Supporting Information

Ugi 4-CR Synthesis of γ- and δ-Lactams

André Boltjes, a George P. Liao, a Ting Zhao, a Eberhardt Herdtweck, b and Alexander Dömling‡* a,c

[a] Department of Drug Design, University of Groningen, The Netherlands  
[b] Technische Universität München  
[c] University of Pittsburgh

Email: A.S.S.Domling@rug.nl
Table of Contents

General ....................................................................................................................................................................2
Synthetic Procedures and characterization data for compounds 5a-j and 6a-j ..............................................3
$^1$H NMR and $^{13}$C NMR spectra of compounds 5a-j and 6a-j .................................................................8
Single Crystal X-Ray Structure Determination of Compounds 6b, 6e, 6f, and 6j ....................................28
SFC-MS Chromatograms of compounds 6a-j .................................................................................................37
PDB Analysis – Interaction distances of gamma lactams found in the PDB database ..........................47
General

All isonitriles were made in house by either performing the Hoffman or Ugi procedure. Other reagents were purchased from Sigma Aldrich, ABCR, Acros and AK Scientific and were used without further purification. All microwave irradiation reactions were carried out in a Biotage Initiator™ Microwave Synthesizer. The Ugi tetrazoles were purified by flash chromatography, on a Teledyne ISCO Rf 200, using RediSep Rf Normal-phase Silica Flash Columns (Silica Gel 60 Å, 230 - 400 mesh) unless otherwise noted. Column chromatography was performed with MP Ecochrom Silica Gel 32–63, 60 Å. $^1$H (500 MHz) and $^{13}$C (125 MHz) NMR spectra were recorded on a Bruker Avance DRX 500. Chemical shift values are reported as part per million ($\delta$) relative to residual solvent peaks (CDCl$_3$, $^1$H $\delta$ = 7.26, $^{13}$C $\delta$ = 77.16 or TMS $^1$H $\delta$ = 0.00 ppm). The coupling constants (J) are reported in Hertz (Hz). Electrospray ionization mass spectra were measured on an API 3000 triple-quadrupole mass spectrometer (Applied Biosystems/MDS Sciex) via a TurboIonSpray source. Data collected and analyzed by the Analyst 1.5 data acquisition software (Applied Biosystems/MDS Sciex).

Crystallographic data were collected on an X-ray single crystal diffractometer equipped with a CCD detector (Bruker APEX II, $\kappa$-CCD), a fine focus sealed tube (Bruker AXS, D8) with MoK$_\alpha$ radiation ($\lambda = 0.71073$ Å), and a graphite monochromator by using the SMART software package. [1] The measurements were performed on single crystals coated with perfluorinated ether. The crystals were fixed on the top of a cactus prickle (Opuntia ficus-india) with perfluorinated ether and transferred to the diffractometer. The crystals were frozen under a stream of cold nitrogen. A matrix scan was used to determine the initial lattice parameters. Reflections were merged and corrected for Lorenz and polarization effects, scan speed, and background using SAINT. [2] Absorption corrections, including odd and even ordered spherical harmonics were performed using SADABS. [2] Space group assignments were based upon systematic absences, $E$ statistics, and successful refinement of the structures. Structures were solved by direct methods with the aid of successive difference Fourier maps, and were refined against all data using WinGX [7] based on SIR-92. [3] If not mentioned otherwise, non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms could be located in the difference Fourier maps and were allowed to refine freely. Full-matrix least-squares refinements were carried out by minimizing $\Sigma w(F_o^2-F_c^2)^2$ with SHELXL-97 [5] weighting scheme. Neutral atom scattering factors for all atoms and anomalous dispersion corrections for the non-hydrogen atoms were taken from International Tables for Crystallography. [4] Images of the crystal structures were generated by PLATON. [6] CCDC 961190 (6b), CCDC 961191 (6e), CCDC 961188 (6f), and CCDC 961189 (6j) contains the supplementary crystallographic data for this compound. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or via https://www.ccdc.cam.ac.uk/services/structure_deposit/
Synthetic Procedures and characterization data for compounds 5a-j and 6a-j

Synthetic procedure 1
Aldehyde (1 mmol), tritylamine (1 mmol) were mixed in methanol (1 mL) and subjected to microwave irradiation for 15 minutes. Subsequently azidotrimethylsilane (1 mmol) and isonitrile (1 mmol) were added and the mixture was again subjected to microwave irradiation for 15 minutes at 100°C. The solvent was evaporated under reduced pressure and the residue was purified using flash chromatography to obtain the product.

Synthetic procedure 2
To a solution of Ugi tetrazole (0.5-1.0 mmol) in 3 mL CH$_2$Cl$_2$ was added TFA (150 µL, 2 mmol). After 1 minute the mixture was filtered through a silica bed washing with 50 mL Heptane:EtOAc 1:1 (v/v) to remove the trityl cation impurity. The amine was collected by washing the silica bed with 50 mL CH$_2$Cl$_2$:MeOH 1:1 (v/v). The mixture was concentrated under reduced pressure and redissolved in dry THF (3 mL). Sodium hydride (5 mmol) was washed with heptanes prior to addition. After 4 hours of stirring, EtOH was added to quench the reaction. The solvents were removed under reduced pressure, and the residue was purified by column chromatography using CH$_2$Cl$_2$:MeOH 20:1 (v/v) to afford the lactam.

Methyl 4-(1-(tert-butyl)-1H-tetrazol-5-yl)-4-(tritylamino)butanoate (5a): The product was obtained using procedure 1 starting from t-butylisocyanide and 3a as a white solid (354 mg, 73%): $R_f$ 0.50 (EtOAc:Hept 1:1).

$^1$H NMR (500MHz, CDCl$_3$): $\delta$ 7.40 (d, $J$ = 7.5, 6H), 7.19 (t, $J$ = 7.5, 9H), 7.13 (t, $J$ = 7.2, 3H), 4.41 (s, 1H), 3.63 (s, 3H), 3.49 (s, 1H), 2.80 – 2.67 (m, 1H), 2.49 – 2.34 (m, 1H), 2.28 – 2.22 (m, 1H), 1.87 – 1.80 (m, 1H), 1.42 (s, 9H) ppm.

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 173.7, 156.8, 145.6, 128.9, 127.9, 126.7, 71.7, 61.8, 51.8, 48.4, 32.3, 29.9, 28.3 ppm. HRMS (ESI): m/z, calcd. for C$_{26}$H$_{37}$O$_2$N$_5$Na [M + Na$^+$]: 506.2527, found 506.2529.

Methyl 4-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)-4-(tritylamino)butanoate (5b): The product was obtained using procedure starting from t-octylisocyanide and 3a as a white solid (269 mg, 50%): $R_f$ 0.50 (EtOAc:Hept 1:1).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.39 (d, $J$ = 7.5, 6H), 7.19 (t, $J$ = 7.5, 6H), 7.14 (t, $J$ = 7.2, 3H), 4.50 – 4.40 (m, 1H), 3.62 (s, 3H), 3.54 (d, $J$ = 9.0, 1H), 2.74 – 2.60 (m, 1H), 2.35 – 2.25 (m, 1H), 2.20 – 2.13 (m, 1H), 1.90 – 1.83 (m, 1H), 1.73 (q, $J$ = 14.8, 2H), 1.52 (s, 3H), 1.43 (s, 3H), 0.81 (s, 9H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 173.6, 157.0, 145.7, 129.0, 127.9, 126.8, 71.7, 66.1, 55.2, 51.7, 48.6, 32.2, 31.6, 31.1, 29.9, 28.5, 28.4 ppm. HRMS (ESI): m/z, calcd. for C$_{33}$H$_{41}$O$_2$N$_5$Na [M + Na$^+$]: 562.3153, found 562.3154.

Methyl 4-(1-phenethyl-1H-tetrazol-5-yl)-4-(tritylamino)butanoate (5c): The product was obtained using procedure 1 starting from phenethylisocyanide and 3a as a white solid (398 mg, 75%): $R_f$ 0.50 (EtOAc:Hept 1:1).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.35 (d, $J$ = 7.5, 6H), 7.27 – 7.09 (m, 13H), 7.00 (d, $J$ = 7.2, 2H), 4.02 – 3.84 (m, 2H), 3.81 – 3.71 (m, 1H), 3.64 (s, 3H), 3.15 – 2.96 (m, 3H), 2.56 – 2.40 (m, 1H), 2.18 – 2.02 (m, 1H), 1.93 – 1.87 (m, 1H), 1.43 – 1.37 (m, 1H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 173.33, 157.0, 145.7, 129.0, 126.8, 71.7, 66.1, 55.2, 51.7, 48.6, 32.2, 31.6, 31.1, 29.9, 28.5, 28.4 ppm. HRMS (ESI): m/z, calcd. for C$_{33}$H$_{33}$O$_2$N$_5$Na [M + Na$^+$]: 562.3153, found 562.3154.
Methyl 4-(1-benzyl-1H-tetrazol-5-yl)-4-(tritylamino)butanoate (5d): The product was obtained using procedure 1 starting from benzylisocyanide and 3a as a white solid (290 mg, 56%): R<sub>f</sub> 0.50 (EtOAc:Hept 1:1). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.32 (d, <sup>J</sup> = 8.1, 6H), 7.24 – 7.27 (m, 3H), 7.20 – 7.11 (m, 9H), 7.05 (d, <sup>J</sup> = 6.7, 2H), 5.21 (d, <sup>J</sup> = 15.3, 1H), 4.76 (d, <sup>J</sup> = 15.3, 1H), 4.14 – 4.10 (m, 1H), 3.58 (s, 3H), 3.00 (d, <sup>J</sup> = 9.2, 1H), 2.47 – 2.41 (m, 1H), 2.20 – 2.07 (m, 1H), 1.96 – 1.89 (m, 1H), 1.59 – 1.53 (m, 1H), 1.33 – 1.24 (m, 1H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 173.31, 157.08, 145.21, 133.28, 129.14, 128.92, 128.58, 128.00, 126.83, 71.49, 51.73, 50.82, 47.06, 31.50, 28.86 ppm. HRMS (ESI): m/z, calcd. for C<sub>32</sub>H<sub>31</sub>O<sub>2</sub>N<sub>5</sub>Na [M + Na<sup>+</sup>]: 540.2372, found 540.2372.

Methyl 4-(1-cyclohexyl-1H-tetrazol-5-yl)-4-(tritylamino)butanoate (5e): The product was obtained using procedure 1 starting from cyclohexylisocyanide and 3a as a white solid (203 mg, 40%): R<sub>f</sub> 0.50 (EtOAc:Hept 1:1). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.40 (d, <sup>J</sup> = 8.1, 6H), 7.20 (t, <sup>J</sup> = 7.5, 6H), 7.15 (t, <sup>J</sup> = 6.8, 3H), 4.16 – 4.02 (m, 1H), 3.78 – 3.68 (m, 1H), 3.61 (s, 3H), 3.12 (d, <sup>J</sup> = 8.3, 1H), 2.68 – 2.49 (m, 1H), 2.34 – 2.13 (m, 2H), 1.96 – 1.76 (m, 4H), 1.76 – 1.57 (m, 4H), 1.37 – 1.18 (m, 3H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 173.33, 156.11, 145.39, 128.74, 127.97, 126.85, 71.80, 57.45, 51.77, 47.09, 33.59, 32.02, 31.99, 28.88, 25.34, 25.29, 24.80 ppm. HRMS (ESI): m/z, calcd. for C<sub>31</sub>H<sub>35</sub>O<sub>2</sub>N<sub>5</sub>Na [M + Na<sup>+</sup>]: 532.2683, found 532.2685.

Methyl 5-(1-(tert-butyl)-1H-tetrazol-5-yl)-5-(tritylamino)pentanoate (5f): The product was obtained using procedure 1 starting from t-butylisocyanide and 3b as a white solid (389 mg, 78%): R<sub>f</sub> 0.50 (EtOAc:Hept 1:1). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.43 (d, <sup>J</sup> = 8.0, 6H), 7.20 (t, <sup>J</sup> = 7.5, 6H), 7.15 (t, <sup>J</sup> = 6.8, 3H), 4.16 – 4.02 (m, 1H), 3.78 – 3.68 (m, 1H), 3.61 (s, 3H), 3.12 (d, <sup>J</sup> = 8.3, 1H), 2.68 – 2.49 (m, 1H), 2.34 – 2.13 (m, 2H), 1.96 – 1.76 (m, 4H), 1.76 – 1.57 (m, 4H), 1.37 – 1.18 (m, 3H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 173.47, 157.18, 145.78, 129.0, 128.95, 127.91, 126.69, 71.75, 61.64, 51.57, 49.33, 37.13, 33.91, 30.02, 19.88 ppm. HRMS (ESI): m/z, calcd. for C<sub>30</sub>H<sub>35</sub>O<sub>2</sub>N<sub>5</sub>Na [M + Na<sup>+</sup>]: 520.2683, found 520.2686.

Methyl 5-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)-5-(tritylamino)pentanoate (5g): The product was obtained using procedure 1 starting from t-octylisocyanide and 3b as a white solid (343 mg, 62%): R<sub>f</sub> 0.50 (EtOAc:Hept 1:1). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.43 (d, <sup>J</sup> = 8.0, 6H), 7.20 (t, <sup>J</sup> = 7.5, 6H), 7.15 (t, <sup>J</sup> = 7.0, 3H), 4.34 – 4.25 (m, 1H), 3.62 (s, 3H), 3.40 (d, <sup>J</sup> = 9.3, 1H), 2.25 (t, <sup>J</sup> = 6.9, 2H), 1.94 – 1.70 (m, 2H), 1.64 – 1.48 (m, 2H), 1.41 (s, 9H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 173.4, 157.2, 145.9, 129.0, 128.95, 127.91, 126.69, 71.75, 61.64, 51.57, 49.33, 37.13, 33.91, 30.02, 19.88 ppm. HRMS (ESI): m/z, calcd. for C<sub>30</sub>H<sub>35</sub>O<sub>2</sub>N<sub>5</sub>Na [M + Na<sup>+</sup>]: 520.2683, found 520.2686.
Methyl 5-(1-phenethyl-1H-tetrazol-5-yl)-5-(tritylamino)pentanoate (5h): The product was obtained using procedure 1 starting from phenethylisocyanide and 3b as a white solid (235 mg, 43%): Rf 0.50 (EtOAc:Hept 1:1). 1H NMR (500 MHz, CDCl3) δ 7.35 (d, J = 7.6, 6H), 7.29 – 7.21 (m, 3H), 7.19 (t, J = 7.4, 6H), 7.16 – 7.10 (m, 3H), 7.00 (d, J = 6.5, 2H), 4.04 – 3.92 (m, 1H), 3.85 – 3.69 (m, 2H), 3.65 (s, 3H), 3.13 – 2.99 (m, 2H), 2.93 (d, J = 8.3, 1H), 2.19 – 2.01 (m, 2H), 1.62 – 1.48 (m, 1H), 1.42 – 1.30 (m, 2H), 1.25 – 1.14 (m, 1H) ppm. 13C NMR (125 MHz, CDCl3) δ 173.3, 157.4, 145.2, 136.8, 129.0, 128.8, 128.6, 128.0, 127.3, 126.8, 71.7, 51.6, 48.7, 48.0, 36.4, 35.5, 33.6, 20.3 ppm. HRMS (ESI): m/z, calcd. for C34H43O2N5Na [M + Na]+: 576.3309, found 576.3310.

Methyl 5-(1-benzyl-1H-tetrazol-5-yl)-5-(tritylamino)pentanoate (5i): The product was obtained using procedure 1 starting from benzylisocyanide and 3b as a white solid (364 mg, 68%): Rf 0.50 (EtOAc:Hept 1:1). 1H NMR (500 MHz, CDCl3) δ 7.36 (d, J = 7.4, 6H), 7.31 – 7.24 (m, 3H), 7.21 (t, J = 7.3, 6H), 7.19 – 7.13 (m, 3H), 7.01 (d, J = 5.5, 2H), 5.29 (d, J = 15.4, 1H), 4.68 (d, J = 15.4, 1H), 4.02 – 3.91 (m, 1H), 1.96 (t, J = 6.9, 2H), 1.54 – 1.43 (m, 1H), 1.32 – 1.16 (m, 3H) ppm. 13C NMR (125 MHz, CDCl3) δ 173.1, 157.3, 145.3, 133.6, 129.1, 128.9, 128.6, 128.0, 127.7, 126.9, 71.6, 51.5, 50.9, 48.0, 36.4, 35.5, 33.6, 20.3 ppm. HRMS (ESI): m/z, calcd. for C33H33O2N5Na [M + Na]+: 554.2527, found 554.2527.

Methyl 5-(1-cyclohexyl-1H-tetrazol-5-yl)-5-(tritylamino)pentanoate (5j): The product was obtained using procedure 1 starting from cyclohexylisocyanide and 3b as a white solid (214 mg, 41%): Rf 0.50 (EtOAc:Hept 1:1). 1H NMR (500 MHz, CDCl3) δ 7.41 (d, J = 7.5, 6H), 7.21 (t, J = 7.3, 6H), 7.15 (t, J = 7.2, 3H), 4.07 – 3.95 (m, 1H), 3.89 – 3.75 (m, 1H), 3.60 (s, 3H), 2.90 (d, J = 7.3, 1H), 2.22 – 2.06 (m, 2H), 1.96 – 1.62 (m, 8H), 1.58 – 1.45 (m, 1H), 1.43 – 1.19 (m, 5H) ppm. 13C NMR (125 MHz, CDCl3) δ 173.3, 156.3, 145.5, 133.6, 129.1, 128.9, 128.6, 128.0, 127.7, 126.9, 71.6, 51.5, 50.9, 48.0, 36.1, 33.6, 20.2 ppm. HRMS (ESI): m/z, calcd. for C32H37O2N5Na [M + Na]+: 546.2840, found 546.2841.

5-(1-(tert-butyl)-1H-tetrazol-5-yl)pyrrolidin-2-one (6a): The product was obtained using procedure 2 starting...
from 5a as a white solid (74 mg, 55%): ¹H NMR (500 MHz, CDCl₃) δ 7.69 (s, 1H), 5.40 – 5.13 (m, 1H), 2.75 – 2.57 (m, 2H), 2.43 – 2.31 (m, 2H), 1.80 – 1.75 (m, 9H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 178.7, 155.8, 61.6, 49.1, 30.3, 29.3, 28.1 ppm. HRMS (ESI): m/z, calcd. for C₉H₁₆O₁N₅ [M + H⁺]: 210.1349, found 210.1350.

5-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)pyrrolidin-2-one (6b): The product was obtained using procedure 2 starting from 5b as a white solid (154 mg, 89%): ¹H NMR (500 MHz, CDCl₃) δ 7.75 (s, 1H), 5.35 – 5.20 (m, 1H), 2.78 – 2.56 (m, 2H), 2.46 – 2.31 (m, 2H), 1.97 (q, J = 15.3, 2H), 1.86 (d, J = 3.4, 6H), 0.79 (s, 9H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 178.7, 156.3, 65.0, 54.3, 49.3, 31.8, 30.8, 30.5, 29.4, 28.2 ppm. HRMS (ESI): m/z, calcd. for C₁₃H₂₄O₁N₅ [M + H⁺]: 266.1975, found 266.1977.

5-(1-phenethyl-1H-tetrazol-5-yl)pyrrolidin-2-one (6c): The product was obtained using procedure 2 starting from 5c as a white solid (60 mg, 32%): ¹H NMR (500 MHz, CDCl₃) δ 7.28 (d, J = 4.2, 3H), 7.06 – 6.91 (m, 2H), 6.82 (s, 1H), 4.71 – 4.46 (m, 2H), 4.44 – 4.25 (m, 1H), 3.37 – 3.11 (m, 2H), 2.54 – 2.37 (m, 1H), 2.33 – 2.08 (m, 2H), 2.08 – 1.87 (m, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 178.3, 155.8, 136.6, 129.3, 129.0, 127.8, 49.3, 47.2, 36.4, 29.3, 26.5 ppm. MS (ESI) (m/z) 258.1 [M+H]⁺. HRMS (ESI): m/z, calcd. for C₁₃H₁₆O₁N₅ [M + H⁺]: 258.1349, found 258.1348.

5-(1-benzyl-1H-tetrazol-5-yl)pyrrolidin-2-one (6d): The product was obtained using procedure 2 starting from 5d as a white solid (98 mg, 72%): ¹H NMR (500 MHz, CDCl₃) δ 7.83 (s, 1H), 7.37 (d, J = 6.3, 3H), 7.28 – 7.17 (m, 2H), 5.67 (dd, J = 47.8, 15.6, 2H), 5.02 – 4.88 (m, 1H), 2.44 – 2.33 (m, 1H), 2.33 – 2.18 (m, 2H), 2.05 – 1.90 (m, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 178.7, 155.5, 133.3, 129.4, 129.2, 127.7, 51.3, 47.9, 29.2, 26.3 ppm. HRMS (ESI): m/z, calcd. for C₁₂H₁₄O₁N₅ [M + H⁺]: 244.1193, found 244.1192.

5-(1-cyclohexyl-1H-tetrazol-5-yl)pyrrolidin-2-one (6e): The product was obtained using procedure 2 starting from 5e as a white solid (110 mg, 95%): ¹H NMR (500 MHz, CDCl₃) δ 7.84 (d, J = 26.2, 1H), 5.18 – 4.93 (m, 1H), 4.37 – 4.14 (m, 1H), 2.74 – 2.55 (m, 2H), 2.53 – 2.33 (m, 2H), 2.13 – 1.91 (m, 6H), 1.78 (d, J = 12.7, 1H), 1.53 – 1.40 (m, 3H), 1.39 – 1.26 (m, 1H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ 178.7, 154.5, 58.2, 47.7, 33.5, 32.7, 29.5, 26.8, 25.2, 25.1, 24.8 ppm. HRMS (ESI): m/z, calcd. for C₁₁H₁₈O₁N₅ [M + H⁺]: 236.1506, found 236.1506.

6-(1-(tert-butyl)-1H-tetrazol-5-yl)piperidin-2-one (6f): The product was obtained using procedure 2 starting
from 5f as a white solid (120 mg, 76%): $^1$H NMR (500 MHz, CDCl$_3$) δ 7.48 (s, 1H), 5.22 – 5.09 (m, 1H), 2.46 – 2.37 (m, 1H), 2.36 – 2.27 (m, 1H), 2.20 – 2.08 (m, 2H), 2.07 – 1.98 (m, 1H), 1.77 (s, 10H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.1, 155.4, 61.6, 47.9, 30.9, 30.2, 28.0, 18.6 ppm. [M+H]$^+$ HRMS (ESI): m/z, calcd. for C$_{10}$H$_{18}$O$_1$N$_5$ [M + H$^+$]: 224.1506, found 224.1507.

6-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)piperidin-2-one (6g): The product was obtained using procedure 2 starting from 5g as a white solid (50 mg, 42%): $^1$H NMR (500 MHz, CDCl$_3$) δ 6.58 (d, $J = 25.2$, 1H), 5.15 (t, $J = 6.1$, 1H), 2.59 – 2.39 (m, 2H), 2.28 – 2.10 (m, 3H), 1.94 (q, $J = 15.3$, 2H), 1.86 (d, $J = 12.9$, 7H), 1.83 – 1.71 (m, 1H), 0.79 (s, 9H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.8, 155.6, 65.2, 54.5, 48.6, 31.9, 31.1, 30.8, 30.7, 30.7, 28.4, 19.0 ppm. HRMS (ESI): m/z, calcd. for C$_{14}$H$_{26}$O$_1$N$_5$ [M + H$^+$]: 280.2132, found 280.2131.

6-(1-phenethyl-1H-tetrazol-5-yl)piperidin-2-one (6h): The product was obtained using procedure 2 starting from 5h as a white solid (43 mg, 40%): $^1$H NMR (500 MHz, CDCl$_3$) δ 7.27 (d, $J = 6.7$, 3H), 7.06 – 6.91 (m, 3H), 4.65 – 4.46 (m, 2H), 4.28 (t, $J = 5.8$, 1H), 3.31 – 3.16 (m, 2H), 2.28 – 2.19 (m, 2H), 1.94 – 1.81 (m, 1H), 1.67 – 1.44 (m, 3H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.1, 155.4, 136.6, 129.2, 128.9, 127.7, 49.4, 46.7, 36.3, 31.0, 26.9, 18.8 ppm. HRMS (ESI): m/z, calcd. for C$_{14}$H$_{18}$O$_1$N$_5$ [M + H$^+$]: 272.1506, found 272.1506.

6-(1-benzyl-1H-tetrazol-5-yl)piperidin-2-one (6i): The product was obtained using procedure 2 starting from 5i as a white solid (78 mg, 99%): $^1$H NMR (500 MHz, CDCl$_3$) δ 7.44 – 7.33 (m, 3H), 7.24 (s, 1H), 7.23 – 7.17 (m, 2H), 5.66 (s, 2H), 4.91 – 4.81 (m, 1H), 2.37 – 2.21 (m, 2H), 1.98 – 1.82 (m, 2H), 1.77 – 1.59 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 172.5, 155.1, 133.6, 129.5, 129.2, 127.5, 151.8, 133.6, 129.5, 129.2, 127.7, 51.6, 47.4, 31.1, 25.0, 18.8 ppm. HRMS (ESI): m/z, calcd. for C$_{13}$H$_{16}$O$_1$N$_5$ [M + H$^+$]: 258.1349, found 258.1349.

6-(1-cyclohexyl-1H-tetrazol-5-yl)piperidin-2-one (6j): The product was obtained using procedure 2 starting from 5j as a white solid (75 mg, 79%): $^1$H NMR (500 MHz, CDCl$_3$) δ 7.50 (s, 1H), 4.95 (t, $J = 5.6$, 1H), 4.38 – 4.19 (m, 1H), 2.48 – 2.32 (m, 2H), 2.23 – 1.91 (m, 10H), 1.91 – 1.82 (m, 1H), 1.82 – 1.70 (m, 1H), 1.51 – 1.39 (m, 2H), 1.39 – 1.30 (m, 1H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.4, 154.1, 58.3, 46.9, 33.6, 32.9, 31.1, 27.5, 25.3, 25.3, 24.8, 18.9 ppm. HRMS (ESI): m/z, calcd. for C$_{12}$H$_{20}$O$_1$N$_5$ [M + H$^+$]: 250.1662, found 250.1662.
$^1$H NMR and $^{13}$C NMR spectra of compounds 5a-j and 6a-j

Compound 5a $^1$H NMR
Compound 5a $^{13}$C NMR

![Compound 5a $^{13}$C NMR spectrum](image-url)
Compound 5b \textsuperscript{1}H NMR

Compound 5b \textsuperscript{13}C NMR
Compound 5c 1H NMR

Compound 5c 13C NMR
Compound 5d $^1$H NMR

![NMR Spectrum](image)

Compound 5d $^{13}$C NMR

![NMR Spectrum](image)
Compound 5e $^1$H NMR

Compound 5e $^{13}$C NMR
Compound 5f $^1$H NMR

Compound 5f $^{13}$C NMR
Compound 5h $^1$H NMR

Compound 5h $^{13}$C NMR

Compound 5i $^1$H NMR
Compound 6b \(^1\)H NMR

Compound 6b \(^{13}\)C NMR
Compound 6c $^1$H NMR

Compound 6c $^{13}$C NMR
Compound 6d $^1$H NMR

Compound 6d $^{13}$C NMR
Compound 6e $^1$H NMR

Compound 6e $^{13}$C NMR
Compound 6f $^1$H NMR

Compound 6f $^{13}$C NMR
Compound 6g $^1$H NMR

Compound 6g $^{13}$C NMR
Compound 6h $^1$H NMR

Compound 6h $^{13}$C NMR
Compound 6i $^1$H NMR

Compound 6i $^{13}$C NMR
Single Crystal X-Ray Structure Determination of Compounds 6b, 6e, 6f, and 6j

**6b:** correction for extinction effects

**Compound 6b**

![Ortep drawing of compound 6b](image)

**Figure F1** – Ortep drawing of compound 6b with 50% ellipsoids. [6]

---

**Colorless fragment**

<table>
<thead>
<tr>
<th>Crystal Size</th>
<th>Operator: *** Herdtweck ***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Formula:</td>
<td>C\textsubscript{13}H\textsubscript{23}N\textsubscript{5}O</td>
</tr>
<tr>
<td>Crystal Color / Shape</td>
<td>Approximate size of crystal fragment used for data collection: 0.20 × 0.25 × 0.43 mm</td>
</tr>
<tr>
<td>Molecular Weight:</td>
<td>265.36 a.m.u.</td>
</tr>
<tr>
<td>( F_{000} ):</td>
<td>576</td>
</tr>
<tr>
<td>Systematic Absences:</td>
<td>h0l: l≠2n; 0k0: k≠2n</td>
</tr>
<tr>
<td>Space Group:</td>
<td>Monoclinic ( P 2_1/c ) (I.T.-No.: 14)</td>
</tr>
<tr>
<td>Cell Constants:</td>
<td>Least-squares refinement of 9399 reflections with the programs &quot;APEX suite&quot; and &quot;SAINT&quot; [1,2]; theta range 2.28° &lt; ( \theta ) &lt; 25.46°; Mo(K( \lambda )) ( \lambda ) = 71.073 pm</td>
</tr>
<tr>
<td>( a ) =</td>
<td>907.24(2) pm</td>
</tr>
<tr>
<td>( b ) =</td>
<td>1147.13(3) pm</td>
</tr>
<tr>
<td>( c ) =</td>
<td>1399.04(3) pm</td>
</tr>
<tr>
<td>( V ) =</td>
<td>1430.93(6) ( \times ) 10\textsuperscript{6} pm\textsuperscript{3}; ( Z ) = 4; ( D_{calc} ) = 1.232 g cm\textsuperscript{-3}; Mos. = 0.65</td>
</tr>
<tr>
<td>Diffractometer:</td>
<td>Kappa APEX II (Area Diffraction System; BRUKER AXS); sealed tube; graphite monochromator; 50 kV; 30 mA; ( \lambda ) = 71.073 pm; Mo(K( \lambda ))</td>
</tr>
<tr>
<td>Temperature:</td>
<td>(-173±1) °C; (100±1) K</td>
</tr>
<tr>
<td>Measurement Range:</td>
<td>2.28° &lt; ( \theta ) &lt; 25.46°; h: -10/10, k: -13/13, l: -16/16</td>
</tr>
</tbody>
</table>
Measurement Time: 2 × 15 s per film
Measurement Mode: measured: 11 runs; 4743 films / scaled: 11 runs; 4743 films
φ- and ω-movement; Increment: Δφ/Δω = 0.50°; dx = 40.0 mm
LP - Correction: Yes [2]
Intensity Correction: No/Yes; during scaling [2]
Absorption Correction: Multi-scan; during scaling; μ = 0.082 mm⁻¹ [2]
Correction Factors: T_{min} = 0.7079, T_{max} = 0.7452
Reflection Data:

- Reflections were integrated and scaled
- 1510 reflections systematic absent and rejected
- 47234 reflections to be merged
- 0.020 R_{int}: (basis F_o^2)
- 2636 independent reflections (all) were used in refinements
- 2468 independent reflections with I_o > 2σ(I_o)
- 100.0 % completeness of the data set
- 265 parameter full-matrix refinement
- 9.9 reflections per parameter

Solution: Direct Methods [3, 7]; Difference Fourier syntheses

Refinement Parameters:

- In the asymmetric unit:
  - 19 Non-hydrogen atoms with anisotropic displacement parameters
  - 23 Hydrogen atoms with isotropic displacement parameters

Hydrogen Atoms:

- All hydrogen atom positions were found in the difference map calculated from the model containing all non-hydrogen atoms. The hydrogen positions were refined with individual isotropic displacement parameters.

Atomic Form Factors:

- For neutral atoms and anomalous dispersion [4, 5, 7]

Extinction Correction:

- F_o(korr) = kF_o [1 + 0.001 · e · F_o^2 · λ³/sin(2θ)]^{1/4}
- SHELXL-97 [5, 7] e refined to ε = 0.0054(9)

Weighting Scheme:

- w = σ(F_o^2) + (a*P)^2 + b*P

with a: 0.0362; b: 0.5542; P: [Maximum(0 or F_o^2) + 2*F_o^2]/3

Shift/Err:

- Less than 0.001 in the last cycle of refinement:

Resid. Electron Density:

- +0.28 e Å⁻³; -0.17 e Å⁻³

R1:

- \[ \Sigma ||F_o|-|F_c||/\Sigma |F_o| \]
- [F_o > 4σ(F_o); N=2468]: = 0.0302
- [all reflcts; N=2636]: = 0.0320

wR2:

- \[ (\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2) \]^{1/2}
- [F_o > 4σ(F_o); N=2468]: = 0.0748
- [all reflcts; N=2636]: = 0.0764

Goodness of fit:

- [\Sigma w(F_o^2-F_c^2)^2/(NO-NV)]^{1/2}
- = 1.033

Remarks:

- Refinement expression \[ \Sigma w(F_o^2-F_c^2)^2 \]
Compound 6e

Figure F2 – Ortep drawing drawing of compound 6e with 50% ellipsoids. [6]

Operator: *** Herdtweck ***
Molecular Formula: C11 H17 N5 O
Crystal Color / Shape Colorless fragment
Crystal Size Approximate size of crystal fragment used for data collection:
0.28 x 0.41 x 0.51 mm
Molecular Weight: 235.30 a.m.u.
\( F_{000} \): 252
Systematic Absences: none
Space Group: Triclinic \( P \) (I.T.-No.: 2)
Cell Constants: Least-squares refinement of 9939 reflections with the programs "APEX suite" and "SAINT" [1,2]; theta range 2.14° < \( \theta \) < 25.38°; Mo(K \( \alpha \) ); \( \lambda = 71.073 \) pm
\( a = \) 654.62(2) pm \( \alpha = \) 65.9412(10)°
\( b = \) 925.70(2) pm \( \beta = \) 81.5752(11)°
\( c = \) 1055.29(3) pm \( \gamma = \) 89.9391(11)°
\( V = 576.41(3) \cdot 10^6 \) pm\(^3\); \( Z = 2; D_{\text{calc}} = 1.356 \) g cm\(^{-3}\); MOS. = 0.64

Diffractometer: Kappa APEX II (Area Diffraction System; BRUKER AXS); sealed tube; graphite monochromator; 50 kV; 30 mA; \( \lambda = 71.073 \) pm; Mo(K \( \alpha \))
Temperature: (-173±1) °C; \( (100\pm1) \) K
Measurement Range: 2.14 < \( \theta \) < 25.38°; h: -7/7, k: -11/11, l: -12/12
Measurement Time: 2 x 15 s per film
Measurement Mode: measured: 14 runs; 5785 films / scaled: 14 runs; 5785 films \( \varphi \)- and \( \omega \)-movement; Increment: \( \Delta \varphi / \Delta \omega = 0.50°; \) dx = 35.0 mm
LP - Correction: Yes [2]
Intensity Correction No/Yes; during scaling [2]
Absorption Correction: Multi-scan; during scaling; \( \mu = 0.093 \) mm\(^{-1}\) [2]
Correction Factors: \( T_{\text{min}} = 0.6876 \quad T_{\text{max}} = 0.7452 \)
Reflection Data: 19536 reflections were integrated and scaled
19536 reflections to be merged
2111 independent reflections
0.016 \quad R_{\text{int}}: \text{(basis } F_o^2) \\
2111 \quad \text{independent reflections (all) were used in refinements} \\
2033 \quad \text{independent reflections with } I_o > 2 \sigma(I_o) \\
99.9 \% \quad \text{completeness of the data set} \\
222 \quad \text{parameter full-matrix refinement} \\
9.5 \quad \text{reflections per parameter} \\

Solution: \quad \text{Direct Methods [3, 7]; Difference Fourier syntheses} \\
Refinement Parameters: \quad \text{In the asymmetric unit:} \\
17 \quad \text{Non-hydrogen atoms with anisotropic displacement parameters} \\
17 \quad \text{Hydrogen atoms with isotropic displacement parameters} \\

Hydrogen Atoms: \quad \text{All hydrogen atom positions were found in the difference map calculated from the model containing all non-hydrogen atoms. The hydrogen positions were refined with individual isotropic displacement parameters.} \\

Atomic Form Factors: \quad \text{For neutral atoms and anomalous dispersion [4, 5, 7]} \\
Extinction Correction: \quad \text{no} \\
Weighting Scheme: \quad w^{-1} = \sigma^2(F_o^2) + (a*P)^2 + b*P \\
\quad \text{with a: 0.0400; b: 0.2260; P: [Maximum(0 or } F_o^2) + 2*F_c^2]/3 \\
Shift/Err: \quad \text{Less than 0.001 in the last cycle of refinement:} \\
Resid. Electron Density: \quad +0.26 \text{ e}^{\text{Error!}/\text{A}^3}; -0.23 \text{ e}^{\text{Error!}/\text{A}^3} \\
R1: \quad \Sigma||F_o|-|F_c||)/\Sigma|F_o| \\
[F_o > 4\sigma(F_o); \quad N=2033]: \quad = 0.0303 \\
[all refctns; \quad N=2111]: \quad = 0.0312 \\
wR2: \quad [\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2} \\
[F_o > 4\sigma(F_o); \quad N=2033]: \quad = 0.0765 \\
[all refctns; \quad N=2111]: \quad = 0.0774 \\
Goodness of fit: \quad [\Sigma w(F_o^2-F_c^2)^2/(NO-NV)]^{1/2} \\
= 1.050 \\
Remarks: \quad \text{Refinement expression } \Sigma w(F_o^2-F_c^2)^2
**Compound 6f**

**Figure F3** – Ortep drawing drawing of compound 6f with 50% ellipsoids. [6]

**Operator:** *** Herdtweck ***

**Molecular Formula:** \( C_{20} H_{36} N_{10} O_{3} \)

\( 2(C_{10} H_{17} N_{5} O), (H_{2} O) \)

**Crystal Color / Shape**

Colourless fragment

**Crystal Size**

Approximate size of crystal fragment used for data collection:

\( 0.10 \times 0.30 \times 0.36 \text{ mm} \)

**Molecular Weight:**

464.59 a.m.u.

**F_{000} :**

1000

**Systematic Absences:**

hkl: h+k≠2n; h0l: l≠2n

**Space Group:** Monoclinic \( C 2/c \) (I.T.-No.: 15)

**Cell Constants:**

Least-squares refinement of 9875 reflections with the programs "APEX suite" and "SAINT" [1,2]; theta range 1.63° < \( \theta < 25.55° \); Mo(K \( \bar{\alpha} \) ); \( \lambda = 71.073 \text{ pm} \)

\( a = 2660.36(6) \text{ pm} \)

\( b = 630.28(1) \text{ pm} \)

\( c = 1546.66(3) \text{ pm} \)

\( V = 2440.37(8) \times 10^{6} \text{ pm}^{3}; Z= 4; D_{\text{calc}} = 1.265 \text{ g cm}^{-3}; \text{Mos.} = 0.60 \)

**Diffractometer:**

Kappa APEX II (Area Diffraction System; BRUKER AXS); sealed tube; graphite monochromator; 50 kV; 30 mA; \( \lambda = 71.073 \text{ pm}; \text{Mo(K \( \bar{\alpha} \) )} \)

**Temperature:**

\((-150±1) \text{ °C}; \quad (123±1) \text{ K} \)

**Measurement Range:**

1.63° < \( \theta < 25.55° \); h: -32/32, k: -7/7, l: -18/18

**Measurement Time:**

2 \times 15 \text{ s per film}
Measurement Mode: measured: 7 runs; 3306 films / scaled: 7 runs; 3306 films

ϕ- and ω-movement; Increment: Δϕ/Δω = 0.50°; dx = 40.0 mm

LP - Correction: Yes [2]
Intensity Correction: No/Yes; during scaling [2]
Absorption Correction: Multi-scan; during scaling; μ = 0.089 mm\(^{-1}\) [2]
Correction Factors: \(T_{\text{min}} = 0.6993\) \(T_{\text{max}} = 0.7452\)

Removing solvent molecules
Besides the solvent molecule, well located in the difference Fourier maps, unresolved solvent molecules remained and had to be removed with the SQUEEZE procedure. [6]

Reflection Data:
35663 reflections were integrated and scaled
2031 reflections systematic absent and rejected
33632 reflections to be merged
2264 independent reflections
0.026 R_{int}: (basis \(F_o^2\))
2264 independent reflections (all) were used in refinements
2037 independent reflections with \(I_o > 2\sigma(I_o)\)
98.7 % completeness of the data set
222 parameter full-matrix refinement
10.2 reflections per parameter

Solution: Direct Methods [3, 7]; Difference Fourier syntheses

Refinement Parameters:
In the asymmetric unit:
17 Non-hydrogen atoms with anisotropic displacement parameters
18 Hydrogen atoms with isotropic displacement parameters

Hydrogen Atoms:
All hydrogen atom positions were found in the difference map calculated from the model containing all non-hydrogen atoms. The hydrogen positions were refined with individual isotropic displacement parameters.

Atomic Form Factors:
For neutral atoms and anomalous dispersion [4, 5, 7]

Extinction Correction:
no

Weighting Scheme:
\(w^{-1} = \sigma(F_o^2)^+(a*P)^2+b*P\)
with a: 0.0466; b: 1.7210; P: [Maximum(0 or \(F_o^2\)+2*\(F_c^2\))/3]

Shift/Err:
Less than 0.001 in the last cycle of refinement:

Resid. Electron Density:
+0.19 e\(\text{Error!}!\)/Å\(^3\); -0.18 e\(\text{Error!}!\)/Å\(^3\)

R1:
\[\Sigma(|F_o|-[F_i]|) / \Sigma|F_o|\]
\([F_o > 4\sigma(F_o)];\ N=2037\]: = 0.0348
\([\text{all reflctns};\ N=2264]\): = 0.0385

wR2:
\[\Sigma w(F_o^2-F_c^2)^2 / \Sigma w(F_o^2)^2\]\(^{1/2}\)
\([F_o > 4\sigma(F_o)];\ N=2037\]: = 0.0887
\([\text{all reflctns};\ N=2264]\): = 0.0911

Goodness of fit:
\[\Sigma w(F_o^2-F_c^2)^2/(NO-NV)\]\(^{1/2}\)
= 1.049

Remarks:
Refinement expression \(\Sigma w(F_o^2-F_c^2)^2\)

Compound 6j
Figure F4 – Ortep drawing drawing of compound 6j with 50% ellipsoids. [6]

Operator: *** Herdtweck ***
Molecular Formula: C₁₂H₁₉N₅O
Crystal Color / Shape: Colorless fragment
Crystal Size: Approximate size of crystal fragment used for data collection:
               0.25 × 0.25 × 0.28 mm
Molecular Weight: 249.32 a.m.u.
F₀₀₀: 1072
Systematic Absences: 0kl: k≠2n; h0l: l≠2n; hk0: h≠2n
Space Group: Orthorhombic \( P_{bca} \) (I.T.-No.: 61)
Cell Constants: Least-squares refinement of 9968 reflections with the programs "APEX suite"
and "SAINT" [1,2]; theta range 2.79° < \( \theta < 25.40° \); Mo(Kα); \( \lambda = 71.073 \) pm
\( a = 991.62(3) \) pm
\( b = 1193.89(3) \) pm
\( c = 2152.52(7) \) pm
\( V = 2548.34(13) \cdot 10^6 \) pm³; \( Z = 8; D_{calc} = 1.300 \) g cm⁻³; Mos. = 0.67
Diffractometer: Kappa APEX II (Area Diffraction System; BRUKER AXS); sealed tube; graphite
monochromator; 50 kV; 30 mA; \( \lambda = 71.073 \) pm; Mo(Kα)
Temperature: \((-150±1)°C;\) \((123±1)\) K
Measurement Range: 2.79° < \( \theta < 25.40° \); h: -11/11, k: -14/14, l: -25/25
Measurement Time: \( 2 \times 10 \) s per film
Measurement Mode: measured: 6 runs; 3381 films / scaled: 6 runs; 3381 films
φ- and ω-movement; Increment: Δφ/Δω = 0.50°; dx = 60.0 mm

LP - Correction: Yes [2]
Intensity Correction No/Yes; during scaling [2]
Absorption Correction: Multi-scan; during scaling; μ = 0.088 mm⁻¹ [2]
Correction Factors: T_min = 0.7060 T_max = 0.7452

Reflection Data:
34576 reflections were integrated and scaled
3008 reflections systematic absent and rejected
2 obvious wrong intensity and rejected (one hkl)
31566 reflections to be merged
2338 independent reflections
0.028 R_m: (basis F_o)
2338 independent reflections (all) were used in refinements
2085 independent reflections with I_o > 2σ(I_o)
99.9 % completeness of the data set
239 parameter full-matrix refinement
9.8 reflections per parameter

Solution: Direct Methods [3, 7]; Difference Fourier syntheses
Refinement Parameters:
In the asymmetric unit:
18 Non-hydrogen atoms with anisotropic displacement parameters
19 Hydrogen atoms with isotropic displacement parameters

Hydrogen Atoms:
All hydrogen atom positions were found in the difference map calculated from
the model containing all non-hydrogen atoms. The hydrogen positions were
refined with individual isotropic displacement parameters.

Atomic Form Factors:
For neutral atoms and anomalous dispersion [4, 5, 7]

Extinction Correction: no
Weighting Scheme:
w⁻¹ = σ²(F_o)²+(a*P)²+b*P
with a: 0.0491; b: 1.2420; P: [Maximum(0 or F_o)²+2*F_c²]/3

Shift/Err:
Less than 0.001 in the last cycle of refinement:
Resid. Electron Density: +0.24 e Å⁻³; -0.24 e Å⁻³

R1:
Σ||F_o|-|F_c||/Σ|F_o| = 0.0359

wR2:
Σw(F_o²-F_c²)²/Σw(F_o²)² = 0.0959

Goodness of fit:
[Σw(F_o²-F_c²)²/(NO-NV)]¹/² = 1.082

Remarks:
Refinement expression Σw(F_o²-F_c²)

References:


SFC-MS Chromatograms of compounds 6a-j

Compound 6a SFC-MS
Compound 6b SFC-MS
Compound 6c SFC-MS
Compound 6d SFC-MS
Compound 6e SFC-MS
Compound 6f SFC-MS
Compound 6g SFC-MS
Compound 6h SFC-MS
Compound 6i SFC-MS
PDB Analysis – Interaction distances of gamma lactams found in the PDB database

O1 Interaction distances

Bond distance in Å

Frequency
N1 Interaction distances

Bond distances in Å

Frequency