Supporting Information
for DOI: 10.1055/s-0040-1707400
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A facile synthesis of ligands for the von Hippel-Lindau E3 ligase

Christian Steinebach, a Sabine Anna Voell, a Lan Phuong Vu, a Aleša Bricelj, b Izidor Sosič, b Gregor Schnakenburg, c and Michael Gütschow* a

a Pharmaceutical Institute, University of Bonn, An der Immenburg 4, 53121 Bonn, Germany
E-mail: guetschow@uni-bonn.de
b Faculty of Pharmacy, University of Ljubljana, Aškerčeva cesta 7, 1000 Ljubljana, Slovenia
c Institute of Inorganic Chemistry, University of Bonn, Gerhard-Domagk-Str. 1, 53121 Bonn, Germany

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Supplementary Notes

Availability of 4-bromobenzaldehydes:
A large set of substituted 4-bromobenzaldehydes is commercially available. Some examples used in this study are depicted in Figure S1. However, as exemplified for compound 4d, this class of compounds is easily accessible from different precursor molecules.

![Chemical structures of 4-bromobenzaldehydes](image)

Figure S1: Commercially available 4-bromobenzaldehydes used in this study.

4-Bromo-2-hydroxy-benzaldehyde (4d)
CAS: 22532-62-3

Method A: ortho-formylation

This compound was synthesized as reported previously. In brief, to a solution of 3-bromophenol (10 mmol, 1.73 g) in anhydrous THF (20 mL) was added Et<sub>3</sub>N (20 mmol, 2.02 g, 2.78 mL) and anhydrous MgCl<sub>2</sub> (20 mmol, 1.90 g). After stirring for 10 min, paraformaldehyde (30 mmol, 0.90 g) was added and the mixture was stirred at reflux for 6 h. The mixture was cooled to rt, 10% aqueous KHSO<sub>4</sub> was added, and the product was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with saturated NH<sub>4</sub>Cl solution and brine (50 mL each), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether/EtOAc 19:1) to give the title compound as a colorless solid. Yield (0.64 g, 32%); mp 70 – 72 °C, lit. mp 50 – 51.5 °C; R<sub>f</sub> = 0.30 (petroleum ether/EtOAc 10:1).
**1H NMR** (600 MHz, DMSO-\(d_6\)) \(\delta\) 7.13 (dd, \(J = 1.9, 8.3\) Hz, 1H), 7.19 (d, \(J = 1.8\) Hz, 1H), 7.56 (d, \(J = 8.4\) Hz, 1H, Ar-H), 10.22 (s, 1H), 11.10 (s, 1H, OH, CHO).

**13C NMR** (151 MHz, DMSO-\(d_6\)) \(\delta\) 120.15 (C-3), 121.99 (C-1), 122.86 (C-5), 129.67 (C-4), 130.55 (C-6), 161.38 (C-2), 190.35 (CO).

**LC-MS** (ESI) (90% H\(_2\)O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-450 nm), \(t_R = 10.03\) min, 95% purity, \(m/z\) [M + H]\(^+\) calcd for C\(_7\)H\(_5\)79BrO\(_2\), 199.95; found, 199.8.

**Method B: Weinreb amide and reduction:**

To a mixture of 4-bromosalicylic acid (5.0 mmol, 1.09 g) and Et\(_3\)N (5.5 mmol, 0.56 g, 0.77 mL) in dry CH\(_2\)Cl\(_2\) (50 mL) was added \(N,O\)-dimethylhydroxylamine (10 mmol, 0.98 g) and EDC \(\times\) HCl (5.5 mmol, 1.05 g) and the mixture was stirred at rt for 16 h. After evaporation of the solvent, the crude material was subjected to column chromatography (gradient of petroleum ether/EtOAc 10:1 to 4:1) to yield the corresponding Weinreb amide as colorless solid. Yield (1.01 g, 78%); mp 96 – 98 °C; \(R_f = 0.32\) (petroleum ether/EtOAc 4:1).

**1H NMR** (600 MHz, DMSO-\(d_6\)) \(\delta\) 3.17 (s, 3H, NCH\(_3\)), 3.52 (s, 3H, OCH\(_3\)), 7.00 (dd, \(J = 1.9, 8.1\) Hz, 1H), 7.03 (d, \(J = 1.8\) Hz, 1H), 7.14 (d, \(J = 8.1\) Hz, 1H, Ar-H), 10.33 (s, 1H, OH).

**13C NMR** (151 MHz, DMSO-\(d_6\)) \(\delta\) 32.02 (NCH\(_3\)), 60.77 (OCH\(_3\)), 118.56, 121.67, 122.70, 122.94, 129.52 (C-1, C-3, C-4, C-5, C-6), 155.23 (C-2), 166.79 (CO).

**LC-MS** (ESI) (90% H\(_2\)O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), \(t_R = 9.16\) min, 99% purity, \(m/z\) [M + H]\(^+\) calcd for C\(_9\)H\(_{10}\)79BrNO\(_3\), 259.99; found, 259.8.

**HRMS** (ESI) \(m/z\) [M + H]\(^+\) calcd for C\(_9\)H\(_{10}\)79BrNO\(_3\), 259.9917; found, 259.9915.

The Weinreb amide was converted to the title aldehyde compound in approximately 53% yield using LiAlH\(_4\) as reducing agent and following standard procedures.\(^2\) In brief, to a solution of the corresponding Weinreb amide (3.0 mmol, 0.78 g) in dry THF (15 mL) under an argon atmosphere at 0 °C, LiAlH\(_4\) (1M in THF, 1.5 mL) was added dropwise. After stirring for 30 min, the colourless mixture was cooled to -15 °C, and 10% KHSO\(_4\) solution (50 mL) and Et\(_2\)O (50 mL) were added. Subsequently, the organic layer was separated and the aqueous layer was extracted with EtOAc (50 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) filtered, and concentrated in vacuo. The crude material was subjected to column chromatography (gradient of petroleum ether/EtOAc 10:1 to 8:1) to yield the title aldehyde as a volatile colorless solid.

The spectroscopic data matched those reported for Method A.
Characteristics of O-acylated side products:

The use of unprotected phenols of type 6d in peptide syntheses inevitably leads to acylated by-products. The following compound represents a possible by-product which was obtained in the coupling between 6d and Boc-Hyp-OH.

\[ \text{O2-[2-[[[25R]-1-tert-Butoxycarbonyl-4-hydroxy-pyrrolidine-2-carbonyl]amino]\n[5-(4-methylthiazol-5-yl)phenyl] 01-tert-butyl (25R)-4-hydroxyppyrrrolidine-1,2-dicarboxylate} \]

Colorless solid; mp 104 – 106 °C; \( R_f = 0.28 \) (CH\(_2\)Cl\(_2\)/MeOH 9:1).

\( ^1H \text{NMR} \) (600 MHz, DMSO-\( d_6 \), the major rotamer) \( \delta \) 1.43 – 1.29 (m, 18H, \( \text{C(C(H\(_3\)_3}) \)), 1.89 – 1.82 (m, 1H), 2.13 – 2.03 (m, 1H), 2.39 – 2.21 (m, 2H, 3-H, 3'”-H), 2.44 (s, 3H, \( \text{CH}_3 \)), 3.55 – 3.32 (m, 4H, 2-H, 4-H, 2”-H, 4’’-H), 4.34 – 4.09 (m, 5H), 4.62 – 4.45 (m, 1H, 5-H, 5’’-H, \( \text{NHCH}_2 \)), 5.03 – 4.97 (m, 1H), 5.21 – 5.16 (m, 1H, OH), 7.22 – 7.17 (m, 1H, 6’-H), 7.53 – 7.29 (m, 2H, 3’-H, 5’-H), 8.47 – 8.33 (m, 1H, NH), 9.02 (s, 1H, 2’’-H).

\( ^{13}C \text{NMR} \) (151 MHz, DMSO-\( d_6 \), the major rotamer) \( \delta \) 172.67, 171.22, 154.20, 153.52 (CO), 152.23 (C-2’’), 148.56 (C-2’), 148.05 (C-4’’), 131.49, 131.17, 130.07, 129.38, 126.65, 122.28 (Ar-C), 79.62, 78.82 (\( \text{C(CH}_3\)\)), 68.81, 67.97 (C-4, C-4’’), 55.18, 55.00, 54.92, 54.74 (C-2, C-5, C-2’’’, C-5’’’), 38.02 (\( \text{NHCH}_2 \)), 36.75, 36.61 (C-3, C-3’’), 28.20, 28.13 (\( \text{C(C(H\(_3\)_3}) \)), 16.02 (\( \text{CH}_3 \)).

\( \text{LC-MS} \) (ESI) (90% H\(_2\)O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 200-400 nm), \( t_R = 10.68 \) min, 97% purity, \( m/z [M + H]^+ \) calcd for C\(_{31}\)H\(_{42}\)N\(_4\)O\(_9\)S, 647.27; found, 647.5.

\( \text{HRMS} \) (ESI) \( m/z [M + H]^+ \) calcd for C\(_{31}\)H\(_{42}\)N\(_4\)O\(_9\)S, 647.2745; found, 647.2735.
Supplementary Schemes

Scheme S1: Synthesis of protected VHL ligands of chemotype 1 including derivatives with new substitution patterns.
**Scheme S2:** Protected VHL ligands of chemotype 2, synthesized following the newly developed protecting group strategy.
Extended Experimental Section

tert-Butyl N-[(4-bromo-2-methyl-phenyl)methyl]carbamate (5b)

CAS: 1352896-24-2

By using the General Procedure I, this compound was prepared on a 5 mmol scale from 4b (1.00 g). The crude product was purified by column chromatography (petroleum ether/EtOAc 9:1) to obtain a colorless solid. Yield (1.28 g, 86%); mp 80 – 82 °C; Rf = 0.30 (petroleum ether/EtOAc 9:1).

$^1$H NMR (600 MHz, DMSO-d$_6$) δ 1.39 (s, 9H, C(CH$_3$)$_3$), 2.25 (s, 3H, CH$_3$), 4.06 (d, J = 6.0 Hz, 2H, CH$_2$), 7.12 (d, J = 8.0 Hz, 1H, Ar-H), 7.30 (t, J = 5.6 Hz, 1H, NH), 7.33 – 7.36 (m, 2H, Ar-H).

$^{13}$C NMR (151 MHz, DMSO-d$_6$) δ 18.15 (CH$_3$), 28.18 (C(CH$_3$)$_3$), 40.80 (CH$_2$), 77.80 (C(CH$_3$)$_3$)$_3$, 119.42 (C-4), 128.37, 129.07 (C-5, C-6), 132.10 (C-3), 137.27, 138.15 (C-1, C-2), 155.62 (CO).

LC-MS (ESI) (90% H$_2$O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), $t_R$ = 11.63 min, 97% purity, m/z [M + H]$^+$ calcd for C$_{13}$H$_{18}$BrNO$_2$, 300.06; found, 300.0.
**tert-Butyl N-[(4-bromo-2-methoxy-phenyl)methyl]carbamate (5c)**

CAS: 1402664-44-1

By using the General Procedure I, this compound was prepared on a 5 mmol scale from 4c (1.08 g). The crude product was purified by column chromatography (petroleum ether/EtOAc 9:1) to obtain a colorless solid. Yield (1.57 g, 99%); mp 68 – 70 °C; \( R_f = 0.30 \) (petroleum ether/EtOAc 9:1).

**\(^1\text{H NMR}\) (600 MHz, DMSO-\(d_6\))** \( \delta \) 1.39 (s, 9H, C(CH\(_3\))\(_3\)), 3.81 (s, 2H, CH\(_3\)), 4.04 (d, \( J = 6.0 \) Hz, 2H, CH\(_2\)), 7.07 (d, \( J = 8.0 \) Hz, 1H), 7.10 – 7.15 (m, 2H, Ar-H), 7.19 (t, \( J = 5.7 \) Hz, 1H, NH).

**\(^{13}\text{C NMR}\) (151 MHz, DMSO-\(d_6\))** \( \delta \) 28.21 (C(CH\(_3\))\(_3\)), 38.00 (CH\(_2\)), 55.78 (OCH\(_3\)), 77.81 (C(CH\(_3\))\(_3\)), 113.60 (C-3), 120.13 (C-4), 122.85 (C-1), 127.14, 128.64 (C-5, C-6), 155.72 (CO), 157.25 (C-2).

**LC-MS** (ESI) (90% H\(_2\)O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), \( t_R = 11.48 \) min, 100% purity, \( m/z [M + H]^+ \) calcd for C\(_{13}\)H\(_{18}\)\(^89\)BrNO\(_3\), 316.05; found, 315.9.
**tert-Butyl N-[(4-bromo-2-fluoro-phenyl)methyl]carbamate (5e)**

CAS: 864262-97-5

By using the General Procedure I, this compound was prepared on a 1 mmol scale from **4e** (0.20 g). The crude product was purified by column chromatography (petroleum ether/EtOAc 10:1) to obtain a colorless solid. Yield (130 mg, 43%); mp 78 – 80 °C; \( R_f = 0.30 \) (petroleum ether/EtOAc 6:1).

**\(^1H\) NMR** (500 MHz, DMSO-\(d_6\)) \( \delta \) 1.37 (s, 9H, CH\(_3\)), 4.11 (d, \( J = 6.0 \) Hz, 2H, CH\(_2\)), 7.24 (t, \( J = 8.2 \) Hz, 1H, NH), 7.34 – 7.42 (m, 2H), 7.47 (dd, \( J = 2.0, 9.7 \) Hz, 1H, Ar-H).

**\(^13C\) NMR** (126 MHz, DMSO-\(d_6\)) \( \delta \) 28.32 (C(CH\(_3\))\(_3\)), 36.99 (CH\(_2\)), 78.21 (C(CH\(_3\))\(_3\)), 118.50 (d, \( J_{CF} = 24.9 \) Hz, C-3), 120.03 (d, \( J_{CF} = 9.6 \) Hz, C-4), 126.53 (d, \( J_{CF} = 14.8 \) Hz, C-1), 127.56 (d, \( J_{CF} = 3.5 \) Hz, C-5), 130.91 (d, \( J_{CF} = 5.3 \) Hz, C-6), 155.79 (CO), 159.87 (d, \( J_{CF} = 249.3 \) Hz, C-2).

**LC-MS (ESI)** (90% H\(_2\)O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), \( t_R = 11.43 \) min, 98% purity, \( m/z \) [M + H]\(^+\) calcd for C\(_{12}\)H\(_{15}\)\(^{81}\)BrFNO\(_2\), 306.03; found, 306.0.
**tert-Butyl N-[(4-bromo-3-chloro-phenyl)methyl]carbamate (5f)**

CAS: 864266-05-7

By using the General Procedure I, this compound was prepared on a 1 mmol scale from 4f (0.22 g). The crude product was purified by column chromatography (petroleum ether/EtOAc 10:1) to obtain a colorless solid. Yield (93 mg, 29%); mp 98 – 100 °C; $R_f = 0.49$ (petroleum ether/EtOAc 6:1).

$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 1.38 (s, 9H, CH$_3$), 4.08 (d, $J = 6.1$ Hz, 2H, CH$_2$), 7.13 (dd, $J = 2.1$, 8.4 Hz, 1H, Ar-H), 7.42 (t, $J = 7.2$ Hz, 1H, NH), 7.45 (d, $J = 2.1$ Hz, 1H), 7.70 (d, $J = 8.2$ Hz, 1H, Ar-H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 28.32 (C(CH$_3$)$_3$), 42.55 (CH$_2$), 78.23 (C(CH$_3$)$_3$), 119.40 (C-4), 127.61, 128.96 (C-3, C-6), 132.95, 133.80 (C-2, C-5), 142.25 (C-1), 155.89 (CO).

LC-MS (ESI) (90% H$_2$O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), $t_R = 11.66$ min, 97% purity, $m/z$ [M + H]$^+$ calcd for C$_{12}$H$_7$BrClNO$_2$, 322.00; found, 321.9.
**tert-Butyl N-[(4-bromo-3-methyl-phenyl)methyl]carbamate (5g)**

CAS: 1220039-91-7

By using the General Procedure I, this compound was prepared on a 1 mmol scale from 4g (0.20 g). The crude product was purified by column chromatography (petroleum ether/EtOAc 10:1) to obtain a colorless solid. Yield (126 mg, 42%); mp 88 – 90 °C; $R_f = 0.30$ (petroleum ether/EtOAc 6:1).

$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 1.38 (s, 9H, C(CH$_3$)$_3$), 2.31 (s, 3H, CH$_3$), 4.04 (d, $J = 6.2$ Hz, 2H, CH$_2$), 6.98 (dd, $J = 2.2$, 8.2 Hz, 1H), 7.19 (d, $J = 2.5$ Hz, 1H, Ar-H), 7.34 (t, $J = 6.5$ Hz, 1H, NH), 7.49 (d, $J = 8.2$ Hz, 1H, Ar-H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 22.52 (CH$_3$), 28.36 (C(CH$_3$)$_3$), 42.91 (CH$_2$), 78.00 (C(CH$_3$)$_3$), 122.17 (C-4), 126.59 (C-6), 129.86 (C-2), 132.01 (C-5), 136.96 (C-1), 140.03 (C-3), 155.88 (CO).

LC-MS (ESI) (90% H$_2$O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), $t_R = 11.65$ min, 99% purity, $m/z$ [M + H]$^+$ calcd for C$_{13}$H$_{18}$BrNO$_2$, 302.05; found, 301.9.
**tert-Butyl N-[(4-bromo-2,6-difluoro-phenyl)methyl]carbamate (5h)**

CAS: 1402673-66-8

By using the General Procedure I, this compound was prepared on a 5 mmol scale from 4h (1.10 g). The crude product was purified by column chromatography (petroleum ether/EtOAc 9:1) to obtain a colorless solid. Yield (1.23 g, 76%); mp 142 – 145 °C; \( R_f = 0.16 \) (petroleum ether/EtOAc 9:1).

**\(^1\)H NMR** (600 MHz, DMSO-\(d_6\)) \( \delta \) 1.36 (s, 9H, CH\(_3\)), 6.31 (suppressed t, \( J = 7.2 \) Hz, 1H, NH), 7.23 – 7.75 (m, 2H, Ar-H); the signal for CH\(_2\) was not visible.

**\(^{13}\)C NMR** (151 MHz, DMSO-\(d_6\)) \( \delta \) 28.07 (C(CH\(_3\))\(_3\)), 52.61 (CH\(_2\)), 78.59 (C(CH\(_3\))\(_3\)), 115.53 (C-3, C-5), 116.26 (C-1), 121.00 (C-4), 153.94 (CO), 160.02 (d, \( J_{CF} = 252.0 \) Hz), 160.08 (d, \( J_{CF} = 252.9 \) Hz, C-2, C-6).

**LC-MS** (ESI) (90% H\(_2\)O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 210-400 nm), \( t_R = 11.72 \) min, 96% purity, \( m/z \) [M + H]\(^+\) calcd for C\(_{12}\)H\(_{14}\)\(^79\)BrF\(_2\)NO\(_2\), 322.02; found, 322.0.
tert-Butyl N-[(4-bromo-2,5-dimethoxy-phenyl)methyl]carbamate (5i)

By using the General Procedure I, this compound was prepared on a 1 mmol scale from 4i (245 mg). The crude product was purified by column chromatography (petroleum ether/EtOAc 10:1) to obtain a colorless solid. Yield (242 mg, 70%); mp 74 – 76 °C; $R_f$ = 0.31 (petroleum ether/EtOAc 6:1).

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 1.39 (s, 9H, CH$_3$), 3.74 (br s, 6H, OCH$_3$), 4.05 (d, $J$ = 6.0 Hz, 2H, CH$_2$), 6.92 (s, 1H), 7.15 (s, 1H, Ar-H), 7.20 (t, $J$ = 6.2 Hz, 1H, NH).

$^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 28.35 (C(CH$_3$)$_3$), 38.38 (CH$_2$), 56.34, 56.68 (OCH$_3$), 78.05 (C(CH$_3$)$_3$), 108.59 (C-4), 112.42, 115.70 (C-3, C-6), 128.45 (C-1), 149.50, 150.93 (C-2, C-5), 155.93 (CO).

LC-MS (ESI) (90% H$_2$O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), $t_R$ = 11.27 min, 99% purity, $m/z$ [M + H]$^+$ calcd for C$_{14}$H$_{20}$BrNO$_4$, 346.06; found, 346.1.
**tert-Butyl N-[(4-bromo-3,5-dimethoxy-phenyl)methyl]carbamate (5k)**

By using the General Procedure I, this compound was prepared on a 1 mmol scale from 4k (245 mg). The crude product was purified by column chromatography (petroleum ether/EtOAc 10:1) to obtain a colorless solid. Yield (277 mg, 80%); mp 98 – 100 °C; \( R_f = 0.16 \) (petroleum ether/EtOAc 6:1).

**\(^1\)H NMR** (500 MHz, DMSO-\(d_6\)) \( \delta \) 1.39 (s, 9H, CH\(_3\)), 3.79 (br s, 6H, OCH\(_3\)), 4.10 (d, \( J = 6.1 \) Hz, 2H, CH\(_2\)), 6.62 (s, 2H, Ar-H), 7.37 (t, \( J = 6.8 \) Hz, 1H).

**\(^{13}\)C NMR** (126 MHz, DMSO-\(d_6\)) \( \delta \) 28.34 (C(CH\(_3\))\(_3\)), 43.68 (CH\(_2\)), 56.34 (OCH\(_3\)), 78.09 (C(CH\(_3\))\(_3\)), 97.76 (C-4), 103.77 (C-2, C-6), 141.62 (C-1), 155.97 (CO), 156.47 (C-3, C-5).

**LC-MS** (ESI) (90% H\(_2\)O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), \( t_R = 10.84 \) min, 98% purity, \( m/z \ [M + H]^+ \) calcd for C\(_{14}\)H\(_{20}\)BrNO\(_4\), 346.06; found, 346.1.
**tert-Butyl N-[[2-methyl-4-(4-methylthiazol-5-yl)phenyl]methyl]carbamate (6b)**

By using the General Procedure II, this compound was prepared on a 2 mmol scale from compound 5b (0.60 g). The crude product was purified by column chromatography (gradient of petroleum ether/EtOAc 10:1 to 2:1) to obtain a colorless oil. Yield (0.34 g, 53%); \(R_f = 0.50\) (petroleum ether/EtOAc 1:1).

**\(^1\)H NMR** (600 MHz, DMSO-\(d_6\)) \(\delta\) 1.40 (s, 9H, \(\text{C(CH}_3\text{)}_3\)), 2.31 (s, 3H, \(\text{CH}_3\)), 2.45 (s, 3H, \(\text{CH}_3\)), 4.14 (d, \(J = 5.9\) Hz, 2H, \(\text{CH}_2\)), 7.25 – 7.30 (m, 3H, Ar-H), 7.34 (t, \(J = 5.8\) Hz, 1H, NH), 8.97 (s, 1H, 2''-H).

**\(^{13}\)C NMR** (151 MHz, DMSO-\(d_6\)) \(\delta\) 15.95 (CH\(_3\)), 18.46 (CH\(_3\)), 28.23 (C(CH\(_3\))\(_3\)), 41.05 (CH\(_2\)), 77.80 (C(CH\(_3\))\(_3\)), 126.25 (C-5''), 127.44, 129.73, 130.29, 131.13 (C-3, C-4, C-5, C-6), 136.02 (C-2), 137.76 (C-1), 147.66 (C-4''), 151.30 (C-2''), 155.71 (CO).

**LC-MS (ESI)** (90% H\(_2\)O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), \(t_R = 11.21\) min, 92% purity, \(m/z\) [M + H]\(^+\) calcd for C\(_{17}\)H\(_{28}\)N\(_2\)O\(_2\)S, 319.14; found, 318.9.
**tert-Butyl N-[[2-methyl-4-(4-methylthiazol-5-yl)phenyl]methyl]carbamate (6c)**

By using the General Procedure II, this compound was prepared on a 2 mmol scale from compound 5c (0.63 g). The crude product was purified by column chromatography (gradient of petroleum ether/EtOAc 10:1 to 2:1) to obtain a colorless oil. Yield (0.45 g, 68%); R\textsubscript{f} = 0.50 (petroleum ether/EtOAc 1:1).

\textbf{\textsuperscript{1}H NMR} (600 MHz, DMSO-\textit{d}_6) \delta 1.40 (s, 9H, C(CH\textsubscript{3})\textsubscript{3}), 2.47 (s, 3H, CH\textsubscript{3}), 3.84 (s, 3H, OCH\textsubscript{3}), 4.13 (d, J = 6.0 Hz, 2H, CH\textsubscript{2}), 7.01 (d, J = 1.4 Hz, 1H), 7.04 (d, J = 7.7 Hz, 1H), 7.19 – 7.24 (m, 2H, Ar-H, NH), 8.98 (s, 1H, 2''-H).

\textbf{\textsuperscript{13}C NMR} (151 MHz, DMSO-\textit{d}_6) \delta 16.00 (CH\textsubscript{3}), 28.24 (C(CH\textsubscript{3})\textsubscript{3}), 38.15 (CH\textsubscript{2}), 55.49 (OCH\textsubscript{3}), 77.79 (C(CH\textsubscript{3})\textsubscript{3}), 111.00 (C-3), 120.90 (C-5''), 127.40, 127.58, 131.01, 131.25 (C-1, C-4, C-5, C-6), 147.91 (C-4''), 151.41 (C-2''), 155.79 (CO), 156.48 (C-2').

\textbf{LC-MS (ESI)} (90% H\textsubscript{2}O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), \textit{t}\textsubscript{R} = 11.12 min, 90% purity, \textit{m/z} [M + H]\textsuperscript{+} calcd for C\textsubscript{17}H\textsubscript{22}N\textsubscript{2}O\textsubscript{3}S, 335.14; found, 334.9.
**General Procedure V: Boc-deprotection and EDC coupling**

The Boc-protected amine (16.5 mmol) was dissolved in dry CH₂Cl₂ (30 mL), followed by the addition of 4M HCl in dioxane (16 mL). The reaction mixture was stirred at rt for 2 h. The solvent was removed under reduced pressure and coevaporated with Et₂O (3 × 20 mL). The residue was further dried in high vacuum.

To a solution of the corresponding carboxylic acid (15 mmol) in dry CH₂Cl₂ (50 mL) EDC × HCl (19.5 mmol, 3.74 g), HOBt hydrate (19.5 mmol, 2.99 g) and DIPEA (45 mmol, 5.82 g, 7.84 mL) were added under argon atmosphere. A solution of the deprotected amine (16.5 mmol) in dry CH₂Cl₂ (10 mL) was added dropwise at 0 °C, followed by stirring of the mixture at rt for 24 h. Subsequently, the solution was diluted with CH₂Cl₂ (200 mL), washed with saturated NaHCO₃ solution, 0.5M HCl and brine (each 200 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo.
**tert-Butyl (2S,4R)-4-hydroxy-2-[(4-{4-methylthiazol-5-yl)phenyl]methylcarbamoyl]pyrrolidine-1-carboxylate (8a)**

CAS: 1448191-54-5

This compound was prepared using the General Procedure V and compound 6a (5.02 g) and Boc-Hyp-OH (3.47 g). The crude product was purified by column chromatography (CH$_2$Cl$_2$/MeOH 20:1) to give a colorless solid. Yield (4.76 g, 76%); mp 74 – 76 °C, lit. mp 78 – 80 °C; $R_f = 0.60$ (CH$_2$Cl$_2$/MeOH 9:1).

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.26 and 1.41 (each s, 9H, the major and minor rotamer, C(CH$_3$)$_3$), 1.81 – 1.91 (m, 1H, 3-H), 2.01 – 2.13 (m, 1H, 3-H), 2.44 (s, 3H, CH$_3$), 3.24 – 3.33 (m, 1H), 3.36 – 3.48 (m, 1H), 4.14 – 4.30 (m, 3H), 4.32 – 4.42 (m, 1H), 5.00 and 5.01 (d, $J = 3.7$ Hz, 1H, major and minor rotamer, OH), 7.34 – 7.45 (m, 4H, 2'-H, 3'-H), 8.46 and 8.49 (t, $J = 6.0$ Hz, 1H, major and minor rotamer, NH), 8.98 (s, 1H, 2''-H).

$^{13}$C NMR (101 MHz, DMSO-$d_6$ the major rotamer) $\delta$ 15.88 (CH$_3$), 27.90 (C(CH$_3$)$_3$), 39.65 (C-3), 41.82 (NHCH$_2$), 54.78, 58.95 (C-2, C-5), 67.84 (C-4), 78.50 (C(CH$_3$)$_3$), 128.13, 128.84 (C-2', C-3'), 129.97, 131.08 (C-5', C-1'), 139.47 (C-4'), 147.82 (C-4''), 151.52 (C-2''), 153.55 (NCO), 172.53 (CONH).

HPLC (95% H$_2$O to 95% MeCN in 10 min, then 95% MeCN for 4 min), $t_R = 5.83$ min, 96% purity, detection at 210 nm.

HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{21}$H$_{27}$N$_3$O$_4$S, 418.1795; found, 418.1785.
**tert-Butyl (2S,4R)-4-hydroxy-2-[[2-methyl-4-(4-methylthiazol-5-yl)phenyl]methylcarbamoyl]pyrrolidine-1-carboxylate (8b)**

By using the General Procedure V, this compound was prepared on a 1.42 mmol scale from compound 6b (0.45 g) and Boc-Hyp-OH (0.30 g). The crude product was purified by column chromatography (EtOAc) to give a colorless solid. Yield (0.26 g, 42%); mp 190 – 192 °C; R₇ = 0.14 (EtOAc).

**¹H NMR** (600 MHz, DMSO-d₆) δ 1.27 and 1.41 (each s, 9H, the major and minor rotamer, C(CH₃)₃), 1.83 – 1.91 (m, 1H, 3-H), 2.01 – 2.12 (m, 1H, 3-H), 2.30 and 2.34 (each s, 3H, the major and minor rotamer, CH₃), 2.44 (s, 3H, CH₃), 3.37 – 3.49 (m, 1H), 4.14 – 4.29 (m, 3H), 4.29 – 4.38 (m, 1H), 4.97 and 4.98 (d, J = 3.3 Hz, 1H, major and minor rotamer, OH), 7.20 – 7.39 (m, 3H, 3'-H, 5'-H, 6'-H), 8.28 – 8.36 (m, 1H, NH), 8.97 (s, 1H, 2''-H).

**¹³C NMR** (126 MHz, DMSO-d₆, the major rotamer) δ 15.88 (CH₃), 18.60 (CH₃), 27.87 (C(CH₃)₃), 38.61 (C-3), 54.73, 58.80 (C-2, C-5), 67.79 (C-4), 78.42 (C(CH₃)₃), 126.12, 128.53, 129.99, 130.36, 131.07 (C-5”, C-Ar), 136.45 (C-2”), 137.05 (C-1’), 147.67 (C-4’”), 151.33 (C-2’”), 153.52 (NCO), 172.35 (CONH); the signal for NHCH₂ is not visible (overlapping solvent peak).

**LC-MS** (ESI) (90% H₂O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), tᵣ = 10.46 min, 98% purity, m/z [M + H]⁺ calcd for C₂₂H₂₉N₃O₄S, 432.19; found, 432.0.
**tert-Butyl (2S,4R)-4-hydroxy-2-[[2-methyl-4-(4-methylthiazol-5-yl)phenyl]methyl-carbamoyl]pyrrolidine-1-carboxylate (8c)**

By using the General Procedure V, this compound was prepared on a 1.35 mmol scale from compound 6c (0.45 g) and Boc-Hyp-OH (0.28 g). The crude product was purified by column chromatography (EtOAc) to give a colorless solid. Yield (0.14 g, 23%); mp 86 – 88 °C; Rf = 0.32 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1).

**<sup>1</sup>H NMR** (500 MHz, DMSO-d<sub>6</sub>) δ 1.28 and 1.41 (each s, 9H, the major and minor rotamer, C(CH<sub>3</sub>)<sub>3</sub>), 1.84 – 1.92 (m, 1H, 3-H), 2.02 – 2.12 (m, 1H, 3-H), 2.46 (s, 3H, CH<sub>3</sub>), 3.38 – 3.47 (m, 1H), 3.85 (s, 3H, OCH<sub>3</sub>), 4.15 – 4.36 (m, 4H), 4.97 and 4.98 (d, J = 3.4 Hz, 1H, major and minor rotamer, OH), 6.99 – 7.04 (m, 2H), 7.25 (d, J = 7.7 Hz, 1H, 3'-H, 5'-H, 6'-H), 8.27 (t, J = 5.9 Hz, 1H, NH), 8.98 (s, 1H, 2''-H).

**<sup>13</sup>C NMR** (126 MHz, DMSO-d<sub>6</sub>) δ 15.90 (CH<sub>3</sub>), 27.87 (C(CH<sub>3</sub>)<sub>3</sub>), 36.88 (C-3), 54.37, 55.51, 58.82 (OCH<sub>3</sub>, C-2, C-5), 67.81 (C-4), 78.43 (C(CH<sub>3</sub>)<sub>3</sub>), 111.15 (C-3’), 120.73 (C-5’), 127.70, 128.36, 131.26 (C-3’, C-5’, C-6’), 147.91 (C-4’), 151.43 (C-2’), 153.51 (NCO), 156.71 (C-2’), 172.58 (CONH); signal for NH<sub>2</sub>CH is not visible (overlapping solvent peak).

**LC-MS** (ESI) (90% H<sub>2</sub>O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), t<sub>R</sub> = 10.29 min, 96% purity, m/z [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>28</sub>N<sub>3</sub>O<sub>5</sub>S, 448.19; found, 448.0.
**tert-Butyl (2S,4S)-2-[[2-tert-butyl(diphenyl)silyl]oxy-4-(4-methylthiazol-5-yl)phenyl]methylcarbamoyl]-4-hydroxy-pyrrolidine-1-carboxylate (8e)**

This compound was prepared using the General Procedure IV, compound 7 (2.0 mmol, 1.12 g), and Boc-d-Hyp-OH (2.0 mmol, 0.46 g). The crude product was purified by column chromatography (gradient of petroleum ether/EtOAc 1:1 to EtOAc) to obtain a colorless solid. Yield (0.66 g, 49%); mp 86 – 88 °C; \(R_f = 0.45\) (EtOAc).

**1H NMR** (600 MHz, DMSO-\(d_6\)) \(\delta\) 1.06 (s, 9H, Si(CH\(_3\))\(_3\)), 1.35 (s, 9H, OC(CH\(_3\))\(_3\)), 1.84 (s, 3H, CH\(_3\)), 1.89 – 1.97 (m, 1H), 2.06 – 2.16 (m, 1H, 3-H), 3.36 – 3.52 (m, 2H, 2-H, 4-H), 4.28 (dt, \(J = 7.9, 15.9\) Hz, 2H, CH\(_2\)), 4.37 – 4.49 (m, 1H, 5-H), 4.54 – 4.68 (m, 2H, 5-H), 5.01 (s, 1H, OH), 6.38 (d, \(J = 7.5\) Hz, 1H), 6.96 (d, \(J = 7.5\) Hz, 1H), 7.27 (d, \(J = 7.9\) Hz, 1H), 7.43-7.51 (m, 6H), 7.71 (t, \(J = 7.5\) Hz, 4H, Ar-H), 8.38 – 8.43 (m, 1H, NH), 8.80 (s, 1H, 2"-H).

**13C NMR** (151 MHz, DMSO-\(d_6\)) \(\delta\) 15.32 (CH\(_3\)), 18.96 (SiC(CH\(_3\))\(_3\)), 26.21 (SiC(CH\(_3\))\(_3\)), 27.95 (OC(CH\(_3\))\(_3\)), 37.30 (C-3), 38.66 (NHCH\(_2\)), 54.83, 58.97 (C-2, C-5), 67.88 (C-4), 78.59 (OC(CH\(_3\))\(_3\)), 118.10 (C-3’), 121.54 (C-5’), 128.19, 128.81, 130.39, 130.46, 131.42, 134.93 (C-Ar), 147.41 (C-4’), 151.46 (C-2’), 153.57 (COO), 172.83 (CONH).

**LC-MS** (ESI) (90% H\(_2\)O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), \(t_R = 12.38\) min, 95% purity, \(m/z \ [M + H]^+\) calcd for C\(_{37}\)H\(_{45}\)N\(_3\)O\(_5\)Si, 672.29; found, 672.4.

**HRMS** (ESI) \(m/z \ [M + H]^+\) calcd for C\(_{37}\)H\(_{45}\)N\(_3\)O\(_5\)Si, 672.2922; found, 672.2905.
(2S,4R)-N-[[2-[tert-Butyl(diphenyl)silyl]oxy-4-(4-methylthiazol-5-yl)phenyl]methyl]-1-[(2S)-2-[(1-fluorocyclopropanecarbonyl)amino]-3,3-dimethyl-butanoyl]-4-hydroxy-pyrrolidine-2-carboxamide (11)

By using the General Procedure IV, this compound was prepared from 9 (2 mmol, 1.57 g) and 1-fluorocyclopropanecarboxylic acid (2 mmol, 0.21 g). The crude product was purified by flash chromatography on silica gel (0% to 5% MeOH in CH₂Cl₂) to yield the title compound as a colorless solid. Yield (1.06 g, 69%); mp 92 – 94 °C; R_f = 0.42 (CH₂Cl₂/MeOH 19:1).

^1H NMR (600 MHz, DMSO-d₆, the major rotamer) δ 0.97 (s, 9H, C(CH₃)₃), 1.06 (s, 9H, SiC(CH₃)₃), 1.14 – 1.26 (m, 2H), 1.28 – 1.41 (m, 2H, 2''^-H), 1.83 (s, 3H, CH₃), 1.93 – 2.00 (m, 1H), 2.08 – 2.15 (m, 1H, 3-H), 3.62 (d, J = 10.5 Hz, 1H), 3.67 (dd, J = 3.9, 10.8 Hz, 1H, 5-H), 4.34 – 4.40 (m, 1H), 4.45 (dd, J = 5.4, 16.3 Hz, 1H), 4.49 – 4.58 (m, 2H), 4.58 – 4.63 (m, 1H, 2-H, 4-H, NHCH, NHCH₂), 5.17 (d, J = 3.7 Hz, 1H, OH), 6.37 (d, J = 1.8 Hz, 1H), 6.95 (dd, J = 1.8, 8.0 Hz, 1H), 7.29 (dd, J = 2.8, 9.3 Hz, 1H), 7.41 – 7.49 (m, 5H), 7.47 (s, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.67 – 7.73 (m, 4H, Ar-H, SiAr-H, CONH), 8.58 (t, J = 6.0 Hz, 1H, CONH), 8.79 (s, 1H, 2''^-H).

^13C NMR (151 MHz, DMSO-d₆, the major rotamer) δ 12.87 (d, J = 10.1 Hz), 13.13 (d, J = 10.0 Hz, C-2''^-), 15.51 (CH₃), 19.13 (SiC(CH₃)₃), 26.33 (CHC(CH₃)₃), 26.42 (SiC(CH₃)₃), 36.20 (C(CH₃)₃), 37.78 (C-3), 38.08 (NHCH₃), 56.73, 56.85, 59.05 (C-2, C-5, NHCH), 69.08 (C-4), 78.28 (d, J = 232.2 Hz, C-1''^-), 118.02 (C-3'), 121.65 (C-5'), 128.37, 128.40, 128.75, 128.85, 130.28, 130.56, 130.71, 131.57, 131.60, 135.12 (C-1', C-4', C-6', C-5''^-, Si-Ar), 147.51 (C-4''), 151.56 (C-2''), 152.39 (C-2'), 168.23 (d, J = 20.7 Hz), 169.13, 172.09 (CO).

LC-MS (ESI) (90% H₂O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), t_R = 12.69 min, 98% purity, m/z [M + H]^+ calcd for C₄₂H₅₁FN₄O₅Si, 771.34; found, 771.7.

HRMS (ESI) m/z [M + H]^+ calcd for C₄₂H₅₁FN₄O₅Si, 771.3406; found, 771.3391.
(2S,4R)-N-[[2-[tert-Butyl(diphenyl)silyl]oxy-4-(4-methylthiazol-5-yl)phenyl]methyl]-4-hydroxy-1-[(2S)-3-methyl-2-(1-oxoisooindolin-2-yl)butanoyl]pyrrolidine-2-carboxamide (12)

By using the General Procedure IV, this compound was prepared from 8d (7 mmol, 5.59 g) and acid 17 (7 mmol, 1.63 g). The crude product was purified by column chromatography (CH₂Cl₂/MeOH 29:1) to obtain a colorless solid. Yield (3.09 g, 56%); mp 126 – 128 °C; Rᶠ = 0.24 (CH₂Cl₂/MeOH 19:1).

¹H NMR (600 MHz, DMSO-dma, the major rotamer) δ 0.75 (d, J = 6.5 Hz, 3H, CH(CH₃)₂), 1.00 (d, J = 6.5 Hz, 3H, CH(CH₃)₂), 1.07 (s, 9H, SiC(CH₃)₃), 1.84 (s, 3H, CH₃), 1.95 – 2.02 (m, 1H), 2.05 – 2.11 (m, 1H, 3-H), 2.31 – 2.39 (m, 1H, CH(CH₃)₂), 3.70 – 3.74 (m, 1H), 3.81 (dd, J = 4.4, 10.7 Hz, 1H, 5-H), 4.38 – 4.34 (m, 1H), 4.52 – 4.44 (m, 3H, 4-H, NHCH₂, CHCH(CH₃)₂), 4.59 – 4.54 (m, 2H, 3a″-H), 4.74 (d, J = 10.8 Hz, 1H, 2-H), 5.10 (d, J = 4.1 Hz, 1H, OH), 6.39 (d, J = 1.7 Hz, 1H), 6.96 (dd, J = 1.7, 7.9 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.54 – 7.42 (m, 7H), 7.75 – 7.59 (m, 7H, Ar-H, SiAr-H), 8.48 (t, J = 5.8 Hz, 1H, CONH), 8.80 (s, 1H, 2″-H).

¹³C NMR (151 MHz, DMSO-dma, the major rotamer) δ 15.35 (CH₃), 18.60 (C(CH₃)₂), 18.91 (SiC(CH₃)₃), 18.97 (C(CH₃)₂), 26.25 (SiC(CH₃)₃), 28.36 (C(CH₃)₂), 37.38 (NHCH₂), 38.22 (C-3), 46.81 (C-3a″), 55.41 (C-5), 57.80 (CHCH(CH₃)₂), 58.76 (C-2), 68.62 (C-4), 117.92 (C-3′), 121.57 (C-5″), 123.00, 123.60, 127.88, 128.21, 128.23, 128.51, 128.72, 130.20, 130.40, 130.53, 131.36, 131.42, 131.56, 134.95, 134.96 (Ar-C), 142.19 (C-7a″), 147.37 (C-4′), 151.42 (C-2″), 152.29 (C-2′), 167.49, 168.15, 171.68 (CO).

LC-MS (ESI) (90% H₂O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 200-400 nm), tᵣ = 12.75 min, 99% purity, m/z [M + H]+ calcd for C₄₅H₅₀N₄O₅SSi, 787.33; found, 787.6.

HRMS (ESI) m/z [M + H]+ calcd for C₄₅H₅₀N₄O₅SSi, 787.3344; found, 787.3319.

23
(2S,4S)-N-[[2-[[tert-Butyl(diphenyl)silyl]oxy]-4-(4-methylthiazol-5-yl)phenyl]methyl]-4-hydroxy-1-[(2S)-3-methyl-2-(1-oxoisindolin-2-yl)butanoyl]pyrrolidine-2-carboxamide (13)

By using the General Procedure IV, this compound was prepared from 8e (0.75 mmol, 0.50 g) and acid 17 (0.75 mmol, 175 mg). The crude product was purified by column chromatography (CH₂Cl₂/MeOH 29:1) to obtain a colorless solid. Yield (0.40 g, 68%); mp 84 – 86 °C; Rf = 0.37 (CH₂Cl₂/MeOH 9:1).

**¹H NMR** (600 MHz, DMSO-d₆) δ 0.72 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.4 Hz, 3H, CH(CH₃)₂), 1.03 (s, 9H, SiCH(CH₃)₂), 1.81 (s, 3H, CH₃), 1.82 – 1.88 (m, 1H), 2.05 – 2.12 (m, 1H, 3-H), 2.33 – 2.42 (m, 1H, CH(CH₃)₂), 3.32 – 3.37 (m, 1H), 3.55 – 3.61 (m, 1H, 5-H), 4.25 – 4.31 (m, 1H), 4.32 – 4.38 (m, 1H), 4.39 – 4.57 (m, 4H), 4.67 (d, J = 10.5 Hz, 1H, 2-H, 4-H, NCH, NHCH₃, NCH₃), 5.12 (d, J = 3.4 Hz, 1H, OH), 6.36 (d, J = 1.8 Hz, 1H), 6.91 (dd, J = 1.7, 8.0 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.41 – 7.50 (m, 9H), 7.75 – 7.66 (m, 6H, Ar-H), 8.51 (t, J = 5.9 Hz, 1H, CONH), 8.80 (s, 1H, 2''-H).

**¹³C NMR** (151 MHz, DMSO-d₆) δ 15.34 (CH₃), 18.25 (CH(CH₃)₂), 18.94 (SiCH(CH₃)₂), 19.84 (CH(CH₃)₂), 26.22 (CH(CH₃)₂), 27.47 (CH(CH₃)₂), 37.36 (C-3), 38.22 (NHCH₂), 46.36 (C-2'''), 55.30 (C-5), 57.77 (C-2), 58.55 (NCH), 68.73 (C-4), 117.91 (C-3'''), 121.57 (C-5'''), 123.11, 123.41 (C-4''', C-7'''), 127.84 (C-6'''), 128.20, 128.43, 128.60, 130.20, 130.38, 130.50, 131.20, 131.40, 131.54, 134.92 (C-Ar, C-1', C-4', C-5', C-6', C-6'', C-7a'''), 142.10 (C-3a'''), 147.37 (C-4''), 151.43 (C-2''), 152.25 (C-2''), 167.32, 167.56, 172.00 (CO).

**LC-MS** (ESI) (90% H₂O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 200-330 nm), tᵣ = 12.59 min, 95% purity, m/z [M + H]+ calcd for C₄₅H₅₀N₄O₅SSi, 787.33; found, 787.6.

**HRMS** (ESI) m/z [M + H]+ calcd for C₄₅H₅₀N₄O₅SSi, 787.3344; found, 787.3325.
**tert-Butyl**  \(N\)-[\(1S\)-1-[(2S,4R)-4-hydroxy-2-[[4-(4-methylthiazol-5-yl)phenyl]methylcarbamoyl]pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl]carbamate (14)

CAS: 1448189-98-7

This compound was prepared using the General Procedure V and compound 8a (6.89 g) and Boc-Tle-OH (3.47 g). The crude product was purified by column chromatography (CH\(_2\)Cl\(_2\)/MeOH 20:1) to give a white solid. Yield (5.65 g, 71%); mp 82 – 83 °C; lit. mp no report found; \(R_f\) = 0.56 (CH\(_2\)Cl\(_2\)/MeOH 9:1).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 0.94 (s, 9H, C(CH\(_3\))\(_3\)), 1.38 (s, 9H, OC(CH\(_3\))\(_3\)), 1.85 – 1.99 (m, 1H, 3-H), 2.00 – 2.12 (m, 1H, 3-H), 2.44 (s, 3H, CH\(_3\)), 3.62 (d, \(J = 10.8\) Hz, 1H), 3.67 (dd, \(J = 4.1, 10.7\) Hz, 1H), 4.17 (d, \(J = 9.2\) Hz, 1H), 4.24 (dd, \(J = 5.6, 16.0\) Hz, 1H), 4.32 – 4.54 (m, 3H, 2-H, 4-H, 5-H, NHCH, CHCH\(_2\)), 5.16 (d, \(J = 3.5\) Hz, 1H, OH), 6.45 (d, \(J = 9.3\) Hz, 1H, BocNH), 7.36 – 7.44 (m, 4H, 2'-H, 3'-H), 8.59 (t, \(J = 6.1\) Hz, 1H, CONH), 8.97 (s, 1H, 2''-H).

\(^{13}\)C NMR (101 MHz, DMSO-\(d_6\), the major rotamer) \(\delta\) 15.95 (CH\(_3\)), 26.30 (C(CH\(_3\))\(_3\)), 28.20 (OC(CH\(_3\))\(_3\)), 35.43 (C(CH\(_3\))\(_3\)), 37.92 (C-3), 41.70 (NHCH\(_2\)), 56.40, 58.41, 58.79 (C-2, C-5, NHCH), 68.96 (C-4), 78.10 (OC(CH\(_3\))\(_3\)), 127.48, 128.69 (C-2', C-3'), 129.69, 131.19 (C-5'', C-1'), 139.48 (C-4'), 147.74 (C-4''), 151.43 (C-2''), 155.36 (NCO), 169.87, 171.95 (CO).

HPLC (95% H\(_2\)O to 95% MeCN in 10 min, then 95% MeCN for 4 min), \(t_R = 6.79\) min, 97% purity, detection at 210 nm.

HRMS (ESI) m/z [M + H]\(^+\) calcd for C\(_{27}\)H\(_{38}\)N\(_4\)O\(_5\)S, 531.2636; found, 531.2625.
**tert-Butyl**  \( N\-[(1S)-1\-((2S,4R)-4\-hydroxy\-2\-[2\-methyl\-4\-(4\-methylthiazol\-5\-yl)phenyl] methylcarbamoyl)pyrrolidine\-1\-carbonyl]\)-2,2\-dimethyl-propyl]carbamate (15)

By using the General Procedure V, this compound was prepared on a 0.55 mmol scale from compound 8b (0.24 g) and Boc-Tle-OH (0.12 g). The crude product was purified by column chromatography (EtOAc) to give a white solid. Yield (0.16 g, 53%); mp 94 – 96 °C; \( R_f = 0.42 \) (CH\(_2\)Cl\(_2\)/MeOH 9:1).

\(^1\text{H NMR}\) (500 MHz, DMSO-\(d_6\)) \( \delta \) 0.92 (s, 9H, C(CH\(_3\))\(_3\)), 1.38 (s, 9H, OC(CH\(_3\))\(_3\)), 1.88 – 1.94 (m, 1H 3-H), 2.00 – 2.07 (m, 1H, 3-H), 2.29 (s, 3H, CH\(_3\)), 2.44 (s, 3H, CH\(_3\)), 3.57 – 3.69 (m, 2H), 4.11 – 4.22 (m, 2H), 4.35 (dd, \( J = 5.9, 15.7 \) Hz, 2H), 4.47 (t, \( J = 7.9 \) Hz, 1H, 2-H), 4.47 (t, \( J = 7.9 \) Hz, 1H, BocNH), 5.11 (d, \( J = 2.1 \) Hz, 1H, OH), 6.39 (d, \( J = 7.7 \) Hz, 1H, BocNH), 7.21 (d, \( J = 7.8 \) Hz, 1H), 7.26 (s, 1H), 7.44 (d, \( J = 7.9 \) Hz, 1H, 3'-H, 5'-H, 6'-H), 8.41 (t, \( J = 5.2 \) Hz, 1H, CONH), 8.96 (s, 1H, 2''-H).

\(^{13}\text{C NMR}\) (126 MHz, DMSO-\(d_6\)) \( \delta \) 15.89 (CH\(_3\)), 18.44 (CH\(_3\)), 26.22 (C(CH\(_3\))\(_3\)), 28.13 (OC(CH\(_3\))\(_3\)), 35.31 (C(CH\(_3\))\(_3\)), 37.87 (C-3), 56.28, 58.34, 58.63 (C-2, C-5, NHCH), 68.86 (C-4), 78.03 (OC(CH\(_3\))\(_3\)), 126.05, 127.88, 129.72, 130.15, 131.16 (C-3', C-4', C-5', C-6', C-5''), 136.25 (C-2'), 136.98 (C-1'), 147.59 (C-4''), 151.26 (C-2''), 155.28 (NCO), 169.76, 171.64 (CO); the signal for NHCH\(_2\) is not visible (overlapping solvent peak).

**LC-MS** (ESI) (90% H\(_2\)O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), \( t_R = 11.40 \) min, 98% purity, \( m/z \) [M + H]\(^+\) calcd for C\(_{28}\)H\(_{40}\)N\(_4\)O\(_5\)S, 545.28; found, 545.3.

**HRMS** (ESI) \( m/z \) [M + H]\(^+\) calcd for C\(_{28}\)H\(_{40}\)N\(_4\)O\(_5\)S, 545.2753; found, 545.2771.
**tert-Butyl N-[(1S)-1-[(2S,4R)-4-hydroxy-2-[[2-methoxy-4-(4-methylthiazol-5-yl)phenyl]methylcarbamoyl]pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl]carbamate (16)**

By using the General Procedure V, this compound was prepared on a 0.25 mmol scale from compound 8c (0.11 g) and Boc-Tle-OH (0.05 g). The crude product was purified by column chromatography (EtOAc) to give a white solid. Yield (0.07 g, 53%); mp 78 – 80 °C; R_f = 0.44 (CH_2Cl_2/MeOH 9:1).

**1H NMR** (500 MHz, DMSO-d_6) δ 0.92 (s, 9H, C(CH_3)_3), 1.39 (s, 9H, OC(CH_3)_3), 1.89 – 1.95 (m, 1H, 3-H), 2.00 – 2.08 (m, 1H, 3-H), 2.46 (s, 3H, CH_3), 3.60 (d, J = 10.9 Hz, 1H), 3.65 (dd, J = 4.1, 10.5 Hz, 1H), 3.85 (s, 3H, OCH_3), 4.17 (dd, J = 4.4, 16.4 Hz, 2H), 4.28 (dd, J = 6.3, 16.4 Hz, 1H), 4.36 (s, 1H), 4.49 (t, J = 8.0 Hz, 1H, 2-H, 4-H, 5-H, NHCH, CHCH_2), 5.11 (d, J = 3.1 Hz, 1H, OH), 6.41 (d, J = 9.3 Hz, 1H, BocNH) 6.94 (dd, J = 1.4, 7.7 Hz, 1H), 7.01 (d, J = 1.4 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H, 3'-H, 5'-H, 6'-H), 8.40 (t, J = 5.8 Hz, 1H, CONH), 8.98 (s, 1H, 2''-H).

**13C NMR** (126 MHz, DMSO-d_6) δ 15.94 (CH_3), 26.21 (C(CH_3)_3), 28.15 (OC(CH_3)_3), 35.32 (C(CH_3)_3), 37.11 (NHCH), 37.80 (C-3), 55.48, 56.27, 58.35, 58.68 (OCH_3, C-2, C-5, NHCH), 68.87 (C-4), 78.05 (OC(CH_3)_3), 110.80 (C-3'), 120.73 (C-5''), 126.86, 127.90, 130.87, 131.29 (C-1', C-4', C-5', C-6'), 147.81 (C-4''), 151.36(C-2''), 155.30 (NCO), 156.48 (C-2'), 169.84 , 171.92 (CO).

**LC-MS (ESI)** (90% H_2O to 100% MeOH in 10 min, then 100% MeOH to 20 min, DAD 220-400 nm), t_R = 11.24 min, 98% purity, m/z [M + H]^+ calcd for C_{28}H_{40}N_4O_6S, 561.27; found, 561.1.

**HRMS (ESI)** m/z [M + H]^+ calcd for C_{28}H_{40}N_4O_6S, 561.2702; found, 561.2752.
(2S)-3-Methyl-2-(1-oxoisooindolin-2-yl)butanoic acid (17)

CAS: 180923-77-7

This compound was synthesized as reported previously. It was crystallized from MeCN, filtered and washed with cold MeCN (10 mL) and petroleum ether (10 mL) to give the product as yellow crystals. Yield (6.00 g, 88%); mp 182 – 184 °C, lit. mp 176 – 178 °C (EtOAc).

\[ \text{1H NMR (500 MHz, DMSO-d}_6\text{)} \delta 0.84 (d, J = 6.6 \text{ Hz}, 3\text{H}), 1.01 (d, J = 6.6 \text{ Hz}, 3\text{H, CH}_3), 2.14 – 2.41 (m, 1\text{H, CH(CH}_3)_2), 4.44 – 4.72 (m, 3\text{H, 3-H, COCH})), 7.37 – 7.59 (m, 1\text{H}), 7.61 (d, J = 4.1 \text{ Hz}, 2\text{H}), 7.70 (d, J = 7.6 \text{ Hz}, 1\text{H, Ar-H}). \]

\[ \text{13C NMR (126 MHz, DMSO-d}_6\text{)} \delta 19.29, 19.59 (\text{CH}_3), 28.36 (\text{CH(CH}_3)_2), 47.44 (\text{C-3}), 59.96 (\text{COCH}), 123.17, 123.74 (\text{C-4, C-7}), 128.11 (\text{C-6}), 131.46, 131.86 (\text{C-5, C-7a}), 142.30 (\text{C-3a}), 168.15 (\text{CO}), 172.00 (\text{COOH}). \]

\[ \text{LC-MS (ESI)} \text{ (90\% H}_2\text{O to 100\% MeOH in 10 min, then 100\% MeOH to 20 min, DAD 220-400 nm), } t_R = 6.46 \text{ min, 99\% purity, } m/z [\text{M + H}]^+ \text{ calcd for C}_{13}\text{H}_{15}\text{NO}_3, 234.11; \text{ found, 233.9.} \]
$^1$H and $^{13}$C NMR Spectra
$^1$H and $^{13}$C NMR spectrum of compound 2
$^1$H and $^{13}$C NMR spectrum of compound 4d
$^1$H and $^{13}$C NMR spectrum of compound 5a
$^1$H and $^{13}$C NMR spectrum of compound 5b
$^1$H and $^{13}$C NMR spectrum of compound 5c
$^1$H and $^{13}$C NMR spectrum of compound 5d
$^1$H and $^{13}$C NMR spectrum of compound 5e
$^1$H and $^{13}$C NMR spectrum of compound 5f
$^1$H and $^{13}$C NMR spectrum of compound 5g
$^1$H and $^{13}$C NMR spectrum of compound 5h
$^{1}H$ and $^{13}C$ NMR spectrum of compound 5i
$^1$H and $^{13}$C NMR spectrum of compound 5k
$^1$H and $^{13}$C NMR spectrum of compound 6a
$^1$H and $^{13}$C NMR spectrum of compound 6b
$^1$H and $^{13}$C NMR spectrum of compound 6c
$^1$H and $^{13}$C NMR spectrum of compound 6d
$^1$H and $^{13}$C NMR spectrum of compound 7
$^1$H and $^{13}$C NMR spectrum of compound 8a
$^1$H and $^{13}$C NMR spectrum of compound 8b
$^1$H and $^{13}$C NMR spectrum of compound 8c
$^1$H and $^{13}$C NMR spectrum of compound 8d
$^1$H and $^{13}$C NMR spectrum of compound 8e
$^1$H and $^{13}$C NMR spectrum of compound 9
$^1$H and $^{13}$C NMR spectrum of compound 10
$^1$H and $^{13}$C NMR spectrum of compound 11
\[ \text{\(^1\)H and \(^{13}\)C NMR spectrum of compound 12} \]
$^1$H and $^{13}$C NMR spectrum of compound 13
$^1$H and $^{13}$C NMR spectrum of compound 14
$^1$H and $^{13}$C NMR spectrum of compound 15
$^1$H and $^{13}$C NMR spectrum of compound 16
$^1$H and $^{13}$C NMR spectrum of compound 17
Crystallographic Data of Compound 14

The equation \( P \times x + Q \times y + R \times z - S = 0 \) was used, where \( P, Q, R, S \) are constants and \( x, y, z \) are fractional coordinates. Least-squares solution was performed with PLATON for Windows.\(^5\)

**Table S1:** Calculations of plane (I).

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<tr>
<th>Atom</th>
<th>Distance (Å)</th>
<th>x</th>
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**Table S2:** Calculations of plane (II).

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**Table S3:** Constants for the plane equations of the form \( P \times x + Q \times y + R \times z - S = 0 \).

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**Table S4:** Selected values of bond lengths, valence angles, and torsion angles.

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<td>C(6A)-C(7A)</td>
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