Synthesis and Evaluation of Novel Pyridine Based PLG Tripeptidomimetics

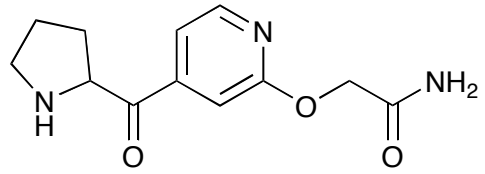
Stina Saitton,[†,‡] Andria L. Del Tredici,[§] Maria Saxin,[‡,^] Tobias Stenström,[‡] Jan Kihlberg,[‡,^] and Kristina Luthman*[,†]

[†]Göteborg University, Department of Chemistry, Medicinal Chemistry, SE-412 96 Göteborg, Sweden; [‡]Umeå University, Department of Chemistry, Organic Chemistry, SE-901 87 Umeå, Sweden; [§]ACADIA Pharmaceuticals Inc., 3911 Sorrento Valley Boulevard, San Diego, CA 92121, USA

(luthman@chem.gu.se)

Contents:

NMR-spectra of biologically evaluated compounds, all as TFA-salts in methanol, and synthetic procedures and characterization data for specified compounds.



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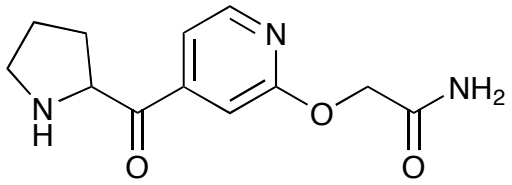

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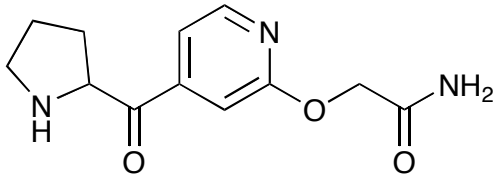

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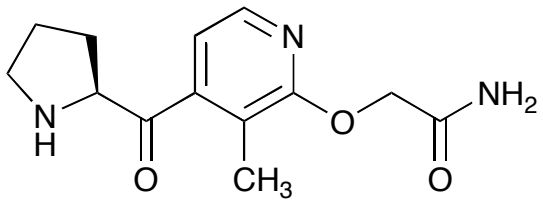

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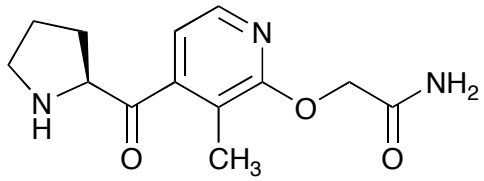

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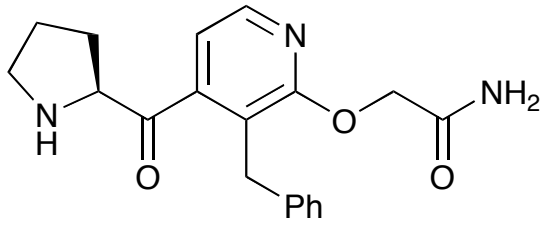

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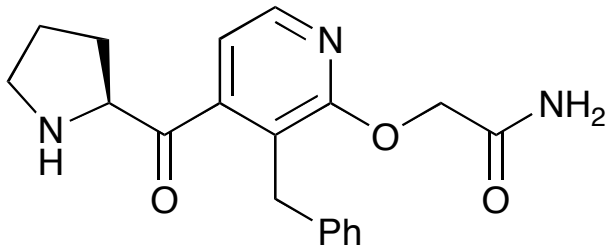

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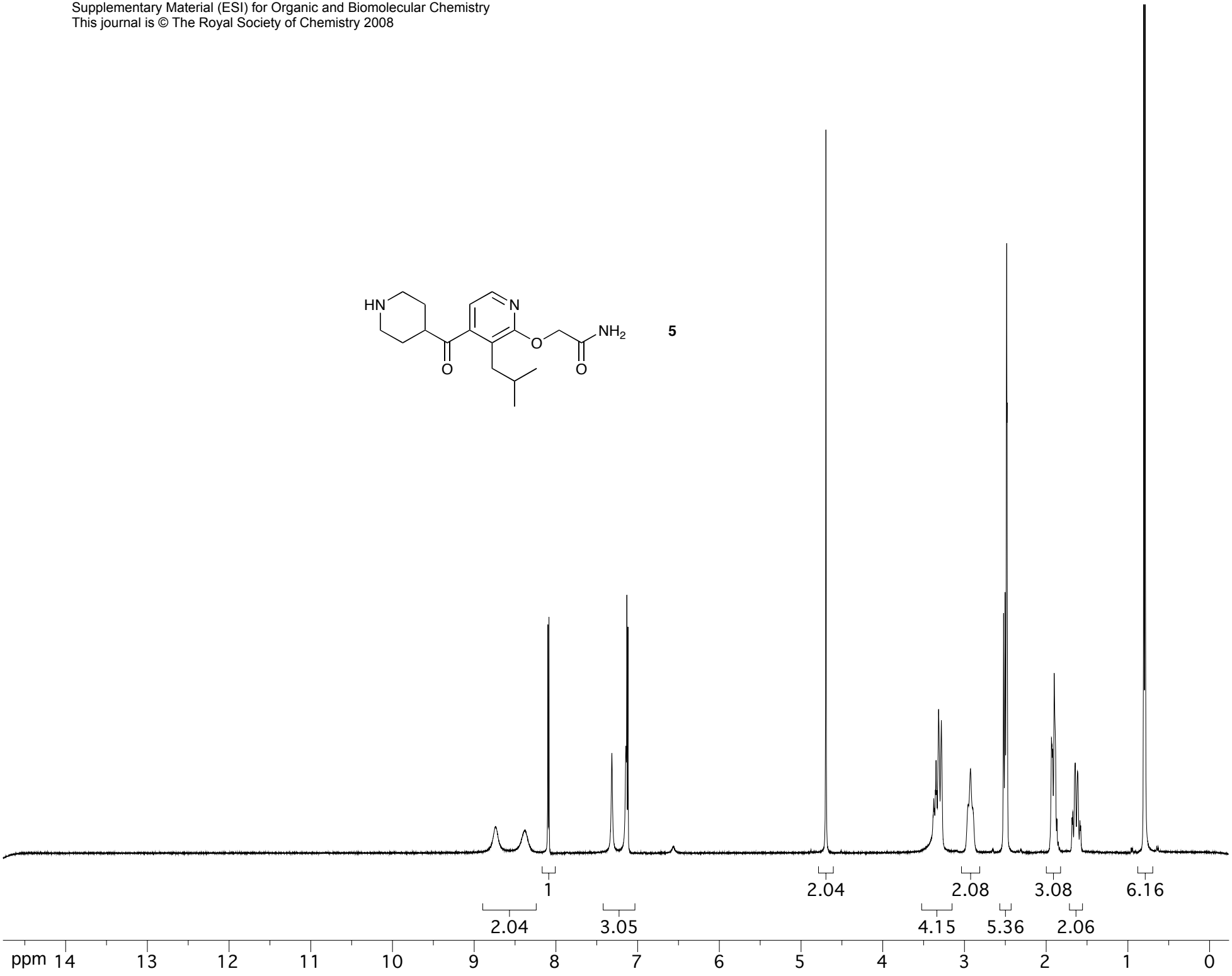

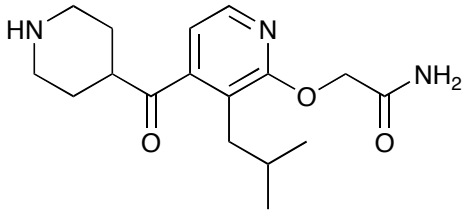

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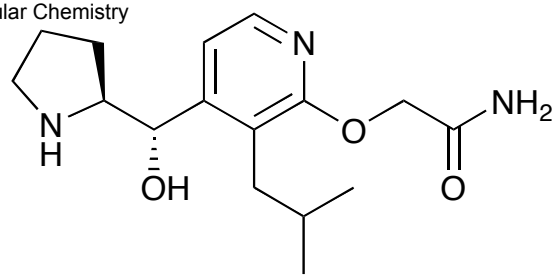

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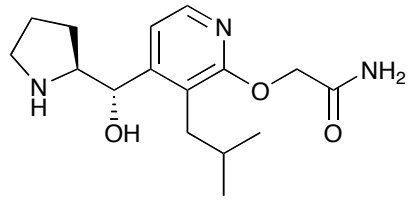

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Synthesis of Boc-protected isonipecotic aldehyde (16).

(1-*tert*-Butoxycarbonylpiperidin-4-yl)-methanol (15). *N*-Morpholine (0.96 mL, 8.7 mmol) and isobutylchloroformate (1.25 g, 9.2 mmol) were added to a stirred solution of *N*-Boc-isonipecotic acid (2.0 g, 8.72 mmol) at -20˚C. After 10 minutes the white slurry was filtered through Celite and $NaBH_4$ (0.98 g, 26.2 mmol) was added to the filtrate. The solution was stirred for another 15 minutes at -20˚C before MeOH (20 ml) was added slowly at 0˚C. After 2 hours, the reaction was quenched by the addition of 2 M HCl (aq, 10 mL) and extracted to EtOAc. The combined organic layers were dried and concentrated to give **15** as white chrystals (1.5 g, 81%): ^{1}H NMR ($CDCl_3$) δ 4.09 (br s, 2H), 3.47 (d, J = 6.1 Hz, 2H), 2.79-2.57 (m, 2H), 2.06 (br s, 1H), 1.69 (d, 2H, J = 14.1 Hz), 1.66-1.56 (m, 1H), 1.43 (s, 9H), 1.19-1.04 (m, 2H); ^{13}C NMR ($CDCl_3$) 154.86, 79.33, 67.47, 43.60 (br), 38.75, 28.58, 28.41; IR (neat) 3959, 2938, 2867, 1662, 1418 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_{22}NO_3$ $[M+H]^+$ 216.1600, found 216.1602.

(1-*tert*-Butoxycarbonylpiperidine-4)-carbaldehyde (16). Dess–Martin periodinane (15.8 mL, 7.47 mmol) was added to a stirred solution of **15** (1.46 g, 6.79 mmol) in CH_2Cl_2 at room temperature. The white mixture was stirred for two hours until it was quenched with Et_2O (30 mL). The organic phase was washed with 1.3 M NaOH (aq, 30 mL) and brine, dried and concentrated to **16** (1.4 g, 82%) as a crude yellow oil, which was used without further purification in the following Grignard reaction.

Synthesis of compound 3 according to the general procedure described in the main text.

4-[(1*R*,1*S*)-Benzyloxy-1-((2*S*)-1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-methyl]-2-fluoro-3-methyl-pyridine (9b). The general procedure applied on alcohol **8b** (0.44 g, 1.42 mmol) in THF (5 mL) yielded a crude oil which was purified by flash chromatography using EtOAc/heptane (1:10) as eluent to afford **9b** (0.46 g, 82%, diastereomeric mixture) as a colorless oil: ^{1}H NMR ($CDCl_3$) (mixture of isomers and

rotamers) δ 7.97-7.85 (m, 1H), 7.31-7.09 (m, 6H), 5.19 (br s, 0.2H), 5.00 (br s, 0.3H), 4.83 (br s, 0.2H), 4.69 (br s, 0.3H), 4.78-4.06 (m, 2.7H), 3.88-3.78 (m, 0.3H), 3.56-2.79 (m, 2H), 2.25 (s, 0.5H), 2.17-2.03 (m, 2.5H), 2.01-1.67 (m, 2H), 1.67-0.91 (m, 11H); ^{13}C NMR ($CDCl_3$) (mixture of isomers and rotamers) δ 162.14 (d, J = 237 Hz), 161.98 (d, J = 236 Hz), 154.54, 154.04, 152.23 (d, J = 4 Hz), 151.66 (d, J = 4 Hz), 144.00, 143.81, 143.74, 143.59, 143.50, 143.34, 137.59, 137.36, 137.00, 128.02, 127.94, 127.79, 127.35, 127.22, 127.12, 126.94, 119.71, 119.33, 118.80, 118.45, 118.12, 117.76, 117.43, 117.12, 79.55, 79.03, 78.67, 76.87, 76.52, 75.98, 72.64, 71.71, 71.53, 71.16, 70.79, 60.12, 59.83, 59.59, 59.08, 56.07, 47.12, 46.28, 46.13, 28.07, 27.94, 27.68, 27.13, 26.05, 25.42, 24.33, 23.97, 23.57, 22.83, 10.34, 10.14, 10.04; IR 2974, 2932, 2881, 1686, 1398 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{30}FN_2O_3$ $[M+H]^+$ 401.2240, found 401.2243.

2-{4-[(1*R*,1*S*)-Benzyloxy-1-((2*S*)-1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)-methyl]-3-methyl-pyridin-2-yloxy}-acetamide (10b). The general procedure was applied on pyridine derivative **9b** (0.40 g, 1.0 mmol) in DMSO (2.5 mL total volume). The reaction was stirred at 55 °C for 4 days. The work-up procedure described above yielded a crude oil which was purified by flash chromatography using EtOAc/heptane (1:1, then 2:1) as eluent to afford **10b** (0.36 g, 80%, diastereomeric mixture) as a colorless oil: ^{1}H NMR ($CDCl_3$) (mixture of isomers and rotamers) δ 8.04-7.93 (m, 1H), 7.36-7.21 (m, 5H), 7.19-7.10 (m, 1H), 6.50-6.34 (m, 2H), 5.32-5.28 (m, 0.2H), 5.11-5.03 (m, 0.3H), 4.88-4.77 (m, 2.5H), 4.55-4.14 (m, 2.7H), 3.95-3.88 (m, 0.3H), 3.63-2.89 (m, 2H), 2.38-2.09 (m, 3H), 2.08-1.04 (m, 13H); ^{13}C NMR ($CDCl_3$) (mixture of isomers and rotamers) δ 172.07, 160.27, 154.97, 154.51, 149.64, 149.07, 143.67, 143.42, 143.21, 138.24, 137.93, 137.59, 128.28, 127.71, 127.48, 127.19, 119.31, 119.10, 116.86, 116.40, 115.97, 79.49, 79.05, 76.44, 71.95, 71.76, 71.36, 70.97, 64.79, 60.55, 59.96, 59.57, 47.56, 47.41, 46.65, 46.35, 28.49, 28.36, 28.14, 27.11, 26.44, 25.87, 24.75, 24.32, 23.92, 23.24, 23.08, 22.58, 14.02, 11.53, 11.37, 11.26; IR 3318, 3063, 2975, 2934, 2881, 1693, 1599, 1395, 1169, 1111, 1069 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{34}N_3O_5$ $[M+H]^+$ 456.2498, found 456.2500.

2-{4-[1-((2*S*)-1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-(1*R*,1*S*)-hydroxy-methyl]-3-methyl-pyridin-2-yloxy}-acetamide (11b). The general procedure was applied on **10b** (0.33 g, 0.72 mmol) and Pd/C (170 mg) in EtOAc (4 mL). The reaction was stirred over night. Work-up afforded **11b** (0.26 mg, 98%) as a colorless oil: ^{1}H NMR ($CDCl_3$) (mixture of isomers) δ 7.97-7.83 (m, 1H), 7.22-7.05 (m, 0.3H), 7.02 (d, 0.7H, *J* = 5.1 Hz), 6.61 (br s, 1H), 6.47-6.36 (m, 1H), 6.02 (br s, 0.6H), 5.41-5.24 (m, 0.3H), 4.87-4.79 (m, 1H), 4.78-4.73 (m, 2H), 4.37-4.17 (m, 0.2H), 4.15-4.08 (m, 0.8H), 3.49-3.08 (m, 2H), 2.21 (s, 3H), 1.95-1.27 (m, 13H); ^{13}C NMR ($CDCl_3$) (mixture of isomers) δ 172.18, 172.10, 160.12, 159.92, 158.01, 151.39, 151.26, 143.55, 117.89, 116.77, 116.07, 80.89, 73.81, 69.65, 64.64, 64.57, 63.43, 47.82, 47.52, 28.41, 28.24, 27.90, 23.92, 11.48; IR 3345, 3055, 2980, 2886, 1667, 1601, 1402, 1265, 1167, 1119 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{28}N_3O_5$ $[M+H]^+$ 366.2029, found 366.2025.

2-{4-[((2*S*)-1-*tert*-Butoxycarbonyl-pyrrolidine-2-yl)-carbonyl]-3-methyl-pyridin-2-yloxy}-acetamide (12b). The general procedure was applied on alcohol **11b** (0.12 g, 0.33 mmol) for 20 hours. Purification by flash chromatography (EtOAc/heptane 2:1) afforded **12b** (87 mg, 73%) as a colorless oil: $[\alpha]_D$ +6.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) (rotamers) δ 8.10 (d, 0.5H, *J* = 5.1 Hz), 8.05 (d, 0.5H, *J* = 5.2 Hz), 7.15 (d, 0.5H, *J* = 5.2 Hz), 7.02 (d, 0.5H, *J* = 5.1 Hz). 6.56-6.30 (m, 2H), 4.94-4.87 (m, 1H), 4.87-4.78 (m, 2H), 3.96-3.55 (m, 1H), 3.53-3.40 (m, 1H), 2.27 (s, 3H), 2.22-2.09 (m, 1H), 2.02-1.77 (m, 3H), 1.44 (s, 4.5H), 1.39 (s, 4.5H); ^{13}C NMR ($CDCl_3$) (two rotamers of equal intensity) δ 203.25, 201.63, 171.59, 171.43, 160.97, 160.78, 154.39, 153.58, 147.29, 146.60, 144.15, 143.93, 118.59, 118.33, 115.44, 115.18, 80.21, 79.89, 64.88, 64.82, 63.96, 63.93, 46.76, 46.58, 29.10, 28.63, 28.28, 28.24, 24.14, 22.96, 12.34, 12.18; IR 3487, 3337, 3055, 2979, 2882, 1689, 1403, 1307, 1266, 1165 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{26}N_3O_5$ $[M+H]^+$ 364.1872, found 364.1878.

2-[3-Methyl-4-((2*S*)-(pyrrolidine-2-yl)-carbonyl)-pyridin-2-yloxy]-acetamide TFA-salt (3). The general procedure was applied on carbamate **12b** (38 mg, 0.10 mmol) in CH_2Cl_2:TFA (4 mL total volume) for 5 minutes. Freeze-drying allowed isolation of the TFA-salt of **3** (30 mg, 76%) as a white solid: $[\alpha]_D$ –37 (*c* 0.5, MeOH); ^{1}H NMR (CD_3OD) δ 8.19 (d, 1H, *J* = 5.3 Hz), 7.31 (d, 1H, *J* = 5.3 Hz), 5.32 (dd, 1H, *J* = 9.1, 7.4 Hz), 4.90 (d, 2H, *J* = 1.1 Hz), 3.53-3.42 (m, 2H), 2.50-2.38 (m, 1H), 2.42 (s, 3H), 2.22-1.89 (m, 3H); ^{13}C NMR (CD_3OD) δ 197.89, 174.13, 163.17, 145.63, 143.82, 122.12, 116.76, 66.43, 65.56, 47.32, 29.24, 24.87, 12.63; HRMS (FAB) calcd for $C_{13}H_{18}N_3O_3$ $[M+H]^+$ 264.1348, found 264.1342.

Synthesis of compound 5 according to the general procedure described in the main text.

(1*R*,1*S*)-(1-*tert*-Butoxycarbonylpiperidin-4-yl)-1-[2-fluoro-3-(2-methyl-allyl)-pyridin-4-yl]-methanol (18). The general procedure applied on pyridine derivative **17** (1.4 g, 5.0 mmol) and aldehyde **16** in THF (45 mL, total volume) yielded a crude oil which was purified by flash chromatography using heptane/EtOAc (2:1) as eluent to afford racemic **18** (0.92 g, 50%) as white crystals: ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 1H, *J* = 5.1 Hz), 7.29 (d, 1H, *J* = 5.1 Hz), 4.80 (s, 1H), 4.68-4.61 (m, 1H), 4.34 (s, 1H), 4.20-4.02 (m, 2H), 3.40 (d, 1H, *J* = 16.4 Hz), 3.28 (d, 1H, *J*=16.4 Hz,), 2.72-2.45 (m, 3H), 1.89-1.64 (m, 5H), 1.43 (s, 9H), 1.38-1.23 (m, 3H); ^{13}C NMR ($CDCl_3$) 162.39 (d, *J* = 238 Hz), 156.01 (d, *J* = 4.7 Hz), 154.69, 145.26 (d, *J* = 15.5 Hz), 143.09, 119.57 (d, *J* = 4.4 Hz), 118.37 (d, *J* = 30.6 Hz), 111.46, 79.49, 72.78, 43.56 (br), 42.40, 32.58, 28.63, 28.39, 27.04, 22.94; IR (neat) 3396, 2926, 2857, 1664, 1407 cm^{-1}; HRMS (FAB): calcd for $C_{20}H_{30}FN_2O_3$ $[M+H]^+$ 365.2240, found 365.2241.

4-[(1*R*,1*S*)-Benzyloxy-(1-*tert*-butoxycarbonyl-piperidin-4-yl)-methyl]-2-fluoro-3-(2-methyl-allyl)-pyridine (19). The general procedure applied on alcohol **18** (0.85 g, 2.3 mmol) in THF (45 mL) yielded a crude oil which was purified by flash chromatography using EtOAc/heptane (1:2) as eluent to afford **19** (1.0 g, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.06 (d, 1H, *J* = 5.1 Hz), 7.30-7.17 (m, 6H), 4.75

(s, 1H), 4.37-4.26 (m, 3H), 4.16-3.96 (m, 3H), 3.31 (d, 1H, *J* = 16.5), 3.22 (d, 1H, *J* = 16.5 Hz), 2.56-2.41 (m, 2H), 1.86-1.58 (m, 5H), 1.44-1.12 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 162.68 (d, *J* = 238 Hz), 154.69, 154.18 (d, *J* = 4.4 Hz), 145.35 (d, *J* = 15.8 Hz), 142.60, 137.66, 128.36, 127.79, 127.65, 119.92 (d, *J* = 3.4 Hz), 119.55 (d, *J* = 30.6 Hz), 111.79, 80.01, 79.39, 71.33, 43.60 (br), 42.55, 32.64, 28.74, 28.40, 27.41, 22.86; IR (neat) 2973, 2930, 2857, 1687, 1407 cm^{-1}; HRMS (FAB) calcd for $C_{27}H_{36}FN_2O_3$ $[M+H]^+$ 455.2710, found 455.2705.

2-{4-[(1*R*,1*S*)-Benzyloxy-1-(1-*tert*-butoxycarbonyl-piperidin-4-yl)-methyl]-3-(2-methyl-allyl)-pyridin-2-yloxy}-acetamide (20). The general procedure was applied on pyridine derivative **19** (0.97 g, 2.1 mmol) in DMSO (2 mL total volume). The reaction was stirred at room temperature over night. The work-up procedure described above yielded a crude oil which was purified by flash chromatography using EtOAc/heptane (2:1) as eluent to afford racemic **20** (0.46 g, 53%) as a white solid: ^{1}H NMR ($CDCl_3$) (rotamers) δ 8.12-8.05 (m, 1H), 7.37-7.22 (m, 5H), 7.10-7.05 (m, 1H), 6.45-6.32 (m, 1H), 5.94-5.75 (m, 1.5H), 5.04 (d, 0.3H, *J* = 15.7 Hz), 4.88-4.71 (m, 2.2H) 4.45-4.27 (m, 3H), 4.17-3.98 (m, 3H), 3.41-3.28 (m, 1H), 2.64-2.46 (m, 2H), 1.98-1.83 (m, 3H), 1.75-1.64 (m, 1H), 1.55 (s, 2H), 1.43 (s, 9H), 1.36-1.14 (m, 3H); ^{13}C NMR ($CDCl_3$) (rotamers) δ 171.89, 171.66, 160.40, 159.16, 154.76, 154.72, 151.37, 151.15, 145.31, 144.77, 144.73, 139.26, 137.94, 137.85, 128.34, 127.73, 127.69, 127.66, 120.70, 119.89, 116.74, 116.16, 115.92, 110.28, 80.32, 79.37, 79.34, 71.25, 70.95, 64.93, 64.26, 43.75 (br), 42.51, 42.38, 33.12, 28.79, 28.43, 28.21, 28.08, 27.78, 25.34, 23.50, 20.00; IR (neat) 3465, 2973, 2936, 2862, 1683, 1399 cm^{-1}; HRMS (FAB): calcd for $C_{29}H_{40}N_3O_5$ $[M+H]^+$ 510.2968, found 510.2974.

2-{4-[1-(1-*tert*-Butoxycarbonyl-piperidin-4-yl)-(1*R*,1*S*)-hydroxy-methyl]-3-isobutyl-pyridin-2-yloxy}-acetamide (21). The general procedure was applied on **20** (0.38 g, 0.73 mmol) and Pd/C (5wt%, 80 mg) in THF (7 mL). The reaction was stirred for three days with additional Pd/C (50 mg) added twice. Work-up afforded **21** (0.23 mg, 72%) as a white foam: ^{1}H NMR (CD_3OD) δ 7.98 (d, 1H, *J* = 5.3

Hz), 7.12 (d, 1H, *J* = 5.3 Hz), 4.93-4.84 (m, 1H), 4.76-4.69 (m, 2H), 4.20-4.02 (m, 2H), 2.80 (dd, 1H, *J* = 13.5, 6.4 Hz), 2.76-2.58 (m, 2H), 2.48 (dd, 1H, *J* = 13.5, 8.0 Hz), 2.07-1.85 (m, 3H), 1.84-1.70 (m, 1H), 1.47 (s, 9H), 1.39-1.22 (m, 2H), 1.01 (d, 3H, *J* = 6.6 Hz), 0.96 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (CD_3OD) δ 174.58, 162.10, 156.43, 154.56, 144.63, 122.76, 117.12, 80.93, 73.34, 65.34, 44.91 (br), 44.34, 34.98, 30.37, 29.84, 28.80, 23.26, 22.66; IR 3374, 3188, 2953, 2867, 1662 and 1431 cm^{-1}; HRMS (FAB) calcd for $C_{22}H_{36}N_3O_5$ $[M+H]^+$ 422.2655, found 422.2654.

2-[4-(1-*tert*-Butoxycarbonyl-piperidine-4-carbonyl)-3-methyl-pyridin-2-yloxy]-acetamide (22). The general procedure was applied on alcohol **21** (40 mg, 0.095 mmol) in CH_2Cl_2 (20 mL) with DMSO (1 mL) as co-solvent for 4 hours. Purification by flash chromatography (EtOAc) afforded **22** (38 mg, 95%) as a white solid: ^{1}H NMR (CD_3OD) δ 8.10 (d, 1H, *J* = 5.1 Hz), 7.09 (d, 1H, *J* = 5.1 Hz), 4.89-4.83 (m, 2H), 4.15-4.07 (m, 2H), 3.27-3.13 (m, 1H), 2.99-2.78 (m, 2H), 2.64 (d, 2H, *J* = 7.4 Hz), 2.08-1.95 (m, 1H), 1.91-1.81 (m, 2H), 1.57-1.43 (m, 11H), 0.90 (d, 6H, *J* = 7.0 Hz); ^{13}C NMR (CD_3OD) δ 207.77, 174.18, 162.86, 156.36, 150.10, 145.43, 123.10, 116.30, 81.18, 65.39, 48.73, 44.33 (br, 36.05, 30.23, 28.75, 28.67, 22.95; IR (neat) 3475, 3375, 3193, 2955, 2867, 1666, 1397 cm^{-1}; HRMS (FAB) calcd for $C_{22}H_{34}N_3O_5$ $[M+H]^+$ 420.2498, found 420.2503.

2-[3-Isobutyl-4-(piperidine-4-carbonyl)-pyridin-2-yloxy]-acetamide TFA-salt (5). The general procedure was applied on carbamate **22** (24 mg, 0.057 mmol) in CH_2Cl_2:TFA (2 mL total volume) for 7 min. Freeze-drying allowed isolation of the TFA-salt of **5** (13 mg, 51%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 8.75 (br s, 1H), 8.40 (br s, 1H), 8.11 (d, 1H, *J* = 5.2 Hz), 7.33 (br s, 1H), 7.16 (br s, 1H), 7.14 (d, 1H, *J* = 5.2 Hz), 4.71 (s, 2H), 3.45-3.26 (m, 3H), 3.01-2.87 (m, 2H), 2.53 (d, 2H, *J* = 7.2 Hz), 1.98-1.86 (m, 3H), 1.72-1.58 (m, 2H), 0.81 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 205.55, 169.71, 161.40, 147.47, 144.26, 120.98, 114.78, 64.08, 44.10, 42.54, 34.39, 28.27, 24.17, 22.45; IR (neat) 2960, 1669, 1198, 1137 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{26}N_3O_3$ $[M+H]^+$ 320.1974, found 320.1970.

Synthesis of compound 6 according to the general procedure described in the main text.

2-{3-Isobutyl-4-[(2S)-pyrrolidine-2-yl]-(1S)-hydroxy-methyl]-pyridin-2-yloxy}-acetamide TFA-salt (6). The general procedure was applied on carbamate **23** (20 mg, 0.049 mmol) in CH_2Cl_2:TFA (2 mL total volume) for 8 minutes. Freeze-drying allowed isolation of the TFA-salt of **6** (12 mg, 56%) as a white solid: $[\alpha]_D$ –2.4 (*c* 0.8, DMSO); ^{1}H NMR (DMSO-d_6) δ 9.26 (br s, 1H), 8.71 (br s, 1H), 8.00 (d, 1H, *J* = 5.3 Hz), 7.27 (s, 1H), 7.16 (s, 1H), 7.09 (d, 1H, *J* = 5.3 Hz), 6.33 (br s, 1H), 5.00 (d, 1H, *J* = 8.1 Hz), 4.70 (d, 1H, *J* = 14.8 Hz), 4.64 (d, 1H, *J* = 14.8 Hz), 3.88-3.35 (m, 2H), 3.33-3.21 (m, 1H), 3.19-3.07 (m, 1H), 2.68 (dd, 1H, *J* = 13.5, 6.9 Hz), 2.54-2.42 (m, 1H), 2.02-1.77 (m, 3H), 1.73-1.61 (m, 1H), 1.58-1.45 (m, 1H), 0.92 (d, 3H, *J* = 6.8 Hz), 0.89 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (DMSO-d_6) δ 169.94, 160.83, 150.26, 143.93, 121.11, 115.26, 67.21, 64.63, 63.99, 44.97, 33.38, 28.48, 26.42, 23.28, 22.65, 22.18.