal of solvents under reduced pressure provided the title product **16** as white solid. ^{1}H NMR (400 MHz, MeOH) δ ppm 2.90 (s, 3 H), 3.06 (t, *J* = 7.73 Hz, 2 H), 3.58 (s, 3 H), 3.67 (t, *J* = 6.85 Hz, 1 H), 3.87 - 4.12 (m, 2 H), 6.60 (s, 1 H), 6.86 (s, 1 H), 6.92 (d, *J* = 4.89 Hz, 1 H), 7.07 - 7.34 (m, 5 H), 7.37 (br. s., 1 H), 7.94 (d, *J* = 5.28 Hz, 1 H), 8.94 (s, 1 H); HRMS (ESMS) calcd. for $C_{23}H_{25}N_7OS$ 448.1910 $(M+H)^+$, found: 448.1913.



(*S*)-2-Amino-3-(4-fluorophenyl)-*N*-(1-methyl-3-(2-(methylamino)pyridin-4-yl)-1H-pyrazol-5-yl)propanamide (17.1). The title compound was prepared starting with 4-(5-Amino-1-methyl-1H-pyrazol-3-yl)-*N*-metylpyridin-2-amine **16.2** and (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-fluorophenyl)propanoic acid according to the procedure as described above for conversion

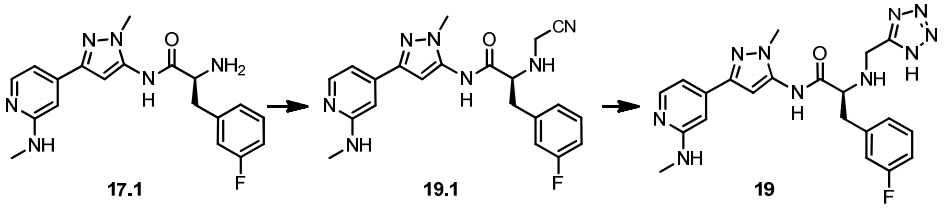
of **3.1** to **3.3.** The crude product was purified by flash chromatography on silica gel using 0-8% MeOH/CH_2Cl_2 for elution (4.70 g, 85%). LCMS (ES) $[M + 1]^+$ m/z 369.2.

(2*S*)-3-(4-Fluorophenyl)-*N*-(3-(2-(methylamino)pyridin-4-yl)-1*H*-pyrazol-5-yl)-2-(thiazol-5-ylmethylamino)propanamide (17). This title compound was prepared starting from (*S*)-2-amino-3-(4-fluorophenyl)-*N*-(1-methyl-3-(2-(methylamino)pyridin-4-yl)-1H-pyrazol-5-yl)propanamide **17.1** (173 mg, 0.49 mmol) according the procedure described above for conversion of **3.3** to **3.** The product was purified by flash chromatography on silica gel using 0-8% MeOH/CH_2Cl_2 for elution to give **17** as colorless solid (119 mg, 54%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 2.90 (s, 3 H), 2.97 - 3.14 (m, *J* = 13.89, 13.89, 13.69, 7.04 Hz, 2 H), 3.32 (t, *J* = 1.56 Hz, 1 H), 3.59 - 3.69 (m, 4 H), 3.89 - 4.05 (m, 2 H), 6.61 (s, 1 H), 6.85 (s, 1 H), 6.92 (dd, *J* = 5.48, 1.56 Hz, 1 H), 7.03 (t, *J* = 8.80 Hz, 2 H), 7.25 (dd, *J* = 8.61, 5.09 Hz, 2 H), 7.38 (d, *J* = 1.96 Hz, 1 H), 7.94 (d, *J* = 5.48 Hz, 1 H), 8.94 (d, *J* = 2.35 Hz, 1 H); HRMS (ESMS) calcd. for $C_{23}FH_{24}N_7OS$ 466.1816 $(M+H)^+$, found: 466.1814.



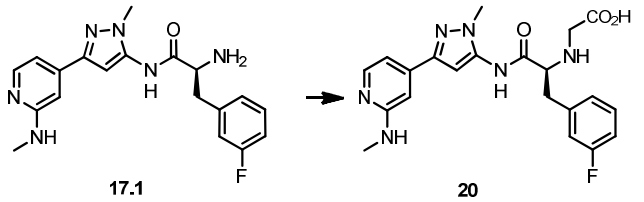
(*S*)-2-(((1H-1,2,3-Triazol-4-yl)methyl)amino)-3-(4-fluorophenyl)-*N*-(1-methyl-3-(2-(methylamino)pyridin-4-yl)-1H-pyrazol-5-yl)propanamide (18). This title compound was prepared starting from (*S*)-2-amino-3-(4-fluorophenyl)-*N*-(1-methyl-3-(2-(methylamino)pyridin-4-yl)-1H-pyrazol-5-yl)propanamide **17.1** (140 mg, 0.38 mmol) and 1H-1,2,3-triazole-4-carbaldehyde (37 mg, 0.38 mmol) according the procedure described above for conversion of **3.3** to **3.** The final crude product was purified by preparative HPLC (10-50% 0.1%TFA/CH_3CN/water, 30 min). The combined desired product fractions were treated with saturated aqueous $NaHCO_3$, and extracted with 30% *i*-PrOH /$CHCl_3$. The organic solution was washed with water. Removal of solvents under reduced pressure provided the title product **18** as white solid (49 mg, 29%). (400 MHz, MeOH) δ ppm ^{1}H NMR (400 MHz, CD_3OD) δ ppm 2.87 - 2.94 (m, 3 H), 3.00 - 3.10 (m, 2 H), 3.56 - 3.67 (m, 4 H), 3.88 - 4.01 (m, 2 H), 6.58 (s, 1 H), 6.86 (s, 1 H), 6.92 (d, *J* = 4.30 Hz, 1 H), 7.05 (t, *J* = 8.80 Hz, 2 H), 7.24 - 7.33 (m, 2 H), 7.68 (s, 1 H),

7.95 (d, J = 5.48 Hz, 1 H); HRMS (ESMS) calcd. for $C_{22}FH_{24}N_9O$ 450.2157 $(M+H)^+$, found: 450.2147.

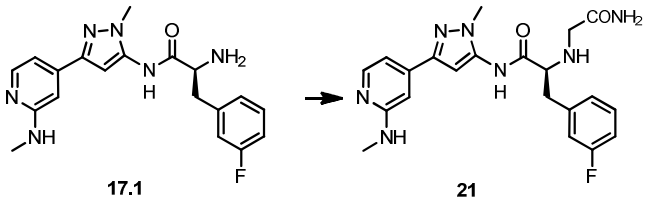


(2S)-2-(Cyanomethylamino)-3-(4-fluorophenyl)-*N*-(1-methyl-3-(2-(methylamino)pyridin-4-yl)-1H-pyrazol-5-yl)propanamide (19.1). To a solution of (S)-2-amino-3-(4-fluorophenyl)-N-(1-methyl-3-(2-(methylamino)pyridin-4-yl)-1H-pyrazol-5-yl)propanamide **17.1** (750 mg, 2.04 μmol) and bromoacetonitrile (244 mg, 214 mmol) in acetonitrile was added *N,N*-diisopropylethylamine (0.43 mL, 2.4μmol). After stirring at 60 °C for 2hr, organic solvents were removed under reduced pressure. Purification of the residue by flash chromatography on silica gel using 0-12% MeOH/CH_2Cl_2 for elution gave the title product **19.1** as yellow syrup (706 mg, 85%). LCMS (ES) $[M + 1]^+$ m/z 408.1.

(2S)-2-((1H-Tetrazol-5-yl)methylamino)-3-(4-fluorophenyl)-*N*-(1-methyl-3-(2-(methylamino)pyridin-4-yl)-1H-pyrazol-5-yl)propanamide (19). To neat tributyltin chloride (1.25 mL, 4.61 mmol) was added sodium azide (500 mg, 7.7 mmol). After sting at 80 °C for 30 min, to the mixture was added a solution of (2S)-2-(cyanomethylamino)-3-(4-fluorophenyl)-*N*-(1-methyl-3-(2-(methylamino)pyridin-4-yl)-1H-pyrazol-5-yl)propanamide **19.1** (178 mg, 437 μmol) in DMF. The resulting mixture was stirred at 160 °C under N2 for 1.5 hr, cooled and diluted with water. The resulting mixture was extracted with 30% *i*-PrOH/$CHCl_3$ (3 × 10 mL), and organic solvents was removed under reduced pressure. After purification of the residue by preparative HPLC (10-90% 0.1%TFA/CH_3CN/water, 30 min), the combined product fractions were treated with 1.0 N HCl (0.50 mL). Removal of solvents under reduced pressure provided **19** as colorless HCl solid (121 mg, 57%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.82 (d, J = 6.65 Hz, 1 H), 7.23 - 7.45 (m, 4 H), 7.11 (t, J = 8.61 Hz, 2 H), 6.88 (s, 1 H), 4.71 (s, 2 H), 4.60 (br. s., 1 H) 3.63 (s, 3 H) 3.42 - 3.54 (m, 1 H), 3.20 - 3.29 (m, 1 H), 3.01 - 3.11 (m, 4 H); HRMS (ESMS) calcd. for $C_{21}FH_{23}N_{10}O$ 451.2110 $(M+H)^+$, found: 451.2130.

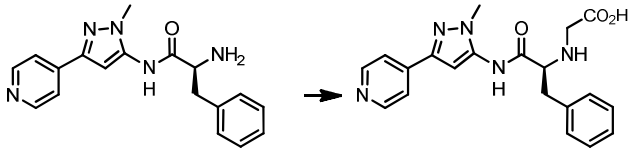


2-((*S*)-3-(4-Fluorophenyl)-1-(1-methyl-3-(2-(methylamino)pyridin-4-yl)-1H-pyrazol-5-ylamino)-1-oxopropan-2-ylamino)acetic acid (20). To a solution of glyoxylic acid monohydrate (58 mg, 0.63 mmol) in dichloroethane/dioxane(1:1, 3.0 mL) was added HOAc (0.050 mL) followed by (2S)-2-amino-3-(4-fluorophenyl)-*N*-(1-methyl-3-(2-(methylamino)pyridin-4-yl)-1H-pyrazol-5-yl)propanamide **17.1** (120 mg, 0.33 mmol). After stirring at 70 °C for 2 min, to the mixture was added sodium triacetoxyborohydride (276 mg, 1.30 mmol). The resulting solution was left stirring at 70 °C for 45 min, cooled to rt, treated with water (2 mL). After removal of solvents under reduced pressure, the residue was redissoved in DMF (3 mL) and purified by preparative HPLC (5-35% 0.1%TFA/CH_3CN/water, 45 min) to provide title compound **20** as colorless solid (61 mg, 44%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.84 (d, *J* = 7.43 Hz, 1 H), 7.36 (dd, *J* = 8.61, 5.09 Hz, 2 H), 7.26 - 7.33 (m, 2 H), 7.08 - 7.20 (m, 2 H), 6.90 (s, 1 H), 4.41 (dd, *J* = 9.00, 6.26 Hz, 1 H), 3.83 - 4.03 (m, 2 H), 3.63 (s, 3 H) 3.36 - 3.47 (m, 1 H), 3.25 (dd, *J* = 13.30, 9.00 Hz, 1 H), 3.07 (s, 3 H); HRMS (ESMS) calcd. for $C_{21}FH_{23}N_6O_3$ 427.1884 $(M+H)_+$, found: 427.1878.



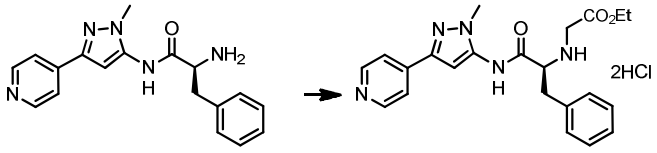
2-((*S*)-3-(4-Fluorophenyl)-1-(1-methyl-3-(2-(methylamino)pyridin-4-yl)-1H-pyrazol-5-ylamino)-1-oxopropan-2-ylamino)acetic acid (21). To a solution of *N*-ethyl-*N*-isopropylpropan-2-amine (85 mg, 0.66 mmol) and (2S)-2-amino-3-(4-fluorophenyl)-*N*-(1-methyl-3-(2-(methylamino)pyridin-4-yl)-1H-pyrazol-5-yl)propanamide **17.1** (121 mg, 0.33 mmol) in CH_3CN(3 mL) was added 2-bromoacetamide (44 mg, 0.33 mmol). The mixture was left stirring at rt for 12 hr. After removal of organic solvents under reduced pressure, purification of the residue by flash chromatography on silica gel using 0-50% MeOH/CH_2Cl_2 for elution gave

the title product **21** as colorless film (20 mg, 14%). ^{1}H NMR (400 MHz, MeOH) δ ppm 2.91 (s, 3 H), 2.97 - 3.12 (m, 2 H), 3.20 - 3.28 (m, 1 H), 3.31 - 3.35 (m, 1 H), 3.36 - 3.41 (m, 1 H), 3.59 (t, *J* = 7.04 Hz, 1 H), 3.65 (s, 3 H), 6.63 (s, 1 H), 6.87 (s, 1 H), 6.93 (dd, *J* = 5.58, 1.47 Hz, 1 H), 7.01 - 7.14 (m, 2 H), 7.24 - 7.40 (m, 2 H), 7.91 - 8.01 (m, 1 H); HRMS (ESMS) calcd. for $C_{21}FH_{24}N_7O_2$ 426.2044 $(M+H)_+$, found: 426.2039.



27 22

(*S*)-2-((1-((1-Methyl-3-(pyridin-4-yl)-1H-pyrazol-5-yl)amino)-1-oxo-3-phenylpropan-2-yl)amino)acetic acid (24). This title product was prepared starting from 1-methyl-3-(pyridin-4-yl)-1H-pyrazol-5-amine **27** according to the procedure as described above for conversion of **17.1** to **20**. The final crude product was purified by preparative HPLC (5-50% 0.1%TFA/CH3CN/water, 45 min) to provide the title product **22** as white solid (42%). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 3.10 - 3.23 (m, 1 H), 3.28 (d, *J* = 6.26 Hz, 1 H), 3.41 - 3.51 (m, 1 H), 3.51 - 3.57 (m, 4 H), 4.17 (dd, *J* = 8.80, 6.46 Hz, 1 H), 6.65 - 6.81 (m, 1 H), 7.25 - 7.47 (m, 5 H), 7.72 - 7.89 (m, 2 H), 8.52 (d, *J* = 6.50 Hz, 2 H); HRMS (ESMS) calcd. for $C_{20}H_{21}N_5O_3$ 380.1713 $(M+H)_+$, found: 380.1722.



27 23

(*S*)-Ethyl 2-((1-((1-methyl-3-(pyridin-4-yl)-1H-pyrazol-5-yl)amino)-1-oxo-3-phenylpropan-2-yl)amino)acetate (23). This title product was prepared starting from 1-methyl-3-(pyridin-4-yl)-1H-pyrazol-5-amine **27** according to a procedure similar to as described above for conversion of **17.1** to **21**, except that ethyl bromoacetate was used. The final crude product was purified by flash chromatography on silica gel using 30% EtOAc/Hexanes for elution to provide the title **23** as free base (77%). The free base of **23** (1.8 g, 4.0 mmol) was dissovled in a mixture solvents of

EtOH/CH_2Cl_2(1/4, 20 mL). The solution was cooled to 0 °C and was treated with HCl solution (2.0M in diethyl ether, 7.0 mL, 14 mmol). After stirring at 0 °C for 10 min, the organic solvents was removed under reduced pressure to give **23** as light yellow di-HCl salt (2.14 g, 100%). ^{1}H NMR (500 MHz, MeOH) δ ppm 1.36 (t, *J* = 7.21 Hz, 3 H), 3.27 - 3.32 (m, 1 H), 3.50 (dd, *J* = 13.45, 6.36 Hz, 1 H), 3.62 (s, 3 H), 4.12 (s, 2 H), 4.36 (q, *J* = 7.09 Hz, 2 H), 4.61 (dd, *J* = 9.17, 6.24 Hz, 1 H), 7.16 (s, 1 H), 7.33 - 7.49 (m, 5 H), 8.42 (d, *J* = 7.09 Hz, 2 H), 8.80 (d, *J* = 6.85 Hz, 2 H); HRMS (ESMS) calcd. for $C_{22}H_{25}N_5O_3$ 408.2025 $(M+H)^+$, found:408.2018.