Supporting Information

for

Consecutive hydrazino-Ugi-azide reactions:
synthesis of acylhydrazines bearing 1,5-
disubstituted tetrazoles

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Detailed experimental procedures, NMR and mass spectra

Table of contents
General Information.............................................................................................................. S2
General procedure for the Ugi-tetrazole reaction ................................................................ S2
Spectra of compounds ..................................................................................................... S14–S66
**General information**

NMR spectra were recorded on a Bruker Ascend instrument using a 5 mm internal diameter probe operating at 600 MHz for $^1$H and at 150 MHz for $^{13}$C in the presence of TMS as internal standard. High resolution ESIMS analyses were carried out on a triple TOF 5600+ (AB Sciex) with internal calibration and direct solution (1 ppm) infusion in positive ion mode. TLC plates were revealed by treatment with a 10% solution of phosphomolybdic acid in ethanol, followed by heating. Melting points were recorded on a Marconi melting point and are uncorrected. Commercially available reagents and solvents were of analytical grade or were purified by standard procedures prior to use. Compounds were analyzed by $^1$H NMR, $^{13}$C NMR and high resolution ESI mass spectra giving data consistent with the proposed structures. Compounds names were given based on ChemDraw® software 7.0.

**General procedure for the hydrazino-Ugi-azide reactions:** To a stirred solution of hydrazide 2a–c (0.40 mmol) in TFE (1.0 mL) were added successively oxo compound 7a–h (0.40 mmol, 0.80 mmol when a ketone was used), trimethylsilylazide (8, TMS azide, 0.40 mmol), methyl isocyanoacetate (9, 0.40 mmol) and ZnCl$_2$ (10 mol %). The resulting mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography to obtain the Ugi tetrazole product.
tetrazol-1-yl]acetic acid methyl ester (10a): Prepared following the general procedure using acetylhydrazide (2a, 0.73 mmol, 0.054 g), isobutyraldehyde (7a, 0.73 mmol, 0.053 g), trimethylsilyl azide (8, 0.73 mmol, 0.084 g), methyl isocyanoacetate (9, 0.73 mmol, 0.066 mL) and ZnCl₂ (0.073 mmol, 0.010 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product 10a in 44% yield (0.086 g, 0.32 mmol) as a yellow oil. Rf (CH₂Cl₂/MeOH 5%) 0.28.

1H NMR (600 MHz, CDCl₃) δ 7.47 (br s, 1H), 5.39 (s, 2H), 5.06 (br s, 1H), 4.31 (d, J = 8.8 Hz, 1H), 3.85 (s, 3H), 2.08–2.01 (m, 1H), 1.88 (s, 3H), 1.21 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H). 13C NMR (150 MHz, CDCl₃): δ 169.8, 167.6, 154.9, 63.0, 53.4, 48.8, 30.7, 20.9, 19.6, 19.2. HRMS (ESI) m/z: calcd. for [M+Na]⁺ C₁₀H₁₈N₆O₃Na: 293.1338; found: 293.1342.

tetrazol-1-yl]acetic acid methyl ester (10b): Prepared following the general procedure using acetylhydrazide (2a, 0.73 mmol, 0.054 g), acetone (7b, 0.146 mmol, 0.107 mL), trimethylsilyl azide (8, 0.73 mmol, 0.084 g), methyl isocyanoacetate (9, 0.73 mmol, 0.066 mL) and ZnCl₂ (0.073 mmol, 0.010 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product 10b in 36% yield (0.067 g, 0.26 mmol) as a white solid. Mp 112–114 °C; Rf (CH₂Cl₂/MeOH 5%) 0.34.

1H NMR (600 MHz, CDCl₃) δ 7.18 (br s, 1H), 5.47 (s, 2H), 4.98 (br s, 1H), 3.86 (s, 3H), 1.92 (s, 3H), 1.63 (s, 6H). 13C NMR (150 MHz, CDCl₃): δ 169.8, 168.2, 158.3, 57.4, 53.4, 49.7, 24.8, 20.8. HRMS (ESI) m/z: calcd. for [M+Na]⁺ C₉H₁₆N₆O₃Na: 279.1182; found: 279.1184.
{5-[1-(N'-Acetylhydrazino)-1-ethylpropyl]-tetrazol-1-yl]acetic acid methyl ester (10c): Prepared following the general procedure using acetylhydrazide (2a, 0.40 mmol, 0.030 g), 3-pentanone (7c, 0.40 mmol, 0.034 g), trimethylsilyl azide (8, 0.40 mmol, 0.046 g), methyl isocyanatoacetate (9, 0.40 mmol, 0.036 mL) and ZnCl₂ (0.040 mmol, 0.0054 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product 10c in 47% yield (0.053 g, 0.19 mmol) as a white solid. Mp 130–132 °C; Rf (CH₂Cl₂/MeOH 5%) 0.31.

1H NMR (600 MHz, CDCl₃) δ 7.08 (br s, 1H), 5.54 (s, 2H), 5.26 (br s, 1H), 3.84 (s, 3H), 2.04–1.98 (m, 2H), 1.96–1.90 (m, 2H), 1.89 (s, 3H), 0.88 (t, J = 7.0 Hz, 6H). 13C NMR (150 MHz, CDCl₃): δ 169.1, 168.4, 157.2, 63.6, 53.4, 49.9, 24.9, 21.0, 7.2. HRMS (ESI) m/z: calcd. for [M+Na]⁺ C₁₁H₂₀N₇O₃Na: 307.1495; found: 307.1500.

{5-[1-(N'-Acetylhydrazino)-2-phenylethyl]-tetrazol-1-yl]acetic acid methyl ester (10d): Prepared following the general procedure using acetylhydrazide (2a, 0.73 mmol, 0.054 g), phenylacetaldehyde (7d, 0.73 mmol, 0.098 g), trimethylsilyl azide (8, 0.73 mmol, 0.084 g), methyl isocyanatoacetate (9, 0.73 mmol, 0.066 mL) and ZnCl₂ (0.073 mmol, 0.010 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product 10d in 30% yield (0.069 g, 0.22 mmol) as a yellow oil. Rf (CH₂Cl₂/MeOH 5%) 0.39.

1H NMR (600 MHz, CDCl₃) δ 7.50 (s, 1H), 7.30–7.27 (m, 3H), 7.08-7.06 (m, 2H), 4.94 and 4.91 (2s, 1H, rotamers), 4.87 (t, J = 7.0 Hz, 1H), 4.79 and 4.76 (2s, 1H, rotamers), 3.79 (s, 3H), 3.23-3.15 (m, 2H), 1.85 (s, 3H). 13C NMR (150 MHz, CDCl₃): δ 169.1, 168.4, 157.2, 63.6, 53.4, 49.9, 24.9, 21.0, 7.2. HRMS (ESI) m/z: calcd. for [M+Na]⁺ C₁₅H₂₁N₇O₃Na: 351.1547; found: 351.1554.

\[
\text{MeO} \quad \text{N}^\text{N} \quad \text{N} \quad \text{N} \quad \text{H} \quad \text{O} \quad \text{CH₃}
\]

\(\{5-[(N'\text{-Acetylhydrazino})\text{-cyclohexyl}]\text{-tetrazol-1-yl}\}\text{acetic acid methyl ester (10e)}\): Prepared following the general procedure using acetylhydrazide (2a, 0.73 mmol, 0.054 g), cyclohexanone (7e, 0.73 mmol, 0.072 g), trimethylsilyl azide (8, 0.73 mmol, 0.084 g), methyl isocyanoacetate (9, 0.73 mmol, 0.066 mL) and ZnCl₂ (0.073 mmol, 0.010 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product 10e in 40% yield (0.093 g, 0.29 mmol) as a white solid. Mp 116–118 °C; Rf (CH₂Cl₂/MeOH 5%) 0.32.

\(^1\text{H NMR (600 MHz, CDCl}_3\): δ 7.17 (d, J = 5.9 Hz, 1H), 5.51 (s, 2H), 5.30 (d, J = 7.3 Hz, 1H), 3.84 (s, 3H), 2.19-2.15 (m, 2H), 1.89 (s, 3H), 1.86-1.82 (m, 2H), 1.77-1.71 (m, 2H), 1.65-1.59 (m, 2H), 1.51-1.48 (m, 2H). \(^{13}\text{C NMR (150 MHz, CDCl}_3\): δ 169.5, 168.1, 157.6, 59.5, 53.4, 49.8, 33.1, 24.9, 21.8, 20.9. HRMS (ESI) m/z: calcd. for [M+Na]+ C₁₂H₂₀N₆O₃Na: 319.1495; found: 319.1501.

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\text{MeO} \quad \text{N}^\text{N} \quad \text{N} \quad \text{N} \quad \text{H} \quad \text{O} \quad \text{CH₃}
\]

\(\{5-[(N'\text{-Acetylhydrazino})\text{-cyclopentyl}]\text{-tetrazol-1-yl}\}\text{acetic acid methyl ester (10f)}\): Prepared following the general procedure using acetylhydrazide (2a, 0.73 mmol, 0.054 g), cyclopentanone (7f, 0.73 mmol, 0.061 g), trimethylsilyl azide (8, 0.73 mmol, 0.084 g), methyl isocyanoacetate (9, 0.73 mmol, 0.066 mL) and ZnCl₂ (0.073 mmol, 0.010 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product 10f in 36% yield (0.074 g, 0.26 mmol) as a yellow solid. Mp 105–107 °C; Rf (CH₂Cl₂/MeOH 5%) 0.36.
$^1$H NMR (600 MHz, CDCl$_3$) δ 7.21 (d, $J$ = 7.5 Hz, 1H), 5.41 (s, 2H), 5.15 (d, $J$ = 7.7 Hz, 1H), 3.84 (s, 3H), 2.29-2.24 (m, 2H), 2.08-2.04 (m, 1H), 1.97-1.92 (m, 2H), 1.90 (s, 3H), 1.84-1.77 (m, 2H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 170.0, 168.1, 158.4, 67.6, 53.4, 49.3, 35.0, 27.0, 24.8, 23.9, 20.9. HRMS (ESI) $m/z$: calcd. for [M+Na]$^+$ C$_{11}$H$_{18}$N$_6$O$_3$Na: 305.1338; found: 305.1350.

![Chemical structure](image)

{5-[1-(N'-Acetylhydrazino)cycloheptyl]-tetrazol-1-yl]acetic acid methyl ester (10g): Prepared following the general procedure using acetylhydrazide (2a; 0.40 mmol, 0.030 g), cycloheptanone (7g, 0.40 mmol, 0.045 g), trimethylsilyl azide (8, 0.40 mmol, 0.046 g), methyl isocyanatoacetate (9, 0.40 mmol, 0.036 mL) and ZnCl$_2$ (0.040 mmol, 0.005 g). Purification by column chromatography (CH$_2$Cl$_2$ → 2% MeOH/CH$_2$Cl$_2$) furnished product 10g in 53% yield (0.066 g, 0.21 mmol) as a white solid. Mp 102–104 °C; R$_f$ (CH$_2$Cl$_2$/MeOH 5%) 0.44.

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.17 (br s, 1H), 5.49 (s, 2H), 5.24 (d, $J$ = 8.1 Hz, 1H), 3.85 (s, 3H), 2.32-2.26 (m, 2H), 1.97-1.93 (m, 2H), 1.90 (s, 3H), 1.70-1.66 (m, 4H), 1.61-1.56 (m, 4H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 169.6, 168.6, 158.8, 63.8, 53.5, 49.9, 35.2, 30.4, 22.3, 20.9. HRMS (ESI) $m/z$: calcd. for [M+Na]$^+$ C$_{13}$H$_{22}$N$_6$O$_3$Na: 333.1651; found: 333.1650.

![Chemical structure](image)

{5-[1-(N'-Acetyl-hydrazino)-1,3-dimethyl-butyl]-tetrazol-1-yl]acetic acid methyl ester (10h): Prepared following the general procedure using acetylhydrazide (2a, 0.40 mmol, 0.030 g), methyl isobutyl ketone (7h, 0.40 mmol, 0.040 g), trimethylsilyl azide (8, 0.40 mmol, 0.046 g),
methyl isocyanoacetate (9, 0.40 mmol, 0.036 mL) and ZnCl₂ (0.040 mmol, 0.005 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product 10h in 47% yield (0.056 g, 0.019 mmol) as a white solid. Mp 94–96 °C; Rᵢ (CH₂Cl₂/MeOH 5%) 0.42.

¹H NMR (600 MHz, CDCl₃) δ 7.15 (br s, 1H), 5.54 (d, J = 17.0 Hz, 1H), 5.38 (s, J = 17.0 Hz, 1H), 5.03 (br s, 1H), 3.86 (s, 3H), 1.91 (s, 3H), 1.72 (s, 3H), 1.70-1.66 (m, 3H), 0.97 (d, J = 6.2 Hz, 3H), 0.52 (d, J = 6.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃): δ 169.9, 168.4, 157.7, 60.7, 53.5, 49.7, 47.2, 24.7, 24.2, 23.2, 21.2, 20.9. HRMS (ESI) m/z: calcd. for [M+Na]⁺ C₁₂H₂₂N₆O₃Na: 321.1651; found: 321.1650.

Methyl isocyanoacetate (9, 0.40 mmol, 0.036 mL) and ZnCl₂ (0.040 mmol, 0.005 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product 10h in 47% yield (0.056 g, 0.019 mmol) as a white solid. Mp 94–96 °C; Rᵢ (CH₂Cl₂/MeOH 5%) 0.42.

¹H NMR (600 MHz, CDCl₃) δ 7.15 (br s, 1H), 5.54 (d, J = 17.0 Hz, 1H), 5.38 (s, J = 17.0 Hz, 1H), 5.03 (br s, 1H), 3.86 (s, 3H), 1.91 (s, 3H), 1.72 (s, 3H), 1.70-1.66 (m, 3H), 0.97 (d, J = 6.2 Hz, 3H), 0.52 (d, J = 6.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃): δ 169.9, 168.4, 157.7, 60.7, 53.5, 49.7, 47.2, 24.7, 24.2, 23.2, 21.2, 20.9. HRMS (ESI) m/z: calcd. for [M+Na]⁺ C₁₂H₂₂N₆O₃Na: 321.1651; found: 321.1650.

(5-{1-[N'-(2-(Benzyloxycarbonyl-amino)acetyl)hydrazino]-1-methylethyl}-tetrazol-1-yl)acetic acid methyl ester (10i): Prepared following the general procedure using Cbz-glycine hydrazide (2b, 0.40 mmol, 0.089 g), acetone (7b, 0.80 mmol, 0.046 g), trimethylsilyl azide (8, 0.40 mmol, 0.046 g), methyl isocyanoacetate (9, 0.40 mmol, 0.036 mL) and ZnCl₂ (0.040 mmol, 0.005 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product 10i in quantitative yield (0.162 g, 0.40 mmol) as a white solid. Mp 120–122 °C; Rᵢ (CH₂Cl₂/MeOH 5%) 0.36.

¹H NMR (600 MHz, CDCl₃) δ 7.77 (d, J = 7.4 Hz, 1H), 7.35-7.29 (m, 5H), 5.47 (s, 2H), 5.45 (br s, 1H), 5.09 (s, 2H), 4.92 (d, J = 7.4 Hz, 1H), 3.83 (d, J = 5.9 Hz, 2H), 3.80 (s, 3H), 1.60 (s, 6H). ¹³C NMR (150 MHz, CDCl₃): δ 169.1, 168.3, 158.1, 156.5, 136.0, 128.5, 128.2, 128.1, 67.2, 57.5, 53.6, 49.8, 43.3, 24.9. HRMS (ESI) m/z: calcd. for [M+Na]⁺ C₁₇H₂₃N₇O₅Na: 428.1658; found: 428.1666.
Butoxycarbonylaminolacetyl)hydrazino]-1-methylethyl]-tetrazol-1-yl)acetic acid methyl ester (10j): Prepared following the general procedure using Boc-glycine hydrazide (2c, 0.40 mmol, 0.076 g), acetone (7b, 0.80 mmol, 0.046 g), trimethylsilyl azide (8, 0.40 mmol, 0.046 g), methyl isocyanatoacetate (9, 0.40 mmol, 0.036 mL) and ZnCl₂ (0.040 mmol, 0.005 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product 10j in 97% yield (0.144 g, 0.39 mmol) as a colorless oil. Rᵣ (CH₂Cl₂/MeOH 5%) 0.34.

¹H NMR (600 MHz, CDCl₃) δ 7.72 (br s, 1H), 5.47 (s, 2H), 5.04 (br s, 1H), 4.93 (br s, 1H), 4.92 (s, 3H), 3.77 (d, J = 5.9 Hz, 2H), 1.62 (s, 6H), 1.41 (s, 9H).

¹³C NMR (150 MHz, CDCl₃): δ 169.6, 167.9, 158.1, 155.9, 80.2, 57.3, 53.4, 49.8, 42.9, 28.1, 24.8. HRMS (ESI) m/z: calcd. for [M+Na]⁺ C₁₄H₂₅N₇O₅Na: 394.1815; found: 394.1814.

(Benzyloxycarbonylaminolacetyl)hydrazino]-cyclohexyl]-tetrazol-1-yl)acetic acid methyl ester (10k): Prepared following the general procedure using Cbz-glycine hydrazide (2b, 0.40 mmol, 0.089 g), cyclohexanone (7e, 0.40 mmol, 0.039 g), trimethylsilyl azide (8, 0.40 mmol, 0.046 g), methyl isocyanatoacetate (9, 0.40 mmol, 0.036 mL) and ZnCl₂ (0.040 mmol, 0.005 g). Purification by column chromatography (CH₂Cl₂ → 2% MeOH/CH₂Cl₂) furnished product 10k in 85% yield (0.151 g, 0.34 mmol) as a white solid. Mp 62–64 °C; Rᵣ (CH₂Cl₂/MeOH 5%) 0.42.

¹H NMR (600 MHz, CDCl₃) δ 7.62 (br s, 1H), 7.36-7.29 (m, 5H), 5.49 (s, 2H), 5.32 (br s, 1H), 5.23 (br s, 1H), 5.08 (s, 2H), 3.80 (s, 5H), 2.18-2.14 (m, 2H), 1.86-1.79 (m, 2H), 1.75-1.69 (m, 2H), 1.64-1.57 (m, 2H), 1.51-1.47 (m, 2H).
\(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 168.8, 168.3, 157.5, 156.4, 136.0, 128.5, 128.2, 128.1, 67.2, 59.7, 53.6, 49.9, 43.3, 33.2, 25.0, 21.8. HRMS (ESI) \(m/z\): calcd. for [M+Na]\(^+\) C\(_{20}\)H\(_{27}\)N\(_7\)O\(_5\)Na: 468.1971; found: 468.1974.

(5-{1-[N'(2-(tert-
Butoxycarbonylamino)acetyl)hydrazino]-cycloheptyl}-tetrazol-1-yl)acetic acid methyl ester (10l): Prepared following the general procedure using Boc-glycine hydrazide (2c, 0.40 mmol, 0.076 g), cyclohexanone (7e, 0.40 mmol, 0.039 g), trimethylsilyl azide (8, 0.40 mmol, 0.046 g), methyl isocyanoacetate (9, 0.40 mmol, 0.036 mL) and ZnCl\(_2\) (0.040 mmol, 0.005 g). Purification by column chromatography (CH\(_2\)Cl\(_2\) \(\rightarrow\) 3% MeOH/CH\(_2\)Cl\(_2\)) furnished product 10l in 57% yield (0.094 g, 0.23 mmol) as a white solid. Mp 68–70 °C; R\(_f\) (CH\(_2\)Cl\(_2\)/MeOH 5%) 0.41.

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.67 (s, 1H), 5.50 (s, 2H), 5.01 (s, 1H), 3.82 (s, 3H), 3.74 (s, 2H), 2.21-2.17 (m, 2H), 1.87-1.82 (m, 2H), 1.76-1.70 (m, 2H), 1.65-1.59 (m, 2H), 1.51-1.47 (m, 2H), 1.41 (s, 9H). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 169.3, 168.1, 157.3, 155.8, 80.4, 59.7, 53.5, 49.9, 43.0, 33.2, 28.2, 24.9, 21.8. HRMS (ESI) \(m/z\): calcd. for [M+Na]\(^+\) C\(_{17}\)H\(_{29}\)N\(_7\)O\(_5\)Na: 434.2128; found: 434.2143.

(5-{1-[N'(2-(tert-
Butoxycarbonylamino)acetyl)hydrazino]-cycloheptyl}-tetrazol-1-yl)acetic acid methyl ester (10m): Prepared following the general procedure using Boc-
glycine hydrazide (2c, 0.40 mmol, 0.076 g), cycloheptanone (7g, 0.40 mmol, 0.045 g), trimethylsilyl azide (8, 0.40 mmol, 0.046 g), methyl isocyanoacetate (9, 0.40 mmol, 0.036 mL) and ZnCl₂ (0.040 mmol, 0.005 g). Purification by column chromatography (CH₂Cl₂ → 4% MeOH/CH₂Cl₂) furnished product 10n in 62% yield (0.106 g, 0.25 mmol) colorless oil. Rf (CH₂Cl₂/MeOH 5%) 0.50.

¹H NMR (600 MHz, CDCl₃) δ 7.68 (s, 1H), 5.49 (s, 2H), 5.04 (s, 1H), 3.83 (s, 3H), 3.76 (d, J = 5.5 Hz, 2H), 2.32-2.28 (m, 2H), 1.96-1.92 (m, 2H), 1.68-1.53 (m, 8H), 1.40 (s, 9H).

¹³C NMR (150 MHz, CDCl₃): δ 169.3, 168.2, 158.6, 155.8, 80.3, 63.8, 53.5, 50.8, 49.9, 43.8, 35.3, 30.4, 28.2, 24.3, 22.3. HRMS (ESI) m/z: calcd. for [M+Na]⁺ C₁₈H₃₁N₇O₅Na: 448.2296; found: 448.2296.

{N'-[1-(1-Hydrazonecarbonylmethyl-1H-tetrazol-5-yl)-1-methylethyl]-hydrazinocarbonylmethyl}carbamic acid tert-butyl ester (11): To a solution of compound 10j (0.371 g, 1.0 mmol) in 2.0 mL of ethanol was added hydrazine hydrate (0.200 g, 4.00 mmol). After refluxing for 5 h, the residue was concentrated in vacuum and purified by column chromatography (CH₂Cl₂ → 10% MeOH/CH₂Cl₂) furnishing product 6 in 55% yield (0.204 g, 0.55 mmol) as a white solid. Mp 44–46 °C; Rf (CH₂Cl₂/MeOH 15%) 0.39.

¹H NMR (600 MHz, DMSO-d₆) δ 9.59 (s, 1H), 9.00 (d, J = 5.9 Hz, 1H), 6.95 (t, J = 6.1 Hz, 1H), 5.51 (s, 2H), 5.37 (d, J = 5.9 Hz, 1H), 4.39 (br, 1H), 3.43 (d, J = 5.9 Hz, 2H), 1.46 (s, 6H), 1.35 (s, 9H). ¹³C NMR (150 MHz, DMSO-d₆): δ 169.1, 165.2, 158.3, 155.8, 78.1, 56.5, 49.5, 34.7, 28.2, 25.1, 18.6, 13.9. HRMS (ESI) m/z: calcd. for [M+Na]⁺ C₁₃H₂₅N₉O₄Na: 394.1927; found: 394.1923.
[5-1-{N'}-[2-(5-1-[N'-2-(tert-
Butoxycarbonylamino)acetyl]hydrazino]-1-methylethyl]-tetrazol-1-
yl)acetyl]hydrazino]-cycloheptyl]-tetrazol-1-yl]acetic acid methyl ester (12a): Prepared following the general procedure using hydrazide 11 (0.13 mmol, 0.048 g), cycloheptanone (7g, 0.13 mmol, 0.014 g), trimethylsilyl azide (8, 0.13 mmol, 0.015 g), methyl isocyanoacetate (9, 0.13 mmol, 0.013 mL) and ZnCl₂ (0.013 mmol, 0.002 g). Purification by column chromatography (CH₂Cl₂ → 4% MeOH/CH₂Cl₂) furnished product 12a in 68% yield (0.055 g, 0.090 mmol) as a white solid. Mp 105–107 °C; Rf (CH₂Cl₂/MeOH 10%): 0.52.

¹H NMR (600 MHz, DMSO-d₆) δ 9.59 (d, J = 4.4 Hz, 1H), 8.94 (d, J = 5.1 Hz, 1H), 6.88 (s, 1H), 5.87 (s, 2H), 5.64 (d, J = 4.4 Hz, 1H), 5.45 (s, 2H), 5.27 (d, J = 5.5 Hz, 1H), 3.71 (s, 3H), 3.39 (d, J = 5.9 Hz, 2H), 2.17-2.13 (m, 2H), 1.96-1.92 (m, 2H), 1.65-1.59 (m, 2H), 1.53-1.48 (m, 4H), 1.41-1.30 (m, 17H).

¹³C NMR (150 MHz, DMSO-d₆): δ 169.0, 167.6, 165.6, 158.0 (2C), 155.7, 78.0, 62.4, 56.1, 54.9, 52.7, 49.6, 49.3, 45.7, 41.7, 35.0, 29.6, 28.1, 24.9, 21.9.


[5-1-{N'}-[2-(5-1-[N'-2-(tert-
Butoxycarbonylamino)acetyl]hydrazino]-1-methylethyl]-tetrazol-1-
yl)acetyl]hydrazino]-1-ethylpropyl]-tetrazol-1-yl]acetic acid methyl ester (12b): Prepared following the general procedure using hydrazide 11 (0.35 mmol, 0.130 g), 3-pentanone (7c, 0.35 mmol, 0.030 g), trimethylsilyl azide (8, 0.35 mmol, 0.040 g), methyl isocyanoacetate (9, 0.35 mmol, 0.032 mL) and
ZnCl₂ (0.035 mmol, 0.005 g). Purification by column chromatography (CH₂Cl₂ → 5% MeOH/CH₂Cl₂) furnished product 12b in 54% yield (0.110 g, 0.19 mmol) as a yellow solid. Mp 101–103 °C; Rₜ (CH₂Cl₂/MeOH 10%) 0.43.

¹H NMR (600 MHz, DMSO-ｄ₆) δ 9.47 (br s, 1H), 8.95 (d, J = 5.5 Hz, 1H), 6.88 (t, J = 6.1 Hz, 1H), 5.93 (s, 2H), 5.66 (br s, 1H), 5.46 (s, 2H), 5.25 (d, J = 5.5 Hz, 1H), 3.70 (s, 3H), 3.39 (d, J = 5.9 Hz, 2H), 1.96-1.90 (m, 2H), 1.80-1.74 (m, 2H), 1.35 and 1.33 (2s, 15H), 0.69 (t, J = 7.5 Hz, 6H). ¹³C NMR (150 MHz, DMSO-ｄ₆): δ 169.0, 167.6, 165.7, 158.0, 156.4, 155.7, 78.0, 62.5, 56.0, 52.7, 49.8, 49.3, 45.7, 41.7, 28.1, 24.8, 24.7, 20.0, 7.03. HRMS (ESI) m/z: calcd. for [M+Na]⁺ C₂₂H₃₉N₁₃O₆Na: 604.3044; found: 604.3035.

[5-(1-{(N'-(2-(5-{1-[(N'-(2{(tert-Butoxycarbonylamino)acetyl)hydrazino)-1-methylethyl}]-tetrazol-1-yl)acetyl)hydrazino)-cyclohexyl}-tetrazol-1-yl}acetyl]hydrazino)-1-methylethyl]-tetrazol-1-yl]acetic acid methyl ester (12c): Prepared following the general procedure using hydrazide 11 (0.26 mmol, 0.095 g), cyclohexanone (7e, 0.26 mmol, 0.025 g), trimethylsilyl azide (8, 0.26 mmol, 0.030 g), methyl isocyanoacetate (9, 0.26 mmol, 0.024 mL) and ZnCl₂ (0.026 mmol, 0.004 g). Purification by column chromatography (CH₂Cl₂ → 4% MeOH/CH₂Cl₂) furnished product 12c in 70% yield (0.108 g, 0.18 mmol) as a yellow solid. Mp 119–121 °C; Rₜ (CH₂Cl₂/MeOH 10%) 0.47.

¹H NMR (600 MHz, DMSO-ｄ₆) δ 9.59 (br s, 1H), 8.92 (d, J = 5.3 Hz, 1H), 6.88 (s, 1H), 5.84 (s, 2H), 5.67 (s, 1H), 5.41 (s, 2H), 5.25 (d, J = 5.3 Hz, 1H), 3.70 (s, 3H), 3.40 (d, J = 5.9 Hz, 2H), 2.05-1.99 (m, 2H), 1.80-1.77 (m, 2H), 1.69-1.60 (m, 2H), 1.47-1.39 (m, 4H), 1.35 and 1.33 (2s, 15H). ¹³C NMR (150 MHz, DMSO-ｄ₆): δ 169.0, 167.6, 165.6, 158.0, 156.8, 155.7, 78.0, 58.2, 56.1, 52.7, 49.5, 49.2, 45.7, 41.7, 32.8, 28.1, 24.9, 21.4. HRMS (ESI) m/z: calcd. for [M+Na]⁺ C₂₃H₉₉N₁₃O₆Na: 616.3044; found: 616.3033.

S12
[5-(1′-{N′-[2-(5-{1′-[N′-(2-(tert-Butoxycarbonylamino)acetyl]hydrazino}-1-methylethyl]-tetrazol-1-yl)acetyl]hydrazino}-cyclopentyl)-tetrazol-1-yl]acetic acid methyl ester (12d): Prepared following the general procedure using hydrazide 11 (0.30 mmol, 0.110 g), cyclopentanone (7f, 0.30 mmol, 0.025 g), trimethylsilyl azide (8, 0.30 mmol, 0.034 g), methyl isocyanoacetate (9, 0.30 mmol, 0.027 mL) and ZnCl$_2$ (0.030 mmol, 0.004 g). Purification by column chromatography (CH$_2$Cl$_2$ $\rightarrow$ 4% MeOH/CH$_2$Cl$_2$) furnished product 12d in 45% yield (0.079 g, 0.14 mmol) as a yellow solid. Mp 114–116 °C; R$_f$ (CH$_2$Cl$_2$/MeOH 10%) 0.47.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.44 (d, $J = 7.0$ Hz, 1H), 8.39 (br s, 1H), 5.47 (s, 2H), 5.41 (s, 2H), 5.27 (br s, 1H), 5.14 (br s, 1H), 4.75 (br s, 1H), 3.86 (s, 3H), 3.77 (d, $J = 5.9$ Hz, 1H), 2.29-2.24 (m, 1H), 2.09-2.02 (m, 1H), 1.95-1.88 (m, 2H), 1.78-1.76 (m, 2H), 1.59 (s, 6H), 1.43 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 169.9, 168.1, 165.6, 158.2, 157.9, 156.0, 80.3, 67.6, 57.5, 53.7, 49.9, 49.4, 42.9, 35.2, 29.7, 28.3, 25.2, 23.8, 14.1. HRMS (ESI) m/z: calcd. for [M+Na]$^+$ C$_{22}$H$_{37}$N$_{13}$O$_6$Na: 602.2887; found: 602.2879.
Spectra of compounds

Figure S1: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 10a.
Figure S2: $^{13}$C NMR (150 MHz, CDCl$_3$) spectrum of compound 10a.
Figure S3: ESI-HRMS of compound 10a.
Figure S4: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 10b.
Figure S5: $^{13}$C NMR (150 MHz, CDCl$_3$) spectrum of compound 10b.
Figure S6: ESI-HRMS of compound 10b.
Figure S7: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 10c.
Figure S8: $^{13}$C NMR (150 MHz, CDCl$_3$) spectrum of compound 10c.
Figure S9: ESI-HRMS of compound 10c.
Figure S10: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 10d.
Figure S11: $^{13}$C NMR (150 MHz, CDCl$_3$) spectrum of compound 10d.
Figure S12: ESI-HRMS of compound 10d.
Figure S13: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 10e.
Figure S14: $^{13}$C NMR (150 MHz, CDCl$_3$) spectrum of compound 10e.
Figure S15: ESI-HRMS of compound 10e.
Figure S16: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 10f.
Figure S17: $^{13}$C NMR (150 MHz, CDCl$_3$) spectrum of compound 10f.
**Figure S18:** ESI-HRMS of compound 10f.

Calc. [M+Na]$^+$ : 305.1338
Figure S19: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 10g.
Figure S20: $^{13}$C NMR (150 MHz, CDCl$_3$) spectrum of compound 10g.
Figure S21: ESI-HRMS of compound 10g.
Figure S22: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 10h.
**Figure S23:** $^{13}$C NMR (150 MHz, CDCl$_3$) spectrum of compound 10h.
Figure S24: ESI-HRMS of compound 10h.

Figure S25: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 10i.
Figure S26: $^{13}$C NMR (150 MHz, CDCl$_3$) spectrum of compound 10i.
Figure S27: ESI-HRMS of compound 10i.

Calc. $[M+Na]^+ : 428.1658$
Figure S28: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 10j.
Figure S29: $^{13}$C NMR (150 MHz, CDCl$_3$) spectrum of compound 10j.
**Figure S30:** ESI-HRMS of compound 10j.
Figure S31: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 10k.
Figure S32: $^{13}$C NMR (150 MHz, CDCl$_3$) spectrum of compound 10k.
Figure S33: ESI-HRMS of compound 10k.
Figure S34: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 10l.
Figure S35: $^{13}$C NMR (150 MHz, CDCl$_3$) spectrum of compound 10l.
Figure S36: ESI-HRMS of compound 10l.
**Figure S37**: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 10m.
Figure S38: $^{13}$C NMR (150 MHz, CDCl$_3$) spectrum of compound 10m.
Figure S39: ESI-HRMS of compound 10m.
Figure S40: $^1$H NMR (600 MHz, DMSO-$d_6$) spectrum of compound 11.
Figure S41: $^{13}$C NMR (150 MHz, DMSO-$d_6$) spectrum of compound 11.
Figure S42: $^1$H NMR (600 MHz, DMSO-$d_6$) spectrum of compound 12a.
Figure S43: $^{13}$C NMR (150 MHz, DMSO-$d_6$) spectrum of compound 12a.
Figure S44: ESI-HRMS of compound 12a.
Figure S45: $^1$H NMR (600 MHz, DMSO-$d_6$) spectrum of compound 12b.
Figure S46: $^{13}$C NMR (150 MHz, DMSO-$d_6$) spectrum of compound 12b.
Figure S47: ESI-HRMS of compound 12b.
Figure S48: $^1$H NMR (600 MHz, DMSO-$d_6$) spectrum of compound 12c.
Figure S49: $^{13}$C NMR (150 MHz, DMSO-$d_6$) spectrum of compound 12c.
Figure S50: ESI-HRMS of compound 12c.
Figure S51: $^1$H NMR (600 MHz, CDCl$_3$) spectrum of compound 12d.
Figure S52: $^{13}$C NMR (150 MHz, CDCl$_3$) spectrum of compound 12d.
Figure S53: ESI-HRMS of compound 12d.