# Supporting Information

# Solid-Phase Synthesis of Peptide Thioureas and Thiazole-Containing Macrocycles through Ru-Catalyzed Ring-Closing Metathesis

**A. Emil Cohrt[a] and Thomas E. Nielsen*[a], [b]**

[a] *Department of Chemistry, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark;*
[b] *Singapore Centre on Environmental Life Sciences Engineering, Nanyang Technological University, Singapore 637551, Singapore*

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**Abbreviations**

Boc: *N-tert*-butoxycarbonyl; HATU: *N*-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; HOAt: 1-hydroxy-7-azabenzotriazole; HMBA: 4-hydroxymethylbenzoic acid; MeIm: 1-Methylimidazole; MSNT: 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole; NEM: *N*-ethyl morpholine; Pbf: 2,2,4,6,7-penta-methyldihydrobenzofuran-5-sulfonyl; PEGA: Polyethylene glycol dimethyl acrylamide; TBTU: *O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'- tetramethyluronium tetrafluorobrate; Trt: Trityl

**General Methods**

All reagents used were commercially available and all solvents were of HPLC grade. Solid-phase synthesis was carried out using syringe techniques in flat-bottomed PE-syringes fitted with PPE filters. The syringes were placed in a special setup equipped with Teflon tubing and Teflon valves, which allow suction to be applied to the syringes. Products were analyzed using a Waters Alliance 2695 HPLC system equipped with a Symmetry® C-18 column 3.5 $\mu$m, 4.6 x 75 mm, column temp; 25 °C, (1 ml/min.) with detection at 215 nm and 254 nm using a diode array detector. Eluent A (0.1% TFA in $H_2O$) and eluent B (0.1% TFA in acetonitrile) were used with a linear gradient (100% A to 100% B) with a run time of 13 min. Analytical LC-MS analysis was performed on a Waters AQUITY UPLC system equipped with PDA and SQD MS detector; column: AQUITY UPLC BEH C18 1.7 $\mu$m, 2.1 x 50mm; column temp: 65 °C; solvent A: 0.1% formic acid (aq); solvent B: 0.1% formic acid (acetonitrile); gradient: 5% B to 100% B in 2.4 min, hold for 0.1 min, total run-time ca. 2.6 min. LC-DAD-HRMS was performed on a Agilent 1100 LC system with a diode array detector (Agilent Technologies, Waldbronn, Germany) equipped with a 50 mm × 2 mm i. d. 3 $\mu$m Luna $C_{18}$ (2) column (Phenomenex, Torrance, CA, USA). Separation was achieved using a linear reverse phase gradient system at 40 °C and a flow rate of 400 $\mu$L/min. The gradient was started at 20% acetonitrile, which was increased to 100% in 8 min (holding this level for 2 min), then reverted to 20% in 1 min (holding this for 4 min.). Both water and acetonitrile contained 20mM formic acid. The LC was coupled to a Micromass LCT orthogonal time-of-flight mass spectrometer equipped with Lock Mass probe and operated in positive electrospray mode. All compounds were analyzed by UPLC-MS/HRMS and $^1$H NMR. Compound sufficient for NMR analysis was obtained by cleaving a resin sample of ca. 100 mg. $^1$H NMR 300 Mhz were recorded on a Varian Mercury 300 BB spectrometer at room temperature. $^1$H NMR 500 MHz spectra were recorded using a Varian Unity Inova-500 spectrometer. All NMR spectra were recorded using $CDCl_3$ or DMSO-$d_6$.

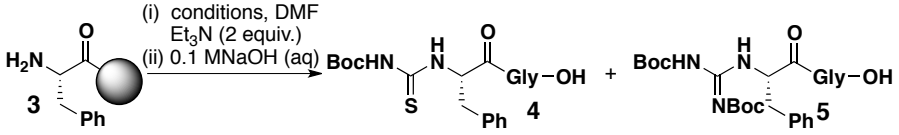
**Solid-Phase Synthesis**

Attachment of the HMBA linker to the amino-functionalized ChemMatrix (0.6 mmol/g) resin was carried out by premixing TBTU (2.88 equiv.), NEM (4 equiv.) and HMBA (3 equiv.) for 5 min. in DMF. The solution was then added to the preswollen resin in DMF and allowed to react for 2 hours followed by washing with DMF (× 6). Coupling of the first amino acid to the HMBA handle was carried out by premixing the Fmoc-AA-OH (3 equiv.), MSNT (3 equiv.) and MeIm (2.25 equiv.) in dry $CH_2Cl_2$. The solution was added to the preswollen resin in dry $CH_2Cl_2$ and allowed to react for 1 hour. The resin was washed with dry $CH_2Cl_2$ (× 3) and the coupling was repeated once. The resin was washed with DMF (× 6) after the coupling. Peptide synthesis was carried out as described for the attachment of HMBA to ChemMatrix. Fmoc-deprotection was accomplished with treatment of the resin with 20% piperidine (DMF) for 2 min. and then 18 min, followed by washing with DMF (× 6). Prior to thiourea formation, the deprotected resin was washed with DMF (× 6), $CH_2Cl_2$ (× 6) and dry $CH_2Cl_2$ (× 3). Formation of the resin-bound Boc-protected thioureas was carried out by mixing *N*,*N*'-di-Boc-thiourea (2 equiv.), $Et_3N$ (3 equiv.) and Mukaiyama's reagent (2 equiv.) in dry $CH_2Cl_2$ for 15 min before filtering off any solids. The filtrate was added to the preswellon resin in dry $CH_2Cl_2$ and allowed to react for 2 hours at room temperature followed by washing of the resin with DMF (× 6) and $CH_2Cl_2$ (× 6). Prior to guanylation, the deprotected resin was washed with DMF (× 6), $CH_2Cl_2$ (× 6), dry $CH_2Cl_2$ (× 3) and dry DMF (× 6). Formation of the resin-bound bis(Boc)-protected guanidines was achieved by adding *N*,*N*'-di-Boc-thiourea (1.5 equiv.) and $Et_3N$ (9 equiv.) in dry DMF to the preswollen resin in dry DMF for 5 min. $HgCl_2$ (3 equiv.) in dry DMF was added to the resin and allowed to react for 2 hours at room temperature followed by washing of the resin with DMF (× 6), 20% piperidine (DMF) (× 6), DMF (× 6) and $CH_2Cl_2$ (× 6). Peptides with Trp(Boc), Arg(Pfp), Asn(Trt) or Gln(Trt) as the last residue needed to be subjected to the guanylation conditions twice to achieve full conversion. Deprotection of resin-bound thioureas (except tryptophan) was performed by adding 0.1 M $SnCl_4$ (dry $CH_2Cl_2$) to resin for 2 × 30 min, followed by washing with $CH_2Cl_2$ (× 6), 20% piperidine

(DMF) (× 6), DMF (× 6) and $CH_2Cl_2$ (× 6). Deprotection of resin-bound guanidines (and thiourea-modified tryptophan derivatives) was performed by adding 0.25 M $SnCl_4$ (dry EtOAc) to the resin for 3 × 2 hours, followed by washing with $CH_2Cl_2$ (× 6), 20% piperidine (DMF) (× 6), DMF (× 6) and $CH_2Cl_2$ (× 6). Synthesis of solid supported thiazoles was achieved by adding the α-halo ketones or masked aldehydes (5 equiv.) in EtOH/$H_2O$ 3:1 to the solid supported deprotected thiourea in a glass vial. The vials were sealed and heated to 60 °C for 16 hours on a shaker, after which the solution was cooled to room temperature. The resin was transferred to plastic syringes fitted with PPE filters and washed with DMF (× 6) and $CH_2Cl_2$ (× 6). Coupling of alkene functionalized amines to **25** was achieved by adding HATU (2 equiv.), HOAt (1 equiv.) and NEM (2 equiv.) in DMF to **25** for 5 min followed by addition of the alkene functionalized amine HCl salt (4 equiv.) and NEM (4 equiv.) in DMF. The reaction was allowed to proceed for 1 hour. The resin was washed with DMF (× 3) and the coupling repeated. The on-bead ring closing metathesis was performed by adding 30 mol% of the metathesis catalysts in dry degassed $CH_2Cl_2$ to give a final concentration of 0.02 M. The syringes were sealed and placed on a shaker for 24 hours at rt. The resin was washed with DMF (× 3), $CH_2Cl_2$ (× 3) and dry degassed $CH_2Cl_2$ (× 3) before be the addition of another portion of catalysts. The syringes were sealed again and placed on the shaker for additional 24 hours. The resin was washed with DMF (× 3), $CH_2Cl_2$ (× 3), 10% TFA (aq) (3 × 10 min), $CH_2Cl_2$ (× 3), 20% piperidine (DMF) (3 × 10 min), DMF (× 6), MeOH (× 6) and $CH_2Cl_2$ (× 3). Release of products from the HMBA functionalized resin for HPLC analysis was achieved by treatment with aqueous NaOH (0.1 M) for 2 hours, followed by neutralization with aqueous HCl (0.1 M) and washing with MeCN (× 4) and $CH_2Cl_2$ (× 2). Release of preparative amounts from 100-200 mg resin was achieved by treatment with aqueous NaOH (0.1 M) for 24 hours followed by neutralization with aqueous HCl (0.1 M) and washings with MeCN (× 4) and $CH_2Cl_2$ (× 2).

**Screening of Reaction Conditions**

**Table S1**. Screening of reaction conditions for the solid-phase synthesis of phenylalanine-derived thiourea and guanidine derivatives.




| entry | conditions | conversion (%)[a] | product distribution (%)[a] | |
|---|---|---|---|---|
| | | | **4** | **5** |
| 1 | **9** (2 equiv.), 24 h. | 0 | - | - |
| 2 | **10** (2 equiv.), 2 h. | 25 | - | 100 |
| 3 | **10** (2 equiv.), 4 h. | 80 | - | 100 |
| 4 | **10** (2 equiv.), 8 h. | 80 | - | 100 |
| 5 | NIS (1 equiv.), **1** (1 equiv.), 4 h. | 87 | 83 | 17 |
| 6[b] | CuCl2 (2 equiv.), **1** (2 equiv.), 2 h.[c] | 69 | 34 | 66 |
| 7[b] | CuCl2 (2 equiv.), **1** (2 equiv.), 2 h.[d] | 84 | 79 | 21 |

[a] The conversion and product distribution was determined by RP-HPLC (215 nm). [b] 3 equiv. of $Et_3N$. [c] Drop-wise addition of $CuCl_2$ to a mixture of **3**, **1** and $Et_3N$ in dry DMF. [d] A mixture of $CuCl_2$, **1** and $Et_3N$ in DMF was allowed to react for 15 min before being added to the resin.

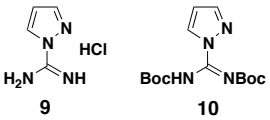
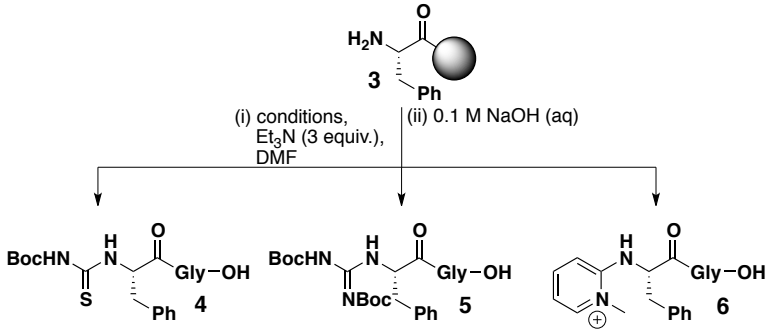


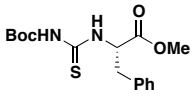

**Table S2**. Screening of reaction conditions for the HgO-mediated guanylation of solid-supported phenylalanine derivative.




| entry | conditions | conversion (%)[a] | product distribution (%)[a] | | |
|---|---|---|---|---|---|
| | | | 4 | 5 | 6 |
| 1 | HgO (2 equiv.), 1 (2 equiv.), 2 h. | 33 | 0 | 100 | 0 |
| 2 | HgO (5 equiv.), 1 (2 equiv.), 4 h.b | 95 | 0 | 86 | 14 |
| 3 | HgO (1.5 equiv.), 1 (1.5 equiv.), 4 h. | 87 | 4 | 85 | 11 |
| 4 | HgO (1.5 equiv.), 1 (1.5 equiv.), 7 h.[b] | 89 | 7 | 77 | 16 |
| 5 | HgO (1.5 equiv.), 1 (1.5 equiv.), 2x2 h. | >95 | 0 | 100 | 0 |

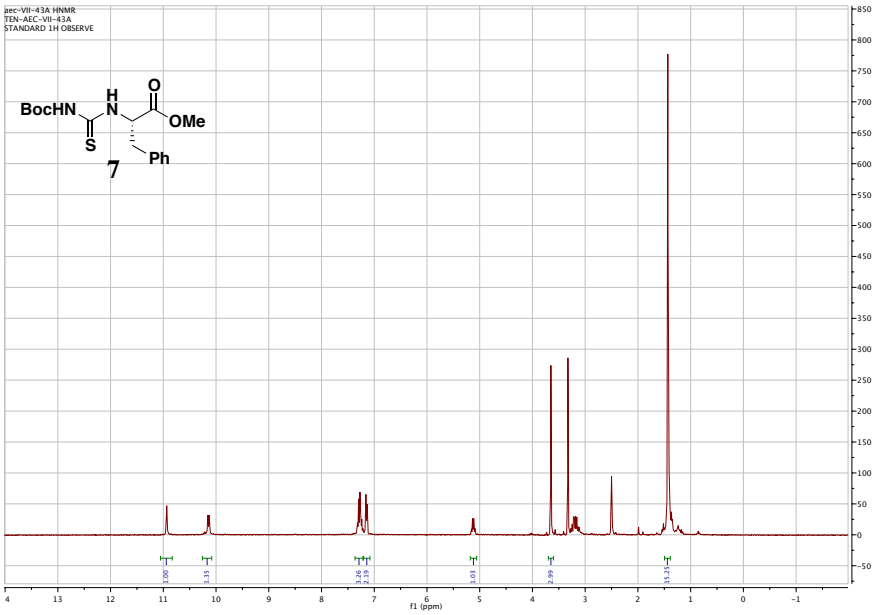
[a] The conversion and product distribution was determined by RP-HPLC (215 nm). [b] Overall product purity was measured to be <30%. The product distribution shows the distribution of identified products.

**(S)-Methyl 2-(3-(Boc)thioureido)-3-phenylpropanoate (7)**

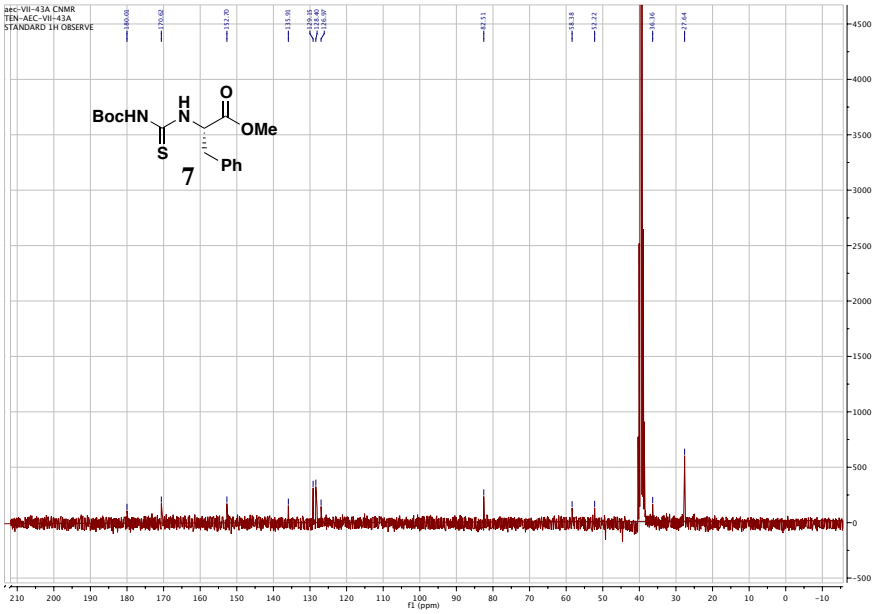



*N,N*'-di-Boc-thiourea (0.13 g, 0.46 mmol), $Et_3N$ (96 µl, 0.70 mmol) and Mukaiyama's reagent (0.12 g, 0.46 mmol) were stirred for 15 min in dry $CH_2Cl_2$ (1.3 ml), before filtering off any solids. The filtrate was added to a solution of (S)-H-Phe-OMe HCl (0.05 g, 0.23 mmol) in dry $CH_2Cl_2$ (1 ml) in a flame dried flask under argon. The reaction mixture was stirred at room temperature for 5 h., then concentrated *in vacuo* and the product purified by flash chromatography (EtOAc/heptane 1:3) to give **7** as a clear oil (8.4 mg, 11%). $^1$H NMR (300 MHz, DMSO-$d_6$): δ 10.94 (1H, s), 10.14 (1H, d, $J$ = 7.3 Hz), 7.42 – 7.07 (5H, m), 5.12 (1H, q, $J$ = 6.6 Hz), 3.65 (3H, s), 3.24 (1H, dd, $J$ = 6.3 Hz, 13.6 Hz), 3.15 (1H, dd, $J$ = 6.8 Hz, 13.9 Hz), 1.43 (9H, s). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 180.0, 170.6, 152.7, 135.9, 129.2 (2C), 128.4 (2C), 127.0, 82.5, 58.4, 52.2, 36.4, 27.6 (3C). HRMS (ESI) calcd for $C_{16}H_{23}N_2O_4S$ $[M + H]^+$ 339.1373, found 339.1397.

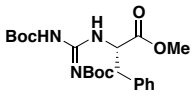
**$^1$H NMR (300 MHz, DMSO-$d_6$)**



**$^{13}$C NMR (75 MHz, DMSO-$d_6$)**



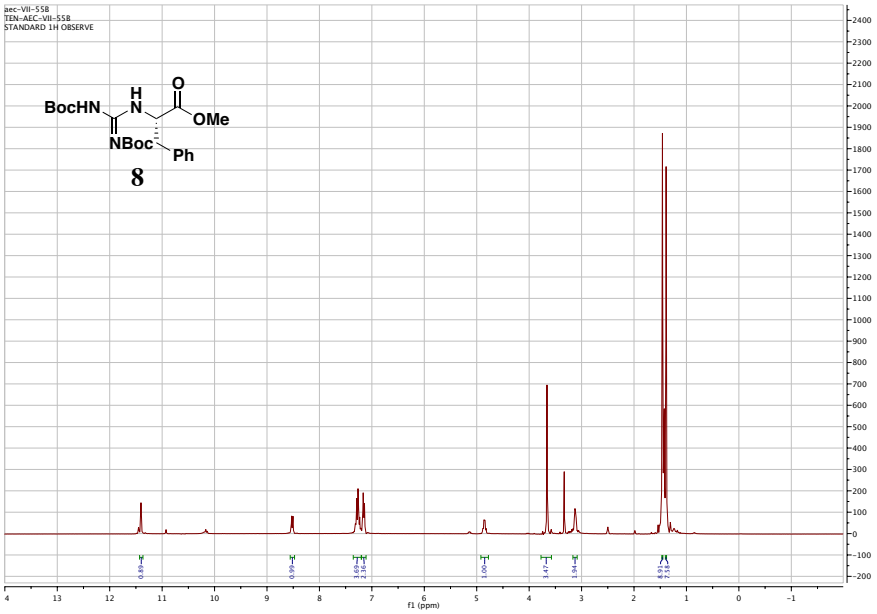

**(S)-Methyl 2-(2,3-bis(Boc)guanidino)-3-phenylpropanoate (8)**



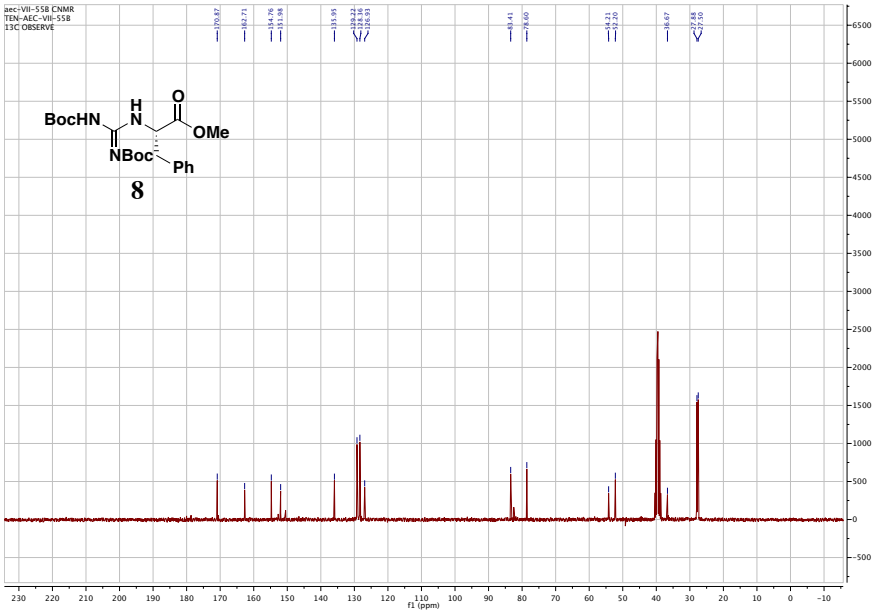

(S)-H-Phe-OMe HCl (0.05 g, 0.23 mmol), *N*,*N*'-di-Boc-thiourea (0.13 g, 0.46 mmol) and $Et_3N$ (96 µl, 0.70 mmol) were added to dry DMF (1 ml) in a flame dried flask under argon. Mukaiyama's reagent (0.12 g, 0.46 mmol) in dry DMF (1.3 ml) was added drop-wise to the resulting solution. The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated *in vacuo* and the product purified by flash chromatography (EtOAc/heptane 1:3) to give **8** as a clear oil (58.3 mg, 60%). $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.40 (1H, s), 8.52 (1H, d, $J$ = 7.5 Hz), 7.44 – 7.06 (5H, m), 4.85 (1H, q, $J$ = 6.8 Hz), 3.66 (3H, s), 3.16 – 3.09 (2H, m), 1.46 (9H, s), 1.39 (9H, s). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 170.8, 162.7, 154.7, 152.0, 136.0, 129.2 (2C), 128.4 (2C), 126.9, 83.4, 78.6, 54.2, 52.2, 36.7, 27.9 (3C), 27.5 (3C). HRMS (ESI) calcd for $C_{21}H_{32}N_3O_6$ $[M + H]^+$ 422.2286, found 422.2294.[1]

[1] Balakrishnan, S.; Zhao, C.; Zondlo, N. J. Convergent and Stereospecific Synthesis of Molecules Containing α-Functionalized Guanidiniums via α-Guanidino Acids. *J. Org. Chem*. **2007**, *72*, 9834-9837

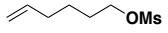
**$^{1}$H NMR (300 MHz, DMSO-$d_6$)**




**$^{13}$C NMR (75 MHz, DMSO-$d_6$)**

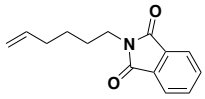



**Hex-5-en-1-yl-methanesulfonate (37)**



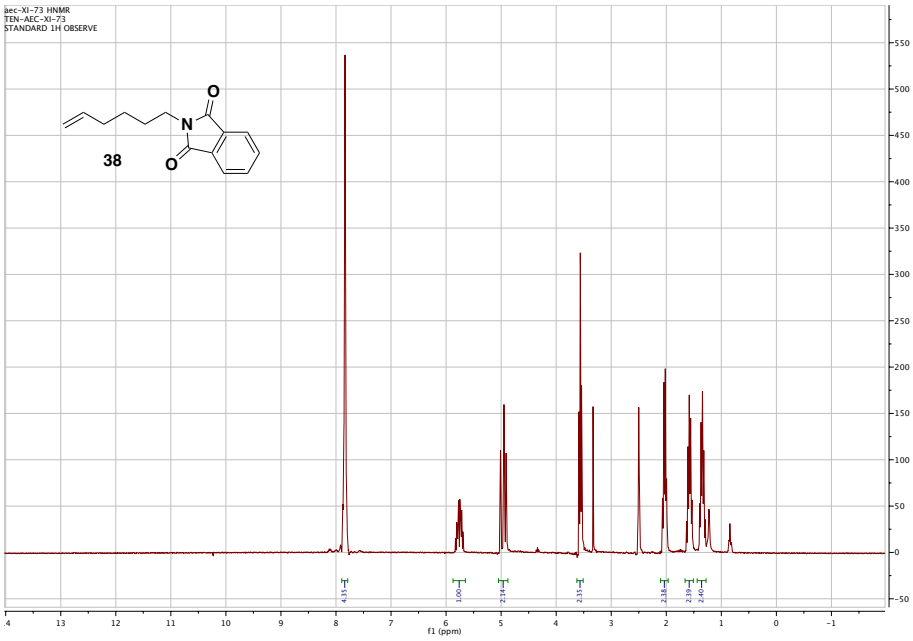

5-Hexen-1-ol (3 ml, 25 mmol) and methanesulfonyl chloride (2.7 ml, 35 mmol) was dissolved in dry $CH_2Cl_2$ (25 ml) and cooled to 0 °C. $Et_3N$ (4.2 ml, 30 mmol) was slowly added and the solution was stirred for 1 h. The reaction mixture was washed with water (2 × 25 ml). The water phase was extracted with EtOAc (25 ml). The combined organic phases were dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo* (the product was used straight away).

**2-Hex-5-enyl-isoindole-1,3-dione (38)**



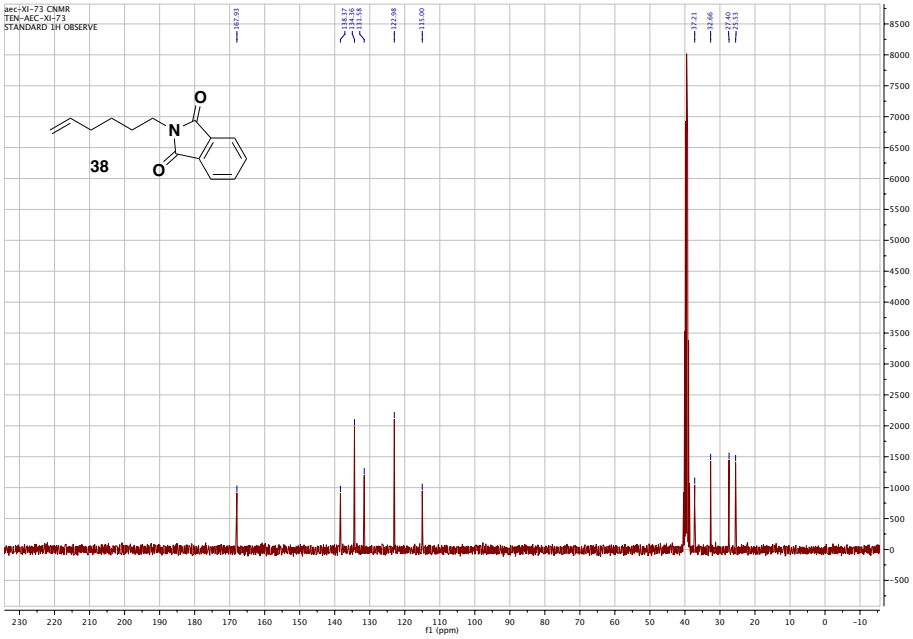
Mesylate **37** (4.5 g, 25 mmol) was dissolve in dry DMF. Potassium phthalimide (6.9 g, 37 mmol) was added and the reaction mixture was heated to 80 °C for 2 h. The solution was cooled to rt. and transferred to a separation funnel with EtOAc (200 ml). The organic solution was washed with $NH_4Cl$ (sat) (2 × 200 ml) and $NaHCO_3$ (sat) (2 × 200 ml). The organic phase was dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography (EtOAc/heptane 1:4 to yield the title product **38** as a clear oil (4,1 g, 82% over two steps). $^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.91 – 7.76 (4H, m), 5.86 – 5.68 (1H, m), 5.03 – 4.89 (2H, m), 3.56 (2H, t, $J$ = 7.0 Hz), 2.03 (2H, q, $J$ = 7.1 Hz), 1.69 – 1.52 (2H, m), 1.43 – 1.28 (2H, m). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 167.9, 138.4, 134.4 (2C), 131.6 (2C), 123.0 (2C), 115.0, 37.2, 32.7, 27.4, 25.5. UPLC-MS (ESI) calcd for $C_{14}H_{16}NO_2$ $[M + H]^+$ 230.3, found 230.2.[2]

**$^1$H NMR (300 MHz, DMSO-$d_6$)**

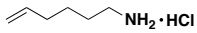



[2] Collins, B. S. L.; Suero, M. G. Copper-Catalyzed Arylative Meyer–Schuster Rearrangement of Propargylic Alcohols to Complex Enones Using Diaryliodonium Salts. *Angew. Chem. Int. Ed.* **2013**, *52*, 5799-5802.

**$^{13}$C NMR (75 MHz, DMSO-$d_6$)**

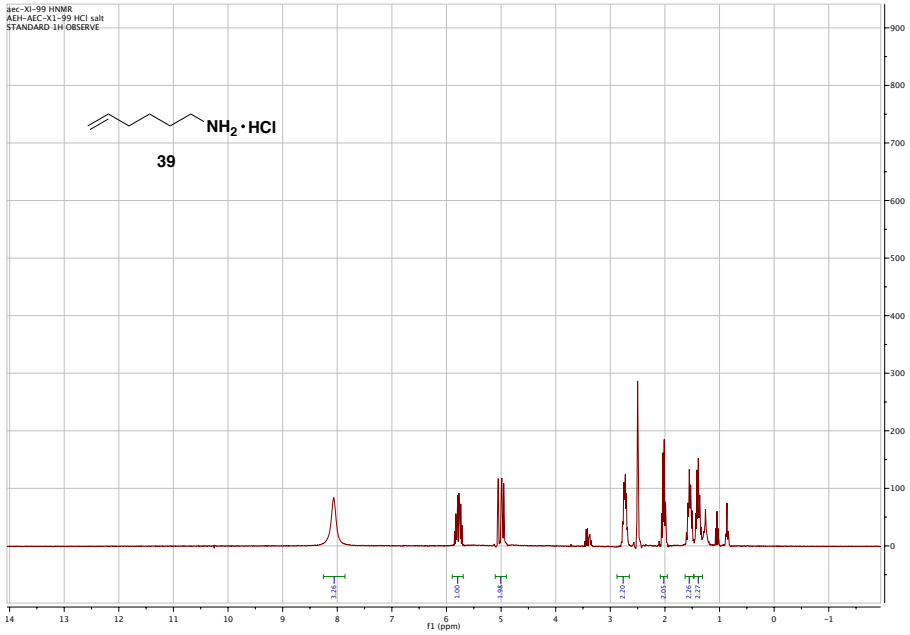



**Hex-5-en-1-amine•HCl (39)**

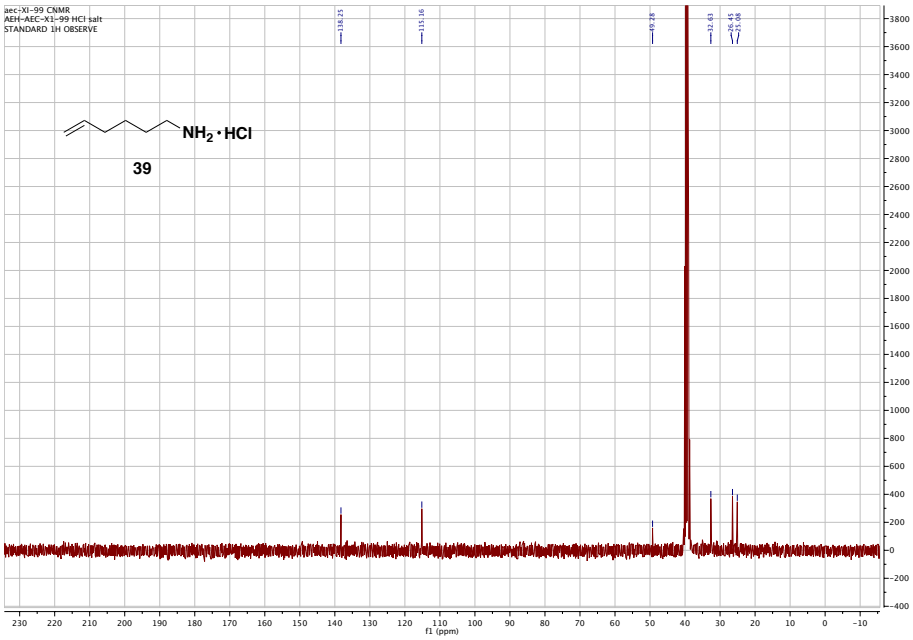



2-Hex-5-enyl-isoindole-1,3-dione **38** (2.5 g, 11 mmol) was dissolved in EtOH (90 ml). Hydrazine mono hydrate (3.2 ml, 33 mmol) was added and the solution was heated to 50 °C for 2 h. The reaction mixture was cooled to rt. The white precipitation was filtered off and washed with EtOH. The acidity of the solution was adjusted to pH 1-2 by addition of conc. HCl. The solution was concentrated *in vacuo* to dryness. The product was dissolved in water (25 ml) and the pH was adjusted to 10-11 by addition of 1 M NaOH. The product was extracted with $Et_2O$ (4 × 50 ml). The organic phase was dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo* at 0 °C. The product was distilled by use of Kugelrohr. The distillate was acidified by addition of 1M HCl ($Et_2O$) and concentrated *in vacuo* to give the title product **39** (0.74 g, 49 %). $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.07 (3H, bs), 5.78 (1H, ddt, $J$ = 16.9, 10.2, 6.6 Hz), 5.10- 4.87 (2H, m), 2.85 – 2.63 (2H, m), 2.06 – 1.96 (2H, m), 1.64 – 1.48 (2H, m), 1.48 – 1.31 (2H, m). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 138.3, 115.2, 49.3, 32.6, 26.5, 25.1.

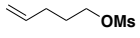
**$^{1}$H NMR (300 MHz, DMSO-$d_6$)**




**$^{13}$C NMR (75 MHz, DMSO-$d_6$)**

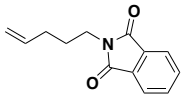



**Pent-4-en-1-yl-methanesulfonate (40)**



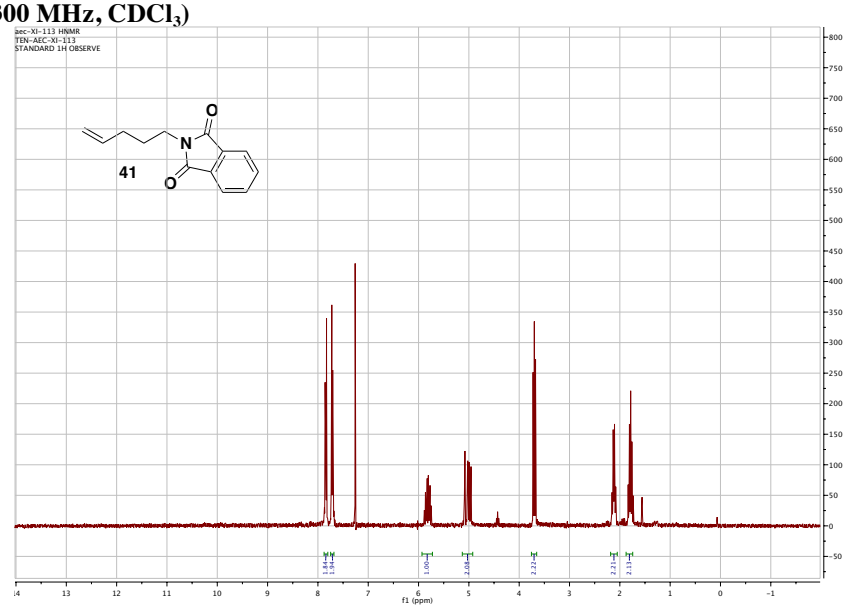

4-Penten-1-ol (3.6 ml, 35 mmol) and methanesulfonyl chloride (3.8 ml, 49 mmol) was dissolved in dry $CH_2Cl_2$ (35 ml) and cooled to 0 °C. $Et_3N$ (5.8 ml, 42 mmol) was slowly added and the solution was stirred for 1 h. The reaction mixture was washed with water (2 × 50 ml). The water phase was extracted with EtOAc (50 ml). The combined organic phases were dried over anhydrous $Na_2SO_4$ and concentrated in vacuo (the product was used straight away).

**2-Pent-4-enyl-isoindole-1,3-dione (41)**

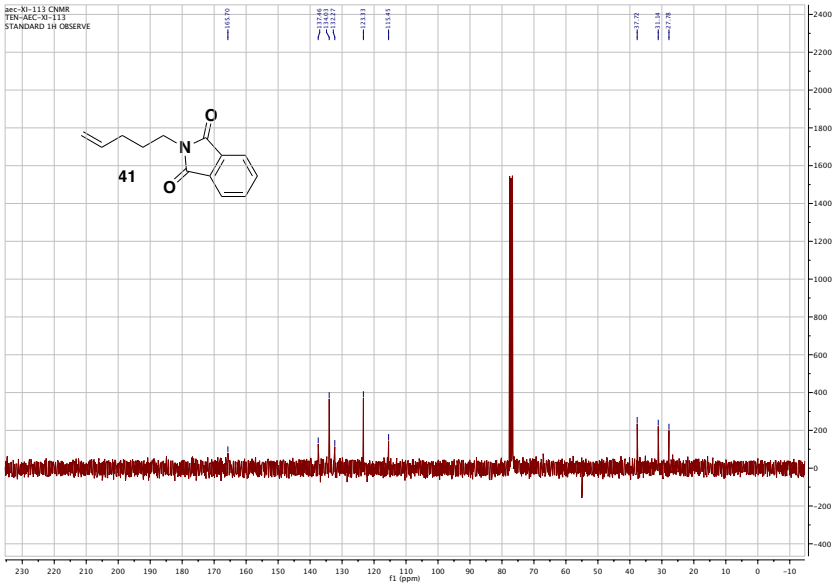


The mesylate **40** (5.7 g, 35 mmol) was dissolved in dry DMF (70 ml). Potassium phthalimide (9.7 g, 52 mmol) was added and the solution was heated to 80 °C for 2 h. The reaction was cooled to rt. and washed with $NH_4Cl$ (sat) (2 × 200 ml) and $NaHCO_3$ (sat) (2 × 200 ml). The organic phase was dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography (EtOAc/heptane 1:4) to give **41** as a clear colourless oil (5.1 g, 68%). %). $^1$H NMR (300 MHz, $CDCl_3$): δ 7.84 (2H, dd, *J* = 5.5, 3.0 Hz), 7.71 (2H, dd, *J* = 5.4, 3.1 Hz), 5.82 (1H, ddt, *J* = 16.9, 10.3, 6.6 Hz), 5.05 (1H, ddd, *J* = 17.2, 3.4, 1.7 Hz), 4.98 (1H, dd, *J* = 10.2, 1.8 Hz), 3.77 – 3.63 (2H, m), 2.12 (2H, dd, *J* = 14.6, 6.8 Hz), 1.80 (2H, dd, *J* = 14.7, 7.5 Hz).$^{13}$C NMR (75 MHz, $CDCl_3$) δ 165.7, 137.5, 134.0 (2C), 132.3 (2C), 123.3 (2C), 115.5, 37.7, 31.1, 27.8.[3]

**$^1$H NMR (300 MHz, $CDCl_3$)**

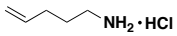



**$^{13}$C NMR (75 MHz, $CDCl_3$)**



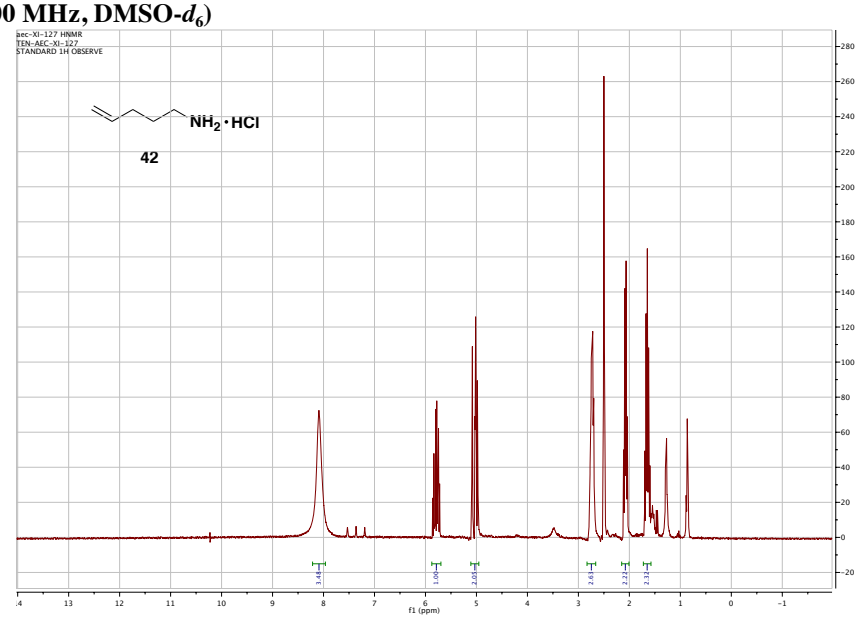

[3] Whittaker, A. M.; Lalic, G. Monophasic Catalytic System for the Selective Semireduction of Alkynes. *Org. Lett.* **2013**, *15*, 1112-1115.

**Pent-4-en-1-amine•HCl (42)**

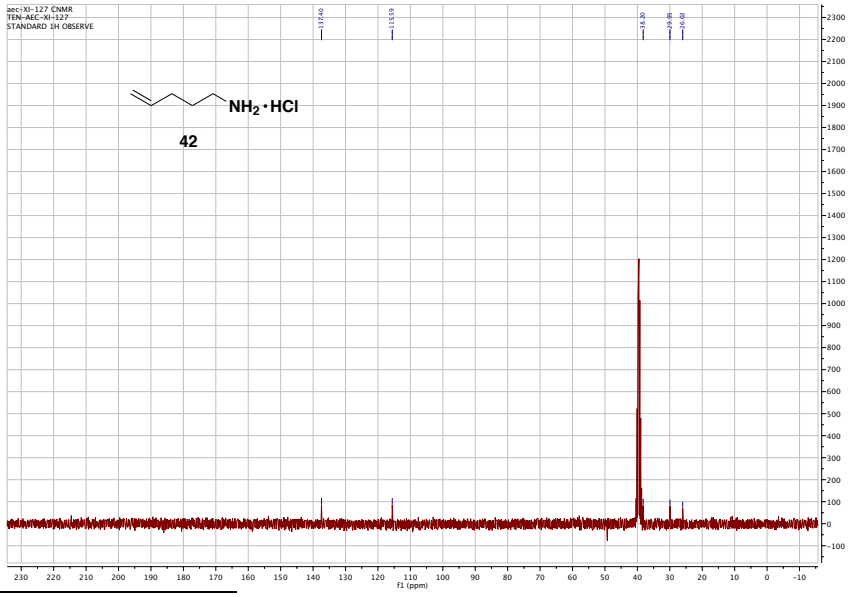



2-Pent-4-enyl-isoindole-1,3-dione **41** (3 g, 14 mmol) was dissolved in EtOH (120 ml). Hydrazine mono hydrate (4.1 ml, 42 mmol) was added and the reaction mixture was heated 50 °C for 19 h. The solution was cooled to rt. The white precipitation was filtered off and washed with EtOH. The acidity of the solution was adjusted to pH 1-2 by addition of conc. HCl. The solution was concentrated *in vacuo* to dryness. The product was dissolved in water (25 ml) and the pH was adjusted to 10-11 by addition of 1 M NaOH. The product was extracted with $Et_2O$ (4 × 50 ml). The organic phase was dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo* at 0 °C. The product was distilled by use of Kugelrohr. The distillate was acidified by addition of 1M HCl ($Et_2O$) and concentrated *in vacuo* to give the title product **42** (0.45 g, 27 %). $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.09 (3H, bs), 5.79 (1H, ddt, $J$ = 16.8, 10.2, 6.5 Hz), 5.10 – 4.96 (2H, m), 2.83 – 2.64 (2H, m), 2.08 (2H, q, $J$ = 6.9 Hz), 1.73 – 1.58 (2H, m).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 137.4, 115.6, 38.2, 30.0, 26.0.[4]

**$^1$H NMR (300 MHz, DMSO-$d_6$)**

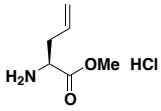



**$^{13}$C NMR (75 MHz, DMSO-$d_6$)**



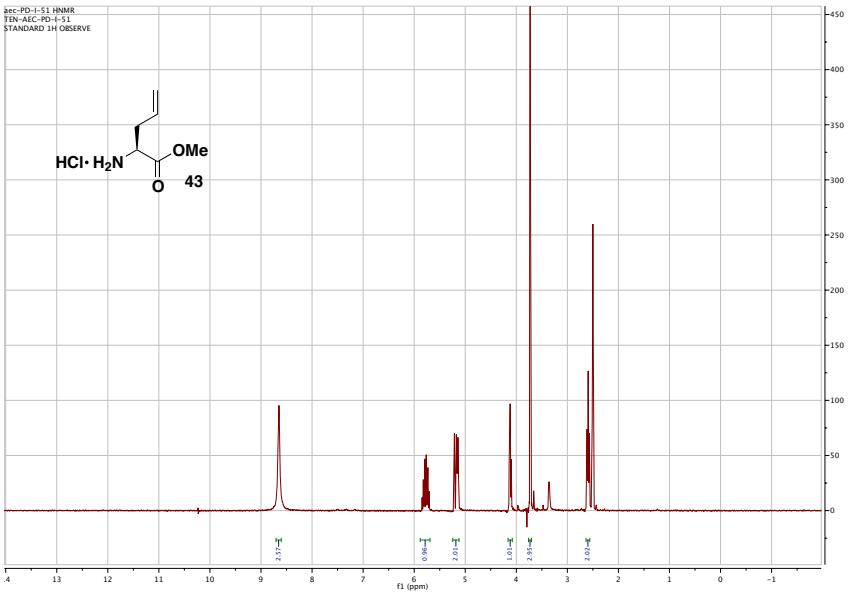

[4] Sohn, J-H.; Kim, K. H.; Lee, H-Y.; No, Z. S.; Ihee, H. Initial Catalyst−Substrate Association Step in Enyne Metathesis Catalyzed by Grubbs Ruthenium Complex Probed by Time-Dependent Fluorescence Quenching. *J. Am. Chem. Soc.* **2008**, *130*, 16506-16507.

**L-Allylglycine methyl ester•HCl (43)**

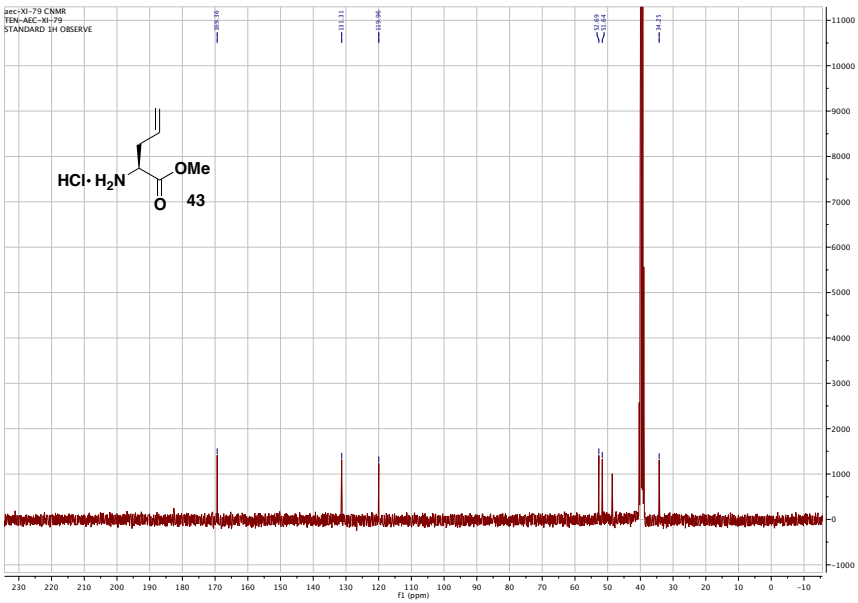



L-H-allylglycine (0.5 g, 4.3 mmol) was dissolved in MeOH (9 ml) and cooled to 0 °C. Thionyl chloride (0.47 ml, 6.5 mmol) was slowly added and the solution was stirred for 22 h at rt. The solution was concentrated *in vacuo*, dissolved in $CH_2Cl_2$ and concentrated again *in vacuo* to give the title product **43** (0.72 g, quant). $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.65 (3H, bs), 5.78 (1H, ddt, $J$ = 17.2, 10.1, 7.2 Hz), 5.23 – 5.12 (2H, m), 4.12 (1H, t, $J$ = 6.1 Hz), 3.73 (3H, s), 2.59 (2H, t, $J$ = 6.6 Hz).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 169.4, 131.3, 120.0, 52.7, 51.6, 34.3.[5]

**$^1$H NMR (300 MHz, DMSO-$d_6$)**

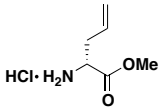



**$^{13}$C NMR (75 MHz, DMSO-$d_6$)**



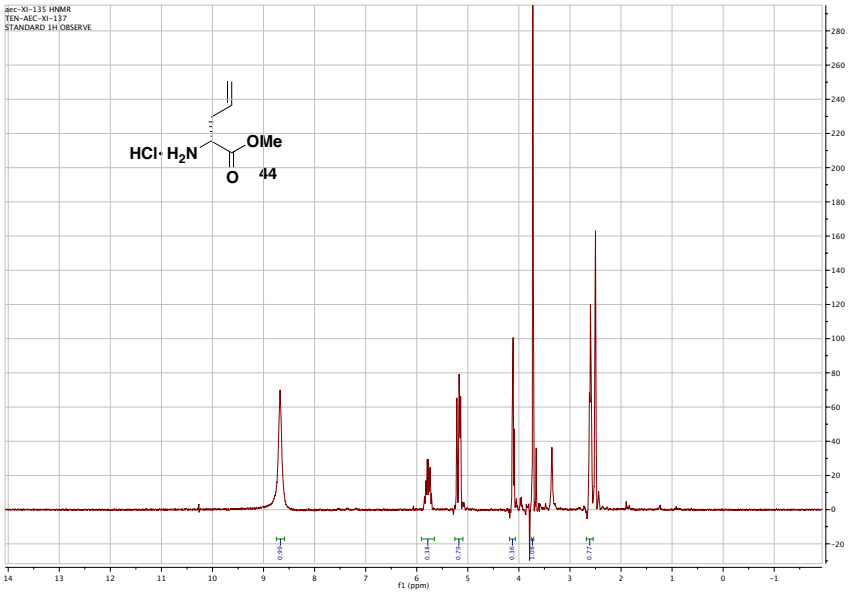

[5] Kaul, R.; Surprenant, S.; Lubell, W. D. Systematic Study of the Synthesis of Macrocyclic Dipeptide β-Turn Mimics Possessing 8-, 9-, and 10- Membered Rings by Ring-Closing Metathesis. *J. Org. Chem.* **2004**, *70*, 3838-3844.

**D-Allylglycine methyl ester•HCl (44)**

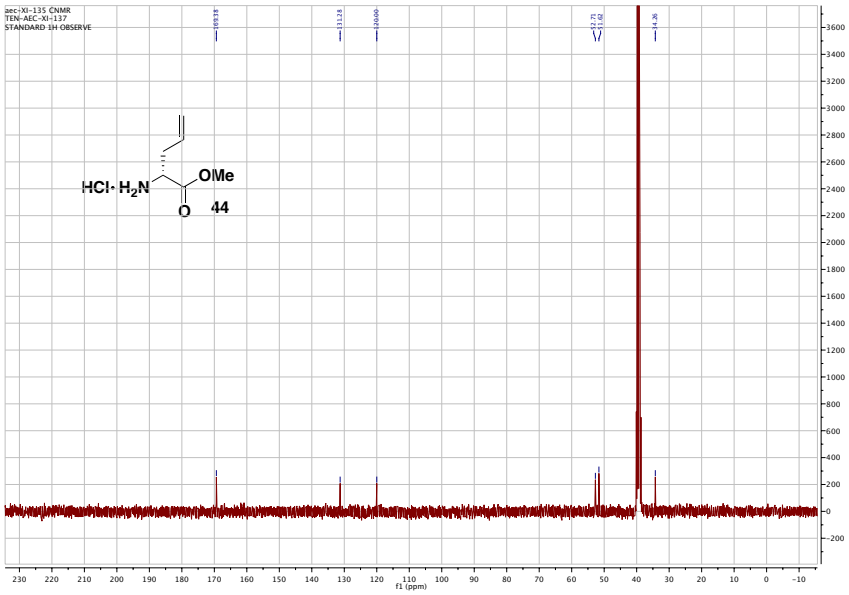



D-H-allylglycine (0.5 g, 4.3 mmol) was dissolved in MeOH (9 ml) and cooled to 0 °C. Thionyl chloride (0.47 ml, 6.5 mmol) was slowly added and the solution was stirred for 22 h at rt. The solution was concentrated *in vacuo*, dissolved in $CH_2Cl_2$ and concentrated again *in vacuo* to give the title product **44** (0.72 g, quant). $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.67 (3H, bs), 5.92 – 5.61 (1H, m), 5.35 – 5.12 (2H, m), 4.11 (1H, t, $J$ = 6.0 Hz), 3.73 (3H, s), 2.60 (2H, t, $J$ = 6.0 Hz).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 169.4, 131.3, 120.0, 52.7, 51.6, 34.3.[6]

**$^1$H NMR (300 MHz, DMSO-$d_6$)**



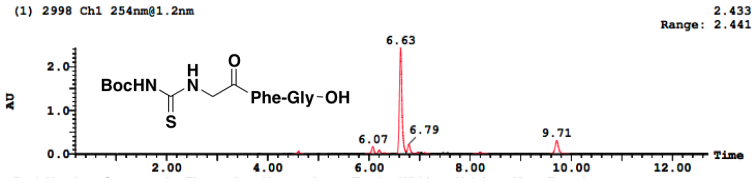

**$^{13}$C NMR (75 MHz, DMSO-$d_6$)**




[6] Goudrea, N.; Brochu, C.; Cameron, D. R.; Duceppe, J-S.; Faucher, A-M.; Ferland, J-M.; Grand-Maître, C.; Poirier, M.; Simoneau, B.; Tsantrizos, Y. S. Potent Inhibitors of the Hepatitis C Virus NS3 Protease: Design and Synthesis of Macrocyclic Substrate-Based β-Strand Mimics. *J. Org. Chem.* **2004**, *69*, 6185-6201.

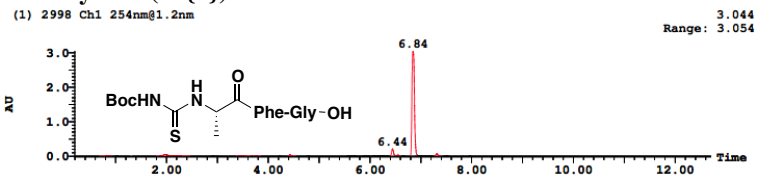
**Synthesis of Boc-Protected Thiourea and Guanidino Peptides**

**BocNHCS-Gly-Phe-Gly-OH (15{1})**



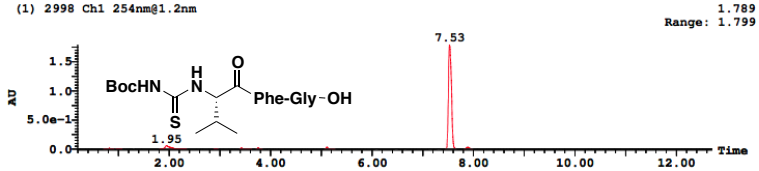

Purity: 86%, $R_f$ = 6.63 min. UPLC-MS (ESI) calcd for $C_{19}H_{27}N_4O_6S$ $[M + H]^+$ 439.2, found 439.3.

**BocNHCS-Ala-Phe-Gly-OH (15{2})**



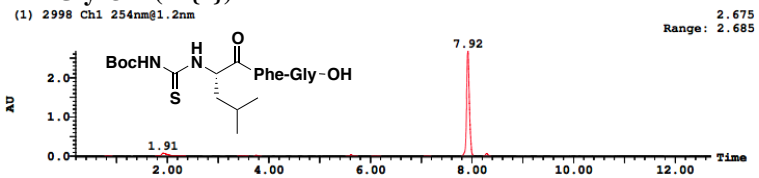

Purity: >95%, $R_f$ = 6.84 min. HRMS (ESI) calcd for $C_{20}H_{29}N_4O_6S$ $[M + H]^+$ 453.1802, found 453.1804.

**BocNHCS-Val-Phe-Gly-OH (15{3})**



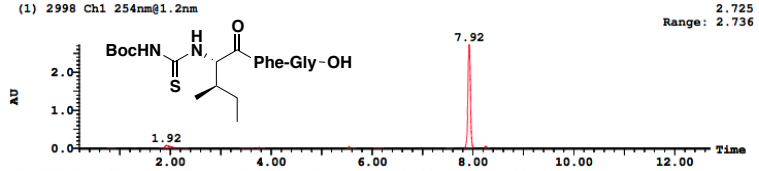

Purity: >95%, $R_f$ = 7.53 min. UPLC-MS (ESI) calcd for $C_{22}H_{33}N_4O_6S$ $[M + H]^+$ 481.2, found 481.4.

**BocNHCS-Leu-Phe-Gly-OH (15{4})**



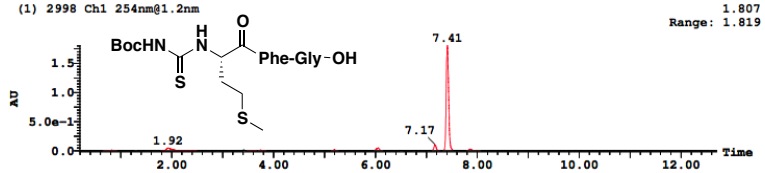

Purity: >95%, $R_f$ = 7.92 min. UPLC-MS (ESI) calcd for $C_{23}H_{35}N_4O_6S$ $[M + H]^+$ 495.2, found 495.4.

**BocNHCS-Ile-Phe-Gly-OH (15{5})**



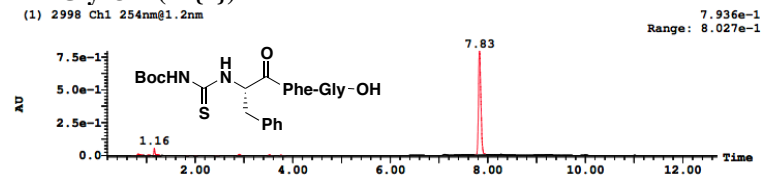

Purity: >95%, $R_f$ = 7.92 min. UPLC-MS (ESI) calcd for $C_{23}H_{35}N_4O_6S$ $[M + H]^+$ 495.2, found 495.4.

**BocNHCS-Met-Phe-Gly-OH (15{6})**



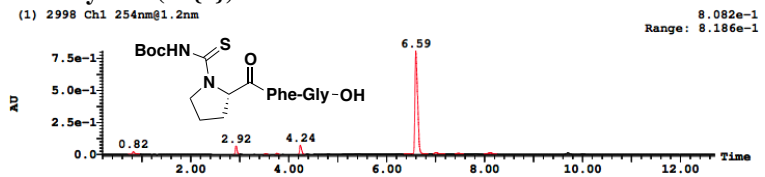

Purity: >95%, $R_f$ = 7.41 min. UPLC-MS (ESI) calcd for $C_{22}H_{33}N_4O_6S_2$ $[M + H]^+$ 513.2, found 513.4.

**BocNHCS-Phe-Phe-Gly-OH (15{7})**



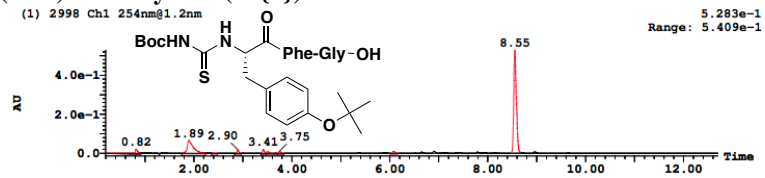

Purity: >95%, $R_f$ = 7.83 min. UPLC-MS (ESI) calcd for $C_{26}H_{33}N_4O_6S$ $[M + H]^+$ 529.2, found 529.4.

**BocNHCS-Pro-Phe-Gly-OH (15{8})**



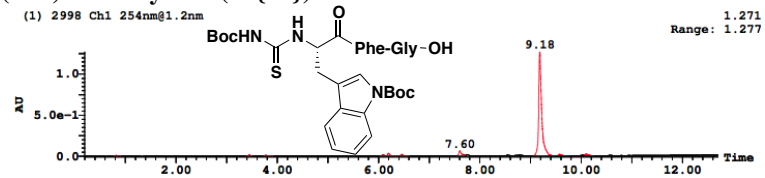

Purity: 87%, $R_f$ = 6.59 min. UPLC-MS (ESI) calcd for $C_{22}H_{31}N_4O_6S$ $[M + H]^+$ 479.2, found 479.4

**BocNHCS-Tyr(*t*-Bu)-Phe-Gly-OH (15{9})**



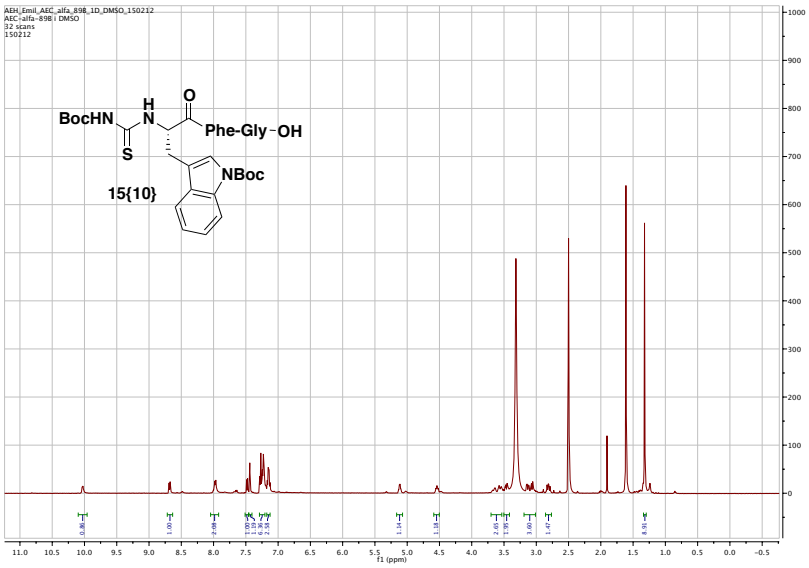

Purity: >95%, $R_f$ = 8.55 min. UPLC-MS (ESI) calcd for $C_{30}H_{41}N_4O_7S$ $[M + H]^+$ 601.3, found 601.5.

**BocNHCS-Trp(Boc)-Phe-Gly-OH (15{10})**

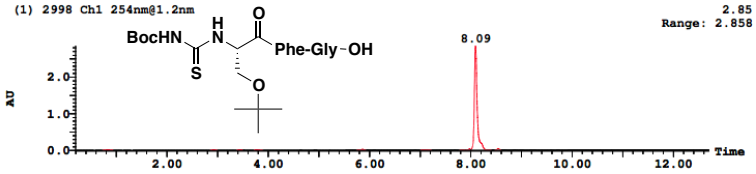



Purity: >95%, $R_f$ = 9.18 min. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 10.03 (1H, d, *J* = 7.3 Hz), 8.69 (1H, d, *J* = 8.4 Hz), 8.02 – 7.91 (2H, m), 7.48 (1H, d, *J* = 7.7 Hz), 7.44 (1H, s), 7.30 – 7.09 (8H, m), 5.12 (1H, d, J = 5.9 Hz), 4.54 (1H, td, *J* = 4.1 Hz, 9.4 Hz), 3.67 – 3.50 (2H, m), 3.46 (1H, dd, *J* = 4.8 Hz, 14.7 Hz), 3.13 (1H, dd, *J* = 5.5 Hz, 14.8 Hz), 3.06 (1H, dd, *J* = 3.9 Hz, 13.8 Hz), 2.81 (1H, dd, *J* = 10.1 Hz, 13.8 Hz), 1.33 (9H, s). HRMS (ESI) calcd for $C_{33}H_{42}N_5O_8S$ $[M + H]^+$ 668.2749, found 668.2750.

**$^1$H NMR (500 MHz, DMSO-$d_6$)**

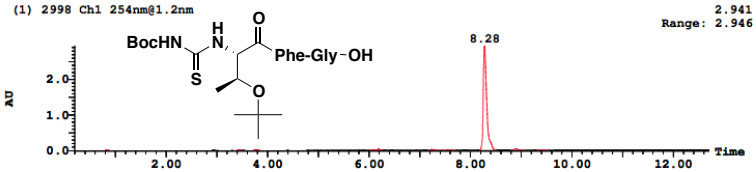



**BocNHCS-Ser(*t*-Bu)-Phe-Gly-OH (15{11})**



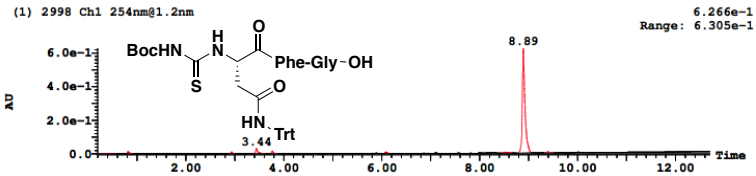

Purity: >95%, $R_f$ = 8.09 min. HRMS (ESI) calcd for $C_{24}H_{37}N_4O_7S$ $[M + H]^+$ 525.2377, found 525.2369.

**BocNHCS-Thr(*t*-Bu)-Phe-Gly-OH (15{12})**



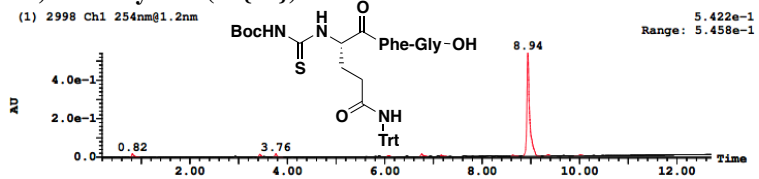

Purity: >95%, $R_f$ = 8.28 min. UPLC-MS (ESI) calcd for $C_{25}H_{39}N_4O_7S$ $[M + H]^+$ 539.3, found 539.5.

**BocNHCS-Asn(Trt)-Phe-Gly-OH (15{13})**



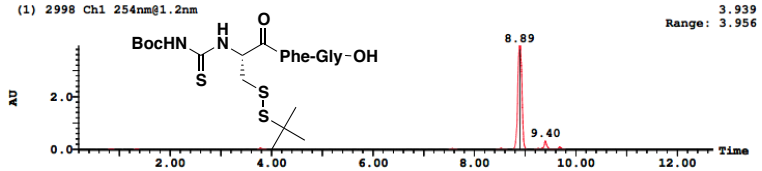

Purity: >95%, $R_f$ = 8.89 min. UPLC-MS (ESI) calcd for $C_{40}H_{44}N_5O_7S$ $[M + H]^+$ 738.3, found 738.4.

**BocNHCS-Gln(Trt)-Phe-Gly-OH (15{14})**



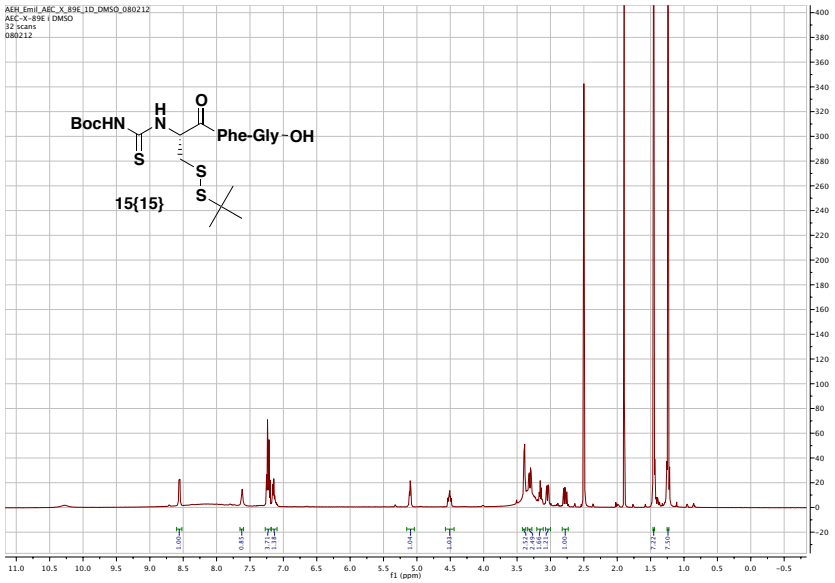

Purity: >95%, $R_f$ = 8.94 min. UPLC-MS (ESI) calcd for $C_{41}H_{46}N_5O_7S$ $[M + H]^+$ 752.3, found 752.4.

**BocNHCS-Cys(S-*t*-Bu)-Phe-Gly-OH (15{15})**

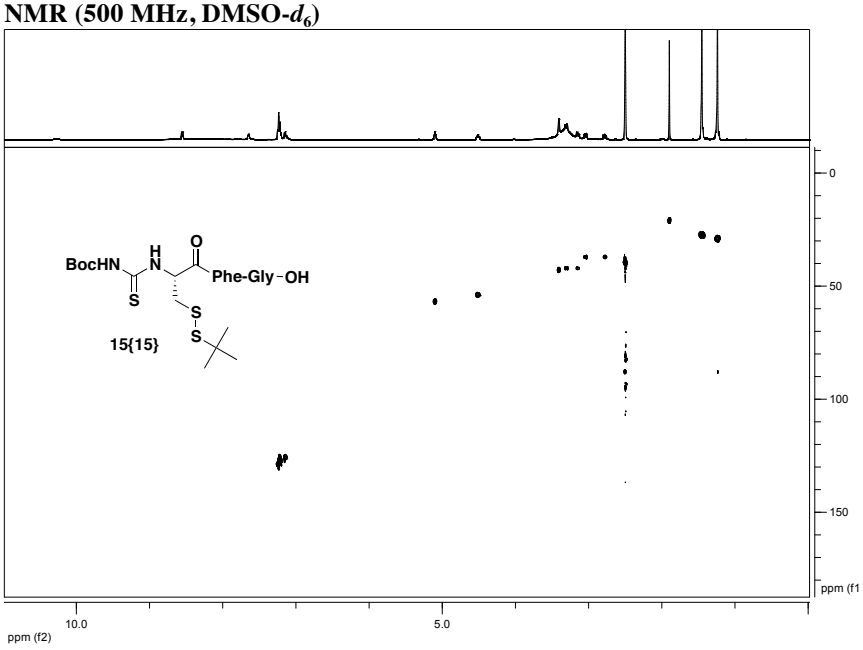



Purity: >95%, $R_f$ = 8.89 min. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 8.56 (1H, d, $J$ = 8.5 Hz), 7.62 (1H, bs), 7.27 – 7.19 (m, 4H), 7.14 (1H, dd, $J$ = 5.7 Hz, 12.6 Hz), 5.10 (1H, t, $J$ = 5.3 Hz), 4.51 (1H, td, $J$ = 4.6 Hz, 9.3 Hz), 3.39 (2H, d, $J$ = 4.5 Hz), 3.31 (1H, dd, $J$ = 4.6 Hz, 13.4 Hz), 3.15 (1H, dd, $J$ = 6.2 Hz, 13.5 Hz), 3.04 (1H, dd, $J$ = 4.4 Hz, 13.8 Hz), 2.78 (1H, dd, $J$ = 9.8 Hz, 13.8 Hz), 1.45 (9H, s), 1.24 (9H, s). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 179.5, 170.2, 169.7, 167.9, 137.8, 128.7 (2C), 127.8 (2C), 126.0, 82.1, 57.0, 54.0, 47.5, 43.0, 42.1, 37.2, 27.7 (3H), 29.1 (3H). UPLC-MS (ESI) calcd for $C_{24}H_{37}N_4O_6S_2$ $[M + H]^+$ 573.2, found 573.4.

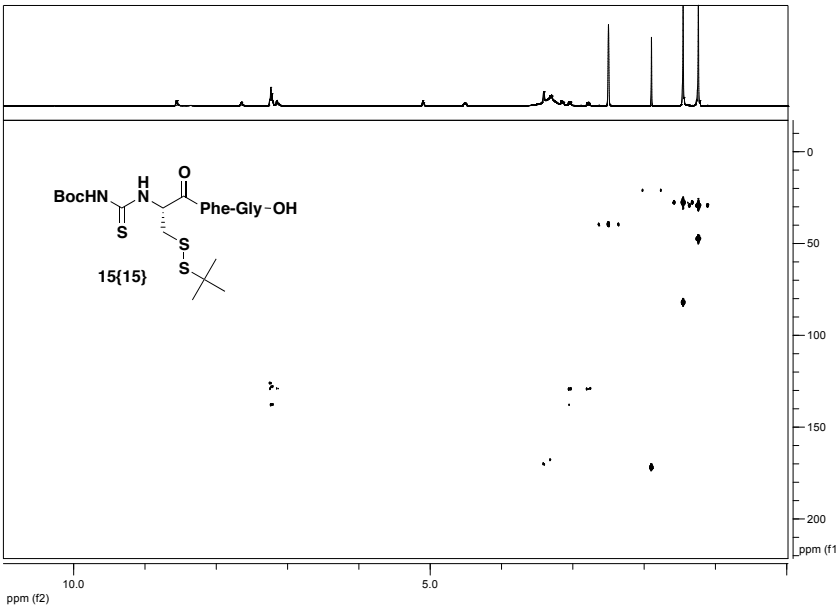
**$^1$H NMR (500 MHz, DMSO-$d_6$)**



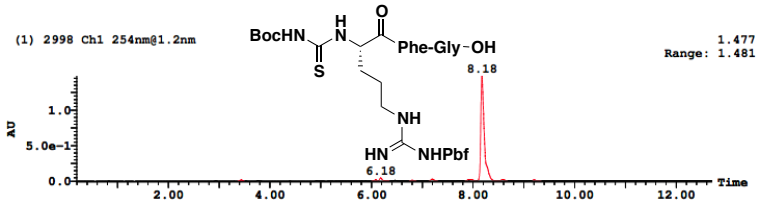

**2D HSQC NMR (500 MHz, DMSO-$d_6$)**



**2D HMBC NMR (500 MHz, DMSO-$d_6$)**

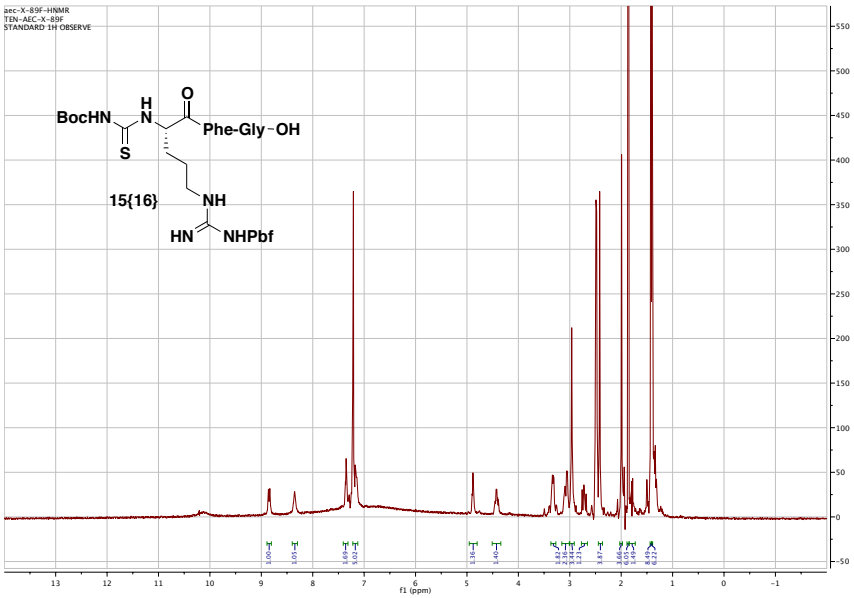



**BocNHCS-Arg(Pbf)-Phe-Gly-OH (15{16})**

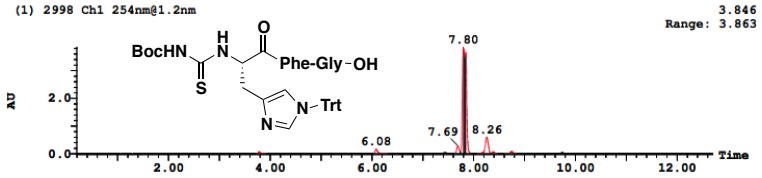



Purity: >95%, $R_f$ = 8.18 min. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.86 (1H, d, $J$ = 8.3 Hz), 8.36 (1H, bs), 7.36 (1H, t, $J$ = 4.0 Hz), 7.28 – 7.11 (5H, m), 4.89 (1H, t, $J$ = 5.2 Hz), 4.49 – 4.38 (1H,m), 3.44 – 3.25 (2H, m), 3.19 – 3.04 (2H, m), 2.97 (2H, bs), 2.83 – 2.65 (1H, m), 2.43 (3H, s), 2.00 (3H, s), 1.87 (6H, s), 1.85 – 1.77 (2H, m), 1.43 (9H, s), 1.41 (6H, s). HRMS (ESI) calcd for $C_{36}H_{52}N_7O_9S_2$ [M + H]$^+$ 790.3262, found 790.3287.

**$^1$H NMR (300 MHz, DMSO-$d_6$)**

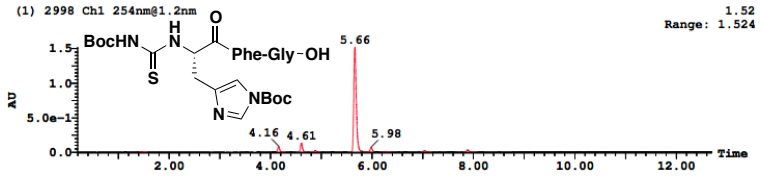


**BocNHCS-His(Trt)-Phe-Gly-OH (15{17})**



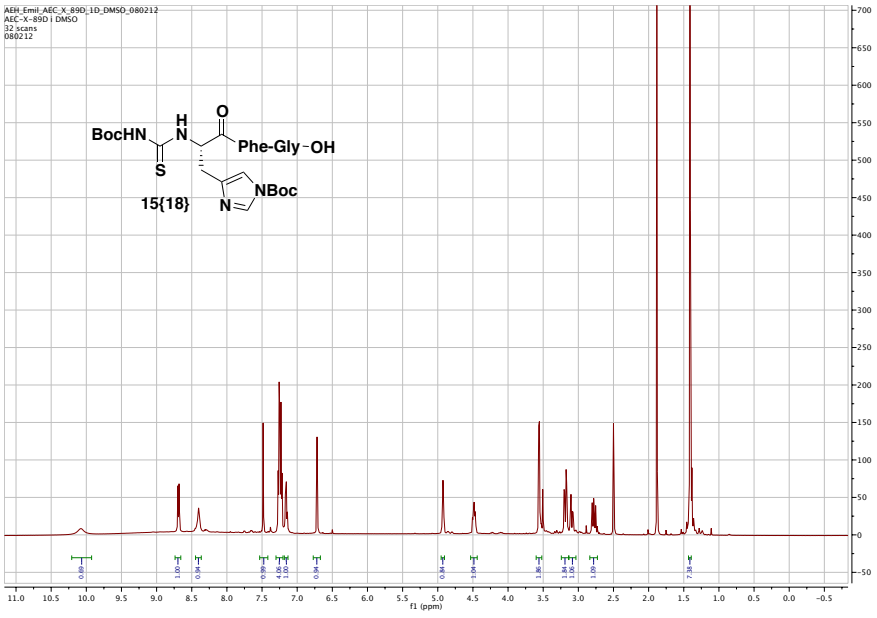

Purity: 83%, $R_f$ = 7.80 min. UPLC-MS (ESI) calcd for $C_{42}H_{45}N_6O_6S$ $[M + H]^+$ 761.3, found 761.6.

**BocNHCS-His(Boc)-Phe-Gly-OH (15{18})**

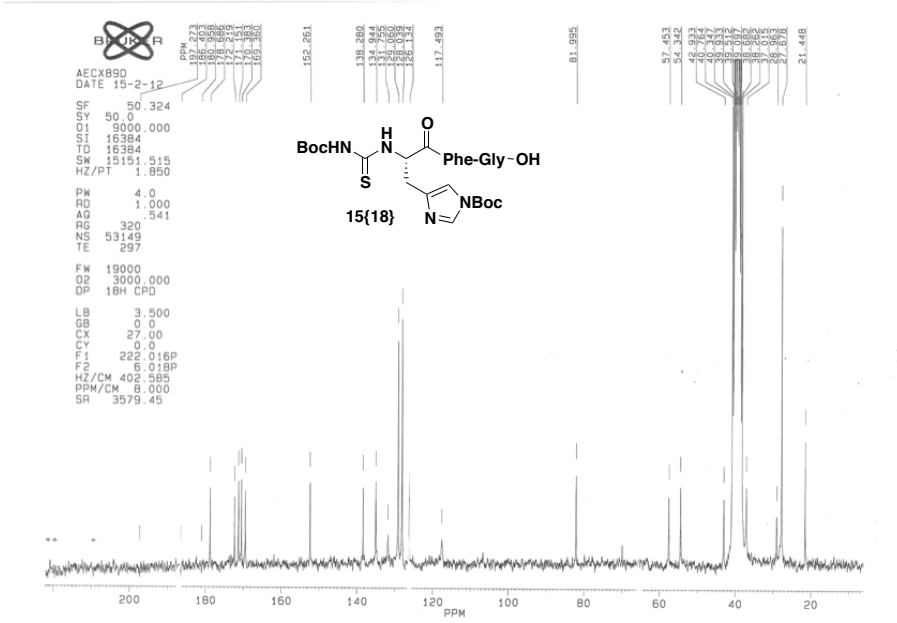



Purity: 92%, $R_f$ = 5.66 min. (The side-chain Boc group was lost during cleavage from the resin). $^1$H NMR (500 MHz, DMSO-$d_6$): δ 10.08 (1H, s), 8.69 (1H, d, $J$ = 8.2 Hz), 8.40 (2H, s), 7.48 (1H, s), 7.29 – 7.21 (5H, m), 7.15 (1H, t, $J$ = 7.0 Hz), 6.72 (1H, s), 4.93 (1H, t, $J$ = 4.8 Hz), 4.54 – 4.44 (1H, m), 3.56 (2H, d, $J$ = 4.9 Hz), 3.25 – 3.14 (1H, m), 3.09 (2H, dd, $J$ = 4.7 Hz, 14.8 Hz), 2.78 (1H, dd, $J$ = 10.6 Hz, 13.9 Hz), 1.41 (9H, s). $^{13}$C NMR (50 MHz, DMSO-$d_6$): δ 181.0, 172.2, 171.2, 170.4, 169.4, 152.3, 138.3, 134.9, 131.8, 129.1 (2C), 128.0 (2C), 126.1, 117.5, 82.0, 57.4, 54.3, 42.9, 37.0, 29.0, 27.7. HRMS (ESI) calcd for $C_{23}H_{31}N_6O_6S$ $[M - Boc]^+$ 519.2020, found 519.2043.

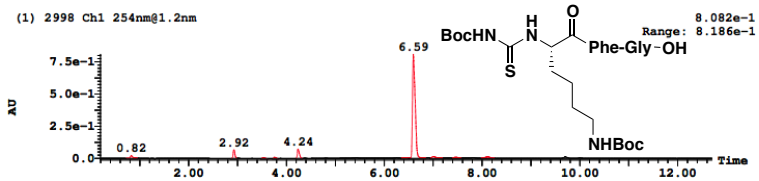
**$^1$H NMR (500 MHz, DMSO-$d_6$)**



**$^{13}$C NMR (50 MHz, DMSO-$d_6$)**

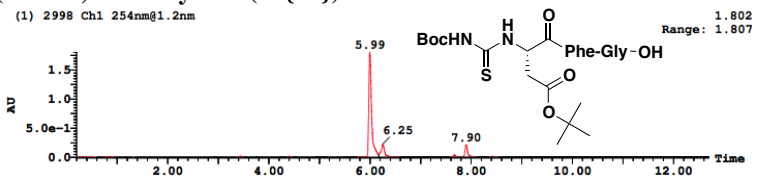



**BocNHCS-Lys(Boc)-Phe-Gly-OH (15{19})**



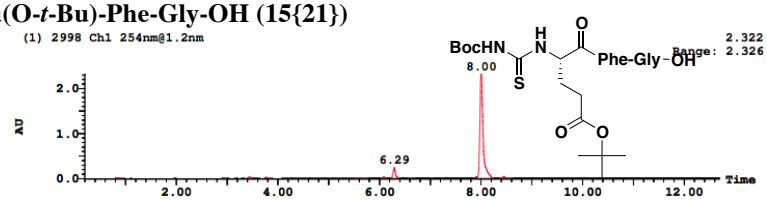

Purity: >95%, $R_f$ = 7.82 min. UPLC-MS (ESI) calcd for $C_{28}H_{44}N_5O_8S$ $[M + H]^+$ 610.3, found 610.5.

**BocNHCS-Asp(O-*t*-Bu)-Phe-Gly-OH (15{20})**



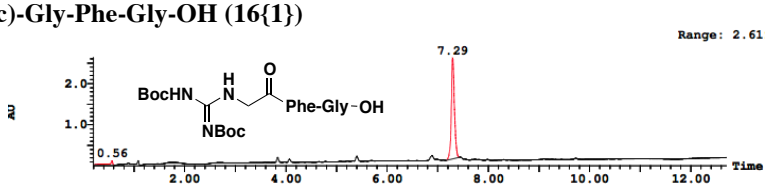

Purity: 78%, $R_f$ = 5.99 min. (The O-*t*-Bu group was lost during cleavage from the resin). UPLC-MS (ESI) calcd for $C_{21}H_{29}N_4O_8S$ $[M - {}^t\mathrm{Bu}]^+$ 497.2, found 497.4.

**BocNHCS-Glu(O-*t*-Bu)-Phe-Gly-OH (15{21})**



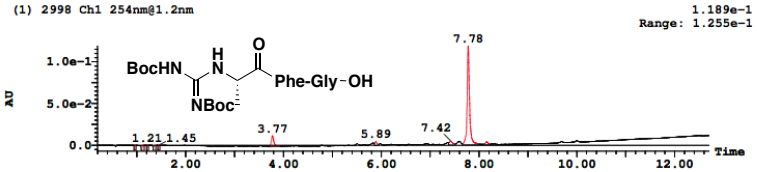

Purity: 92%, $R_f$ = 8.00 min. UPLC-MS (ESI) calcd for $C_{26}H_{39}N_4O_8S$ $[M + H]^+$ 567.2, found 567.4.

**BocNHCN(Boc)-Gly-Phe-Gly-OH (16{1})**



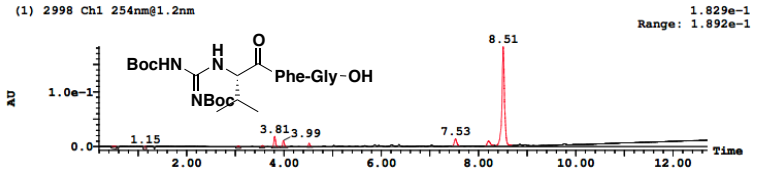

Purity: >95%, $R_f$ = 7.29 min. UPLC-MS (ESI) calcd for $C_{24}H_{36}N_5O_8$ $[M + H]^+$ 522.3, found 522.5.

**BocNHCN(Boc)-Ala-Phe-Gly-OH (16{2})**



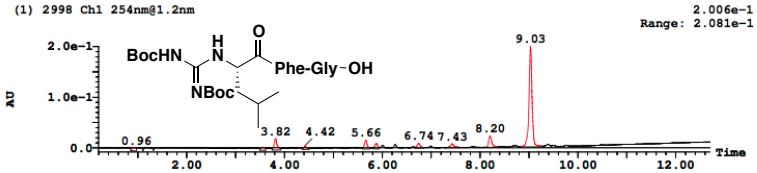

Purity: 90%, $R_f$ = 7.78 min. UPLC-MS (ESI) calcd for $C_{25}H_{38}N_5O_8$ $[M + H]^+$ 536.3, found 536.5.

**BocNHCN(Boc)-Val-Phe-Gly-OH (16{3})**



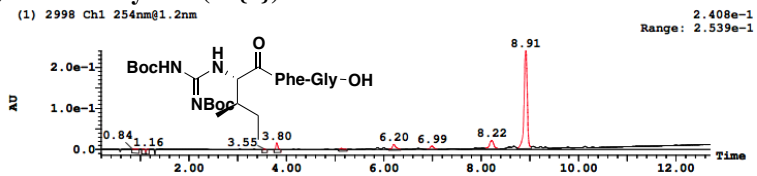

Purity: 87%, $R_f$ = 8.51 min. HRMS (ESI) calcd for $C_{27}H_{42}N_5O_8$ $[M + H]^+$ 564.3028, found 564.3065.

**BocNHCN(Boc)-Leu-Phe-Gly-OH (16{4})**



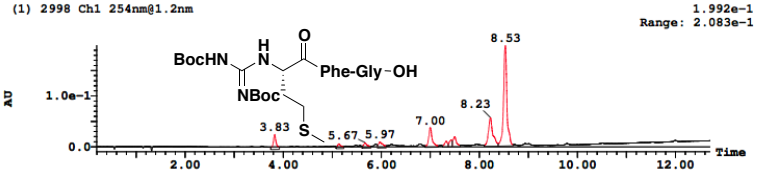

Purity: >95%, $R_f$ = 9.03 min. UPLC-MS (ESI) calcd for $C_{28}H_{44}N_5O_8$ $[M + H]^+$ 578.3, found 578.5.

**BocNHCN(Boc)-Ile-Phe-Gly-OH (16{5})**



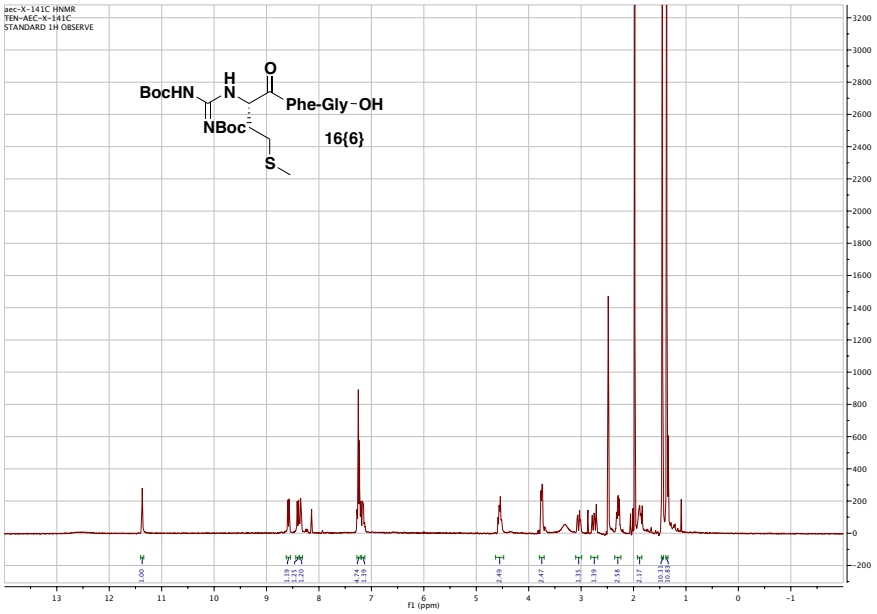

Purity: >95%, $R_f$ = 8.91 min. UPLC-MS (ESI) calcd for $C_{28}H_{44}N_5O_8$ $[M + H]^+$ 578.3, found 578.6.

**BocNHCN(Boc)-Met-Phe-Gly-OH (16{6})**

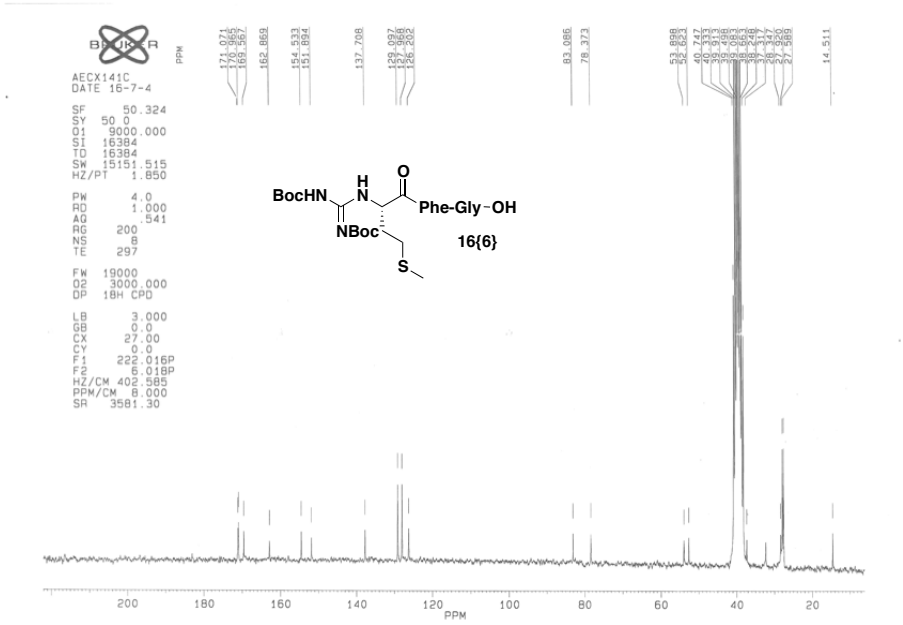



Purity: 75%, $R_f$ = 8.53 min. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.39 (1H, s), 8.60 (1H, d, J = 7.6 Hz), 8.42 (1H, d, *J* = 8.3 Hz), 8.37 (1H, t, *J* = 5.8 Hz), 7.34 – 7.10 (5H, m), 4.61 – 4.52 (2H, m), 3.77 (2H, dd, *J* = 2.7 Hz, 5.7 Hz), 3.06 (1H, dd, *J* = 4.1 Hz, 13.8 Hz), 2.77 (1H, dd, *J* = 9.9 Hz, 13.5 Hz), 2.31 (2H, dd, *J* = 6.6 Hz, 9.0 Hz), 1.95 – 1.85 (2H, m), 1.47 (9H, s), 1.39 (9H, s). $^{13}$C NMR (50 MHz, DMSO-$d_6$): δ 171.1, 171.0, 169.6, 162.9, 154.5, 151.9, 137.7, 129.1 (2C) 128.0 (2C), 126.2, 83.1, 78.4, 53.9, 52.6, 37.3, 32.3, 28.4, 27.9 (3C), 27.6 (3C), 14.5. HRMS (ESI) calcd for $C_{27}H_{42}N_5O_8S$ $[M + H]^+$ 596.2749, found 596.2779.

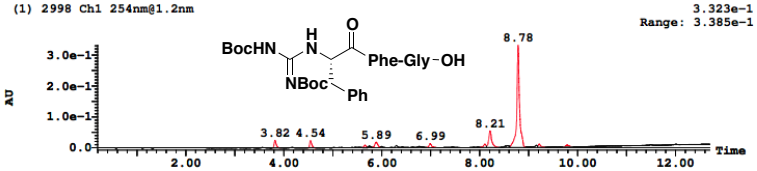
**$^{1}$H NMR (300 MHz, DMSO-$d_6$)**




**$^{13}$C NMR (50 MHz, DMSO-$d_6$)**

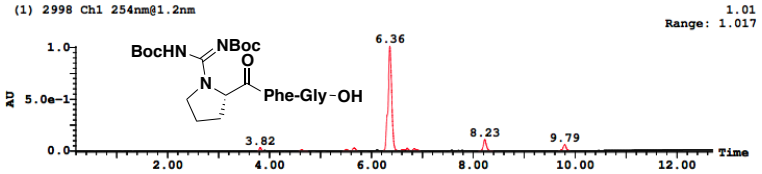



**BocNHCN(Boc)-Phe-Phe-Gly-OH (16{7})**



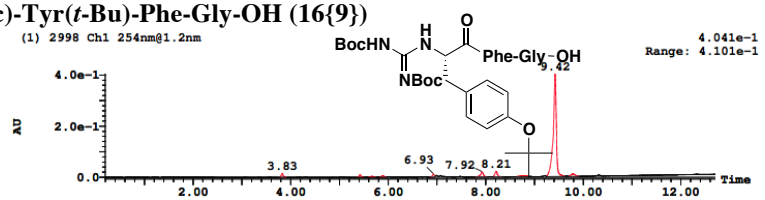

Purity: 74%, $R_f$ = 8.78 min. UPLC-MS (ESI) calcd for $C_{31}H_{42}N_5O_8$ $[M + H]^+$ 612.3, found 612.5.

**BocNHCN(Boc)-Pro-Phe-Gly-OH (16{8})**



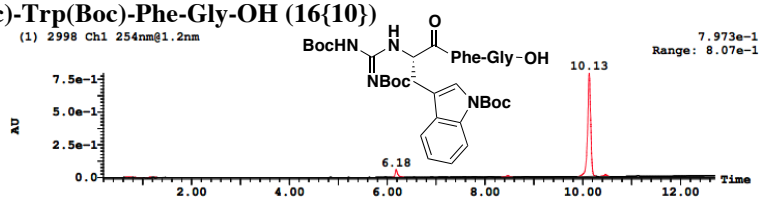

Purity: 90%, $R_f$ = 6.36 min. UPLC-MS (ESI) calcd for $C_{27}H_{40}N_5O_8$ $[M + H]^+$ 562.3, found 562.5.

**BocNHCN(Boc)-Tyr(*t*-Bu)-Phe-Gly-OH (16{9})**



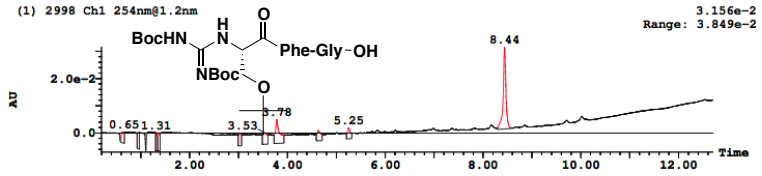

Purity: 85%, $R_f$ = 9.42 min. UPLC-MS (ESI) calcd for $C_{35}H_{50}N_5O_9$ $[M + H]^+$ 684.4, found 684.6.

**BocNHCN(Boc)-Trp(Boc)-Phe-Gly-OH (16{10})**



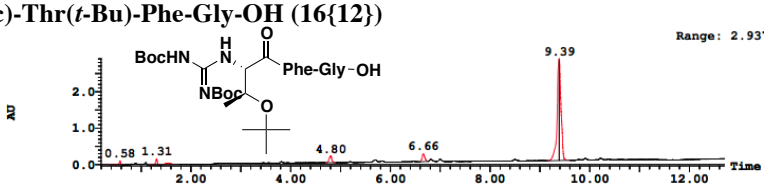

Purity: 94%, $R_f$ = 10.13 min. UPLC-MS (ESI) calcd for $C_{38}H_{51}N_6O_{10}$ $[M + H]^+$ 751.4, found 751.6.

**BocNHCN(Boc)-Ser(*t*-Bu)-Phe-Gly-OH (16{11})**



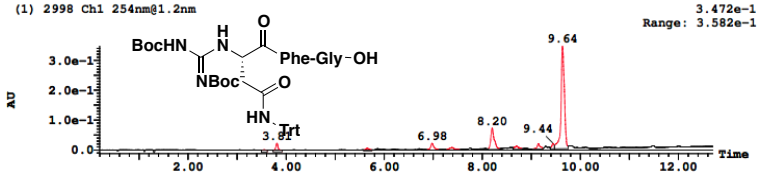

Purity: 90%, $R_f$ = 8.44 min. UPLC-MS (ESI) calcd for $C_{29}H_{46}N_5O_9$ $[M + H]^+$ 608.3, found 608.6.

**BocNHCN(Boc)-Thr(*t*-Bu)-Phe-Gly-OH (16{12})**



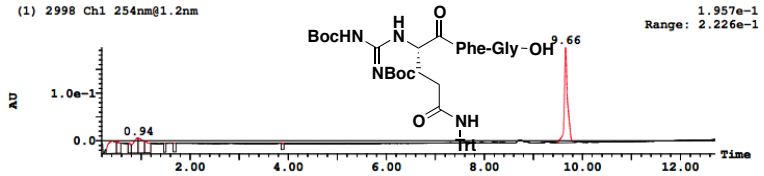

Purity: >95%, $R_f$ = 9.39 min. UPLC-MS (ESI) calcd for $C_{30}H_{48}N_5O_9$ $[M + H]^+$ 622.3, found 622.5.

**BocNHCN(Boc)-Asn(Trt)-Phe-Gly-OH (16{13})**



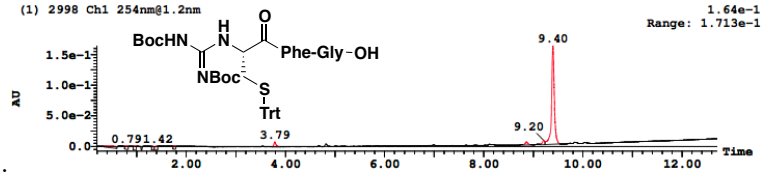

Purity: 78%, $R_f$ = 9.64 min. UPLC-MS (ESI) calcd for $C_{45}H_{53}N_6O_9$ $[M + H]^+$ 821.4, found 821.6.

**BocNHCN(Boc)-Gln(Trt)-Phe-Gly-OH (16{14)**



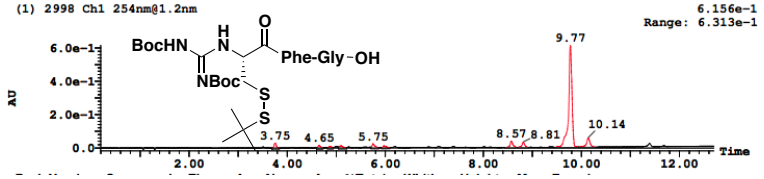

Purity: >95%, $R_f$ = 9.66 min. UPLC-MS (ESI) calcd for $C_{46}H_{55}N_6O_9$ $[M + H]^+$ 835.4, found 835.7.

**BocNHCN(Boc)-Cys(Trt)-Phe-Gly-OH (16{15})**



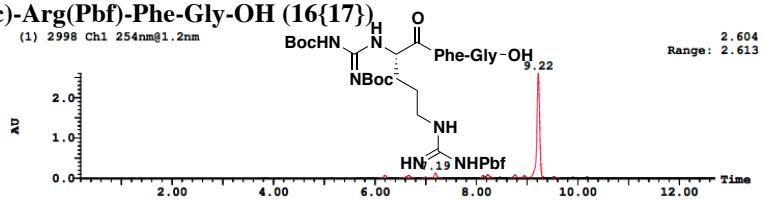

Purity: >95%, $R_f$ = 9.40 min. UPLC-MS (ESI) calcd for $C_{44}H_{52}N_5O_8S$ $[M + H]^+$ 810.4, found 810.6.

**BocNHCN(Boc)-Cys(S-*t*-Bu)-Phe-Gly-OH (16{16})**



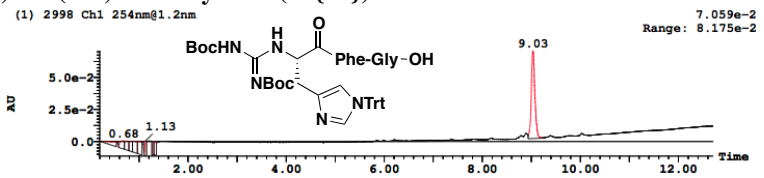

Purity: 79%, $R_f$ = 9.77 min. HRMS (ESI) calcd for $C_{29}H_{46}N_5O_8S_2$ $[M + H]^+$ 656.2782, found 656.2806.

**BocNHCN(Boc)-Arg(Pbf)-Phe-Gly-OH (16{17})**



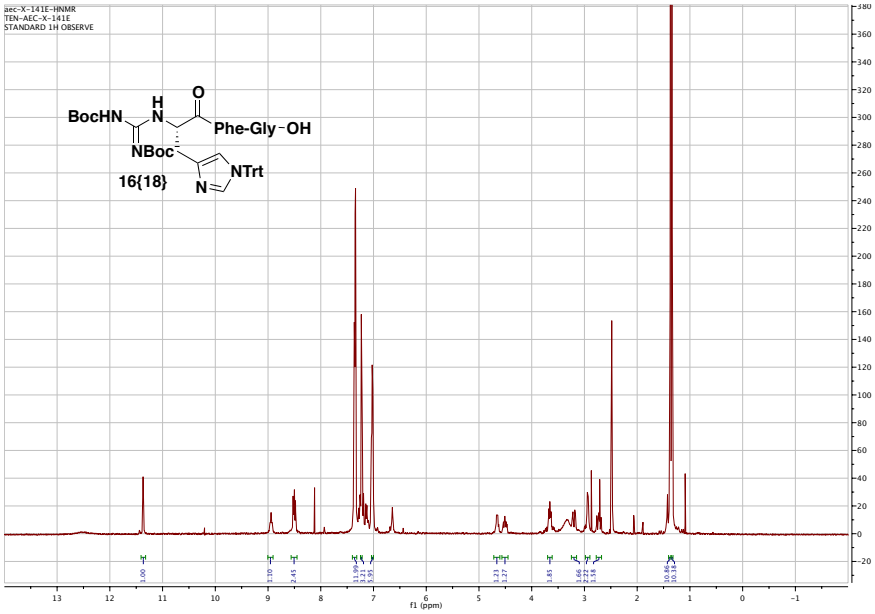

Purity: >95%, $R_f$ = 9.22 min. UPLC-MS (ESI) calcd for $C_{41}H_{61}N_8O_{11}S$ $[M + H]^+$ 873.4, found 873.7.

**BocNHCN(Boc)-His(Trt)-Phe-Gly-OH (16{18})**

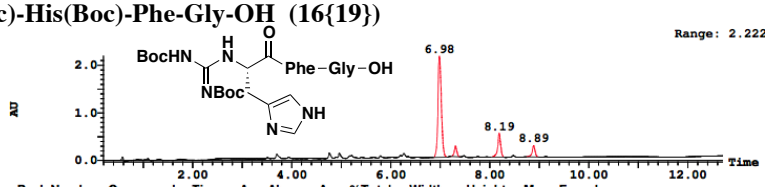



Purity: >95%, $R_f$ = 9.03 min. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 11.39 (1H, s), 8.96 (1H, t, $J$ = 5.2 Hz), 8.60 – 8.44 (2H, m), 7.42 – 7.33 (11H, m), 7.27 – 7.21 (3H, m), 7.04 (6H, dd, $J$ = 2.9 Hz, 6.7 Hz), 4.67 (1H, d, $J$ = 7.5 Hz), 4.52 (1H, dd, $J$ = 5.6 Hz, 13.7 Hz), 3.67 (2H, t, $J$ = 6.5 Hz), 3.29 (1H, dd, $J$ = 3.8 Hz, 13.8 Hz), 2.98 – 2.93 (2H, m), 2.74 (1H, dd, $J$ = 10.4 Hz, 13.8 Hz), 1.39 (9H, s), 1.36 (9H, s). HRMS (ESI) calcd for $C_{47}H_{54}N_7O_8$ $[M +H]^+$ 844.4028, found 844.4077.

**$^1$H NMR (300 MHz, DMSO-$d_6$)**

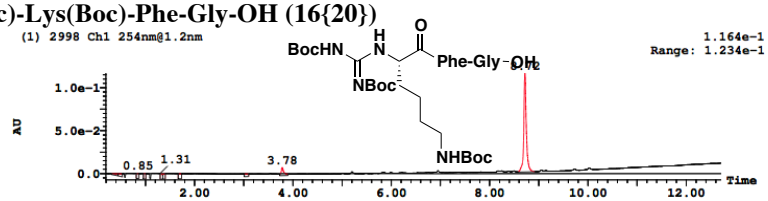



**BocNHCN(Boc)-His(Boc)-Phe-Gly-OH (16{19})**



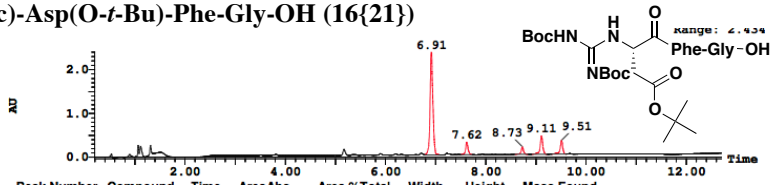

Purity: 89%, $R_f$ = 6.98 min. (The side-chain Boc group was lost during cleavage from the resin). UPLC-MS (ESI) calcd for $C_{33}H_{48}N_7O_{10}$ [M - Boc]$^+$ 702.3, found 702.6.

**BocNHCN(Boc)-Lys(Boc)-Phe-Gly-OH (16{20})**



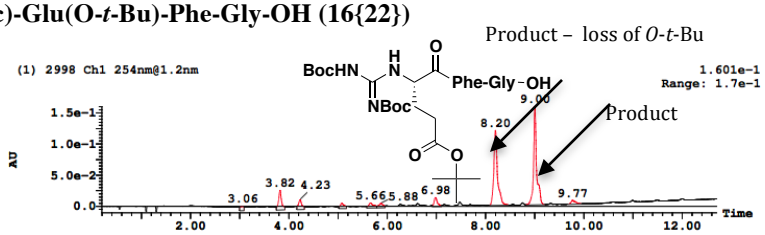

Purity: 91%, $R_f$ = 8.72 min. UPLC-MS (ESI) calcd for $C_{33}H_{53}N_6O_{10}$ [M + H]$^+$ 693.4, found 693.6.

**BocNHCN(Boc)-Asp(O-*t*-Bu)-Phe-Gly-OH (16{21})**




Purity: 75%, $R_f$ = 6.91 min. (The O-*t*-Bu group was lost during cleavage from the resin). HRMS (ESI) calcd for $C_{26}H_{38}N_5O_{10}$ [M - *t*Bu]$^+$ 580.2613, found 580.2621.

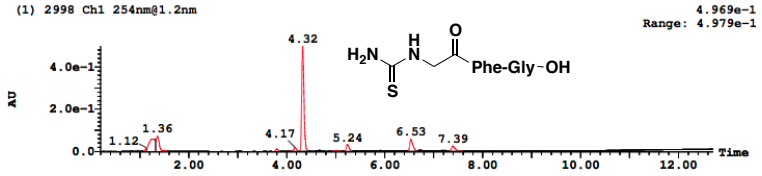
**BocNHCN(Boc)-Glu(O-*t*-Bu)-Phe-Gly-OH (16{22})**




Purity: 90%, $R_f$ = 9.01 min. UPLC-MS (ESI) calcd for $C_{31}H_{48}N_5O_{10}$ $[M + H]^+$ 650.3, found 650.6.

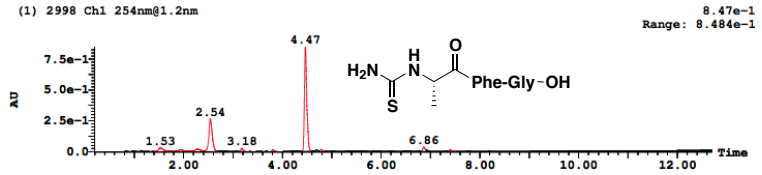
**Synthesis of Thiourea and Guanidino Peptides**

**$NH_2CS$-Gly-Phe-Gly-OH**



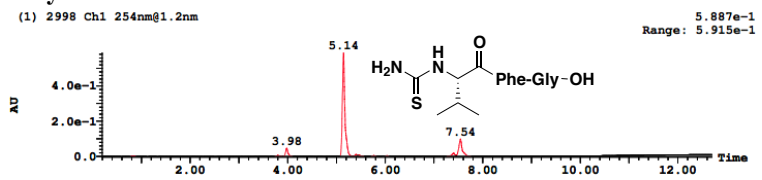

Purity: 76%, $R_f$ = 4.32 min. UPLC-MS (ESI) calcd for $C_{14}H_{19}N_4O_4S$ $[M + H]^+$ 339.1, found 339.3.

**$NH_2CS$-Ala-Phe-Gly-OH**



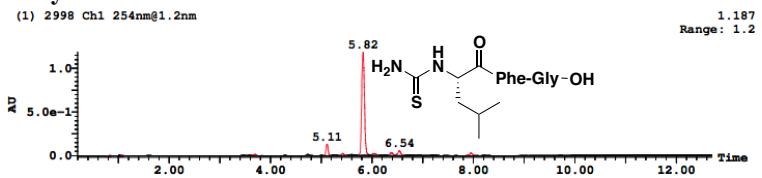

Purity: 93%, $R_f$ = 4.47 min. UPLC-MS (ESI) calcd for $C_{15}H_{21}N_4O_4S$ $[M + H]^+$ 353.1, found 353.3.

**$NH_2CS$-Val-Phe-Gly-OH**



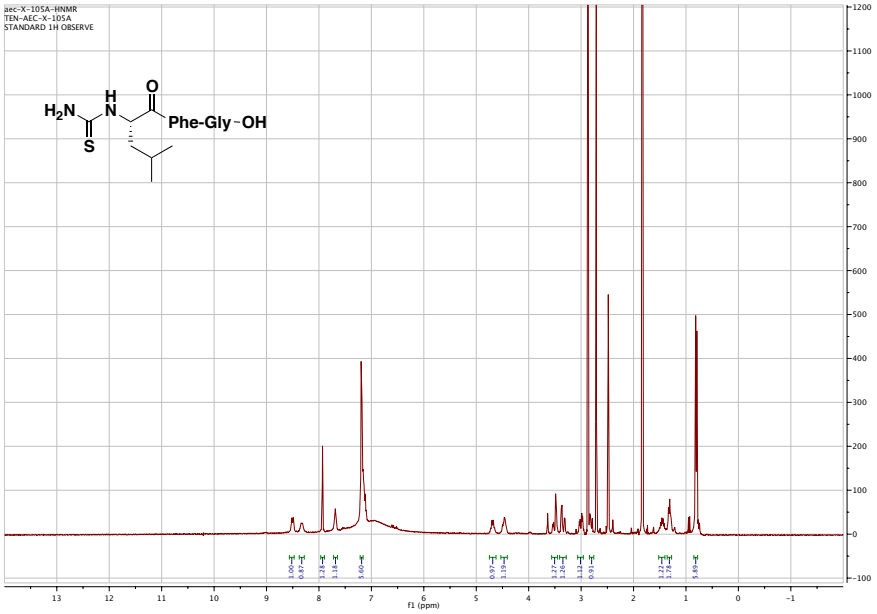

Purity: 88%, $R_f$ = 5.14 min. UPLC-MS (ESI) calcd for $C_{17}H_{25}N_4O_4S$ $[M + H]^+$ 381.2, found 381.3.

**$NH_2CS$-Leu-Phe-Gly-OH**

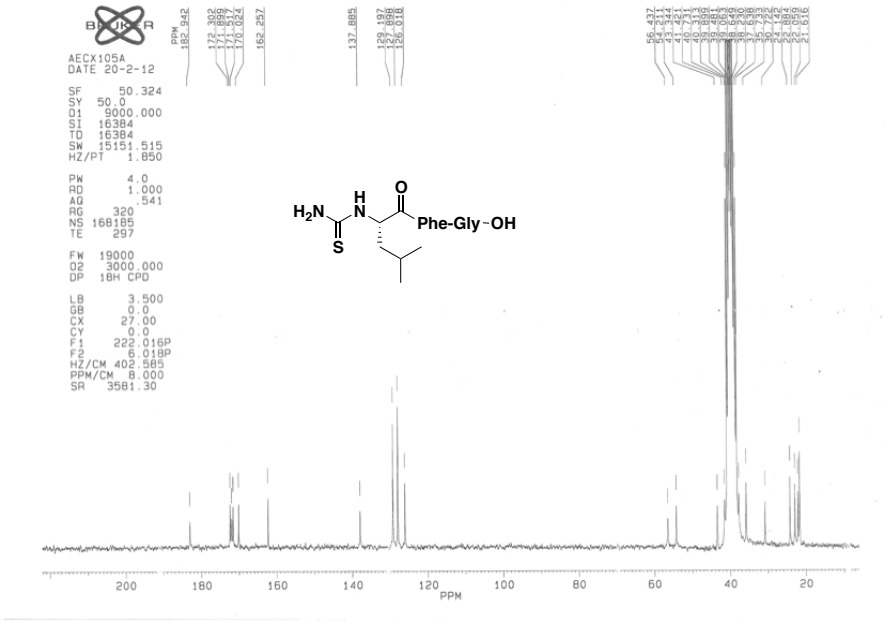



Purity: 92%, $R_f$ = 5.82 min. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 8.52 (1H, d, $J$ = 7.6 Hz), 8.36 (1H, bs), 7.95 (2H, s), 7.71 (1H, bs), 7.28 – 7.10 (5H, m), 4.71 (1H, d, $J$ = 7.7 Hz), 4.48 (1H, d, J = 4.1 Hz), 3.52 (1H, dd, $J$ = 5.2 Hz, 16.8 Hz), 3.36 (1H, dd, $J$ = 4.1 Hz, 17.1 Hz), 3.02 (1H, dd, $J$ = 4.3 Hz, 13.7 Hz), 2.88 – 2.82 (1H, m), 1.47 (2H, p, $J$ = 6.2 Hz), 1.38 – 1.28 (1H, m), 0.80 (6H, d, J = 6.3 Hz). $^{13}$C NMR (50 MHz, DMSO-$d_6$): δ 182.9, 172.3, 171.5, 170.0, 137.9, 129.2 (2C), 127.9 (2C), 126.0, 56.4, 54.2, 43.3, 41.4, 37.7, 24.1, 22.1, 21.6. HRMS (ESI) calcd for $C_{18}H_{27}N_4O_4S$ $[M + H]^+$ 395.1748, found 395.1748.

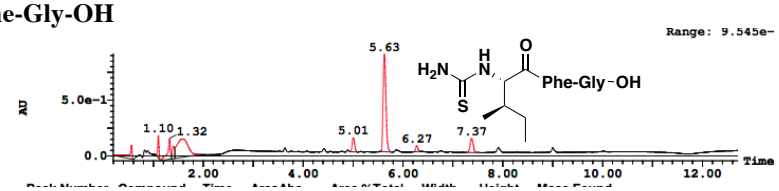
**$^{1}$H NMR (300 MHz, DMSO-$d_6$)**




**$^{13}$C NMR (50 MHz, DMSO-$d_6$)**

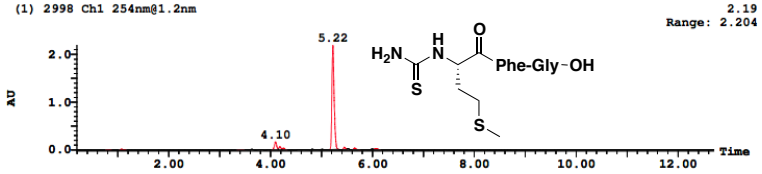



**$NH_2CS$-Ile-Phe-Gly-OH**



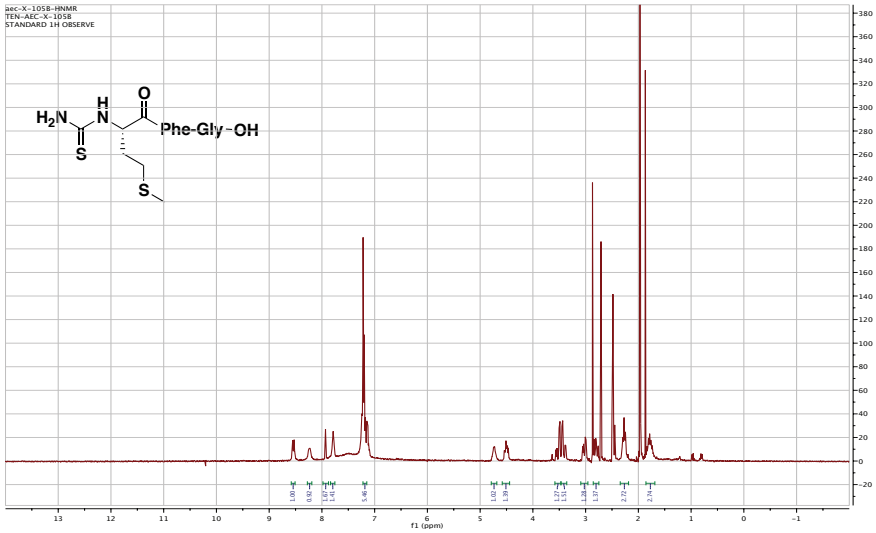

Purity: 91%, $R_f$ = 5.63 min. UPLC-MS (ESI) calcd for $C_{18}H_{27}N_4O_4S$ $[M + H]^+$ 395.2, found 395.4.

**$NH_2CS$-Met-Phe-Gly-OH**

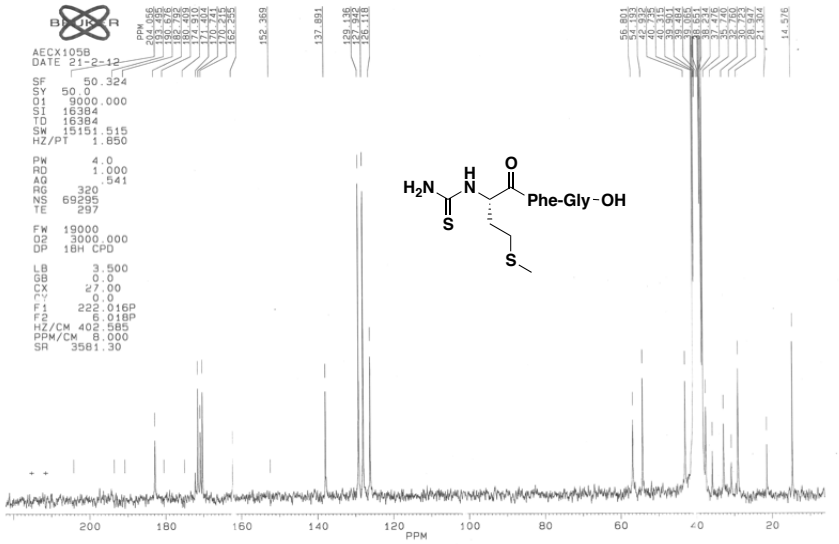



Purity: 92%, $R_f$ = 5.22 min. **1**H NMR (500 MHz, DMSO-$d_6$): δ 8.56 (1H, d, $J$ = 8.4 Hz), 8.24 (1H, bs), 7.95 (2H, s), 7.80 (1H bs), 7.33 – 7.11 (5H, m), 4.74 (1H, d, $J$ = 6.8 Hz), 4.52 (1H, td, $J$ = 4.2 Hz, 9.5 Hz), 3.54 (1H, dd, $J$ = 5.1 Hz, 17.1 Hz), 3.43 (1H, dd, $J$ = 4.5 Hz, 17.0 Hz), 3.04 (1H, dd, $J$ = 4.4 Hz, 13.9 Hz), 2.82 (1H, dd, $J$ = 10.2 Hz, 13.8 Hz), 2.34 – 2.24 (2H, m), 1.93 (3H, s), 1.88 – 1.71 (2H, m). $^{13}$C NMR (50 MHz, DMSO-$d_6$): δ 182.8, 171.4, 170.7, 170.2, 137.9, 129.1 (2C), 127.9 (2C), 126.1, 56.8, 54.2, 42.9, 37.5, 32.8, 29.0, 14.6. HRMS (ESI) calcd for $C_{17}H_{25}N_4O_4S_2$ $[M + H]^+$ 413.1312, found 413.1310.

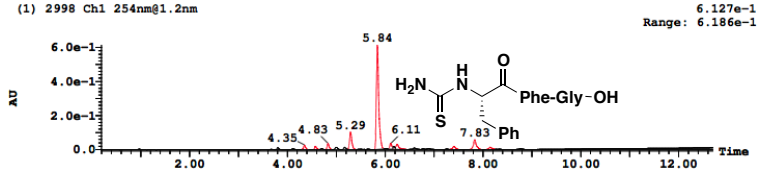
**$^1$H NMR (300 MHz, DMSO-$d_6$)**




**$^{13}$C NMR (50 MHz, DMSO-$d_6$)**

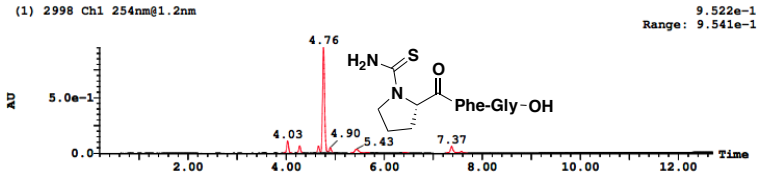


**$NH_2CS$-Phe-Phe-Gly-OH**



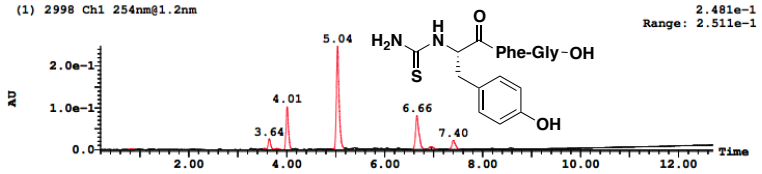

Purity: 79%, $R_f$ = 5.84 min. UPLC-MS (ESI) calcd for $C_{21}H_{25}N_4O_4S$ $[M + H]^+$ 429.2, found 429.4.

**$NH_2CS$-Pro-Phe-Gly-OH**



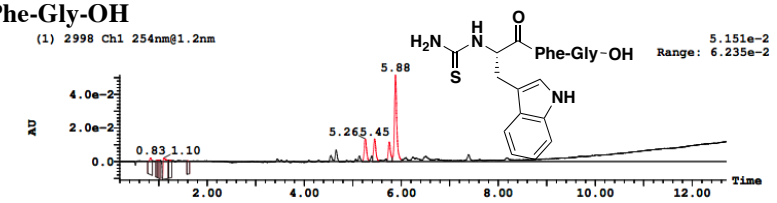

Purity: 91%, $R_f$ = 4.76 min. UPLC-MS (ESI) calcd for $C_{17}H_{23}N_4O_4S$ $[M + H]^+$ 379.1, found 379.3.

**$NH_2CS$-Tyr-Phe-Gly-OH**



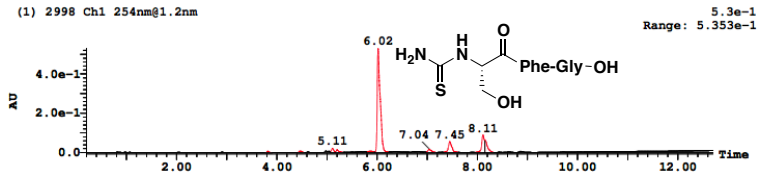

Purity: 76%, $R_f$ = 5.04 min. UPLC-MS (ESI) calcd for $C_{21}H_{25}N_4O_5S$ $[M + H]^+$ 445.2, found 445.3.

**$NH_2CS$-Trp-Phe-Gly-OH**



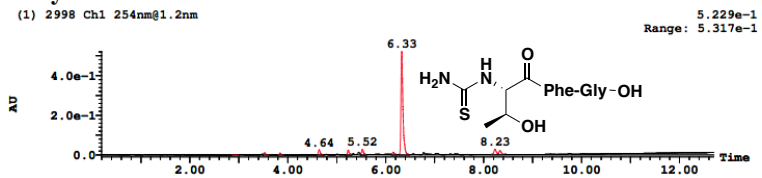

Purity: 75%, $R_f$ = 5.88 min. UPLC-MS (ESI) calcd for $C_{23}H_{26}N_5O_4S$ $[M + H]^+$ 468.2, found 468.3.

**$NH_2CS$-Ser-Phe-Gly-OH**



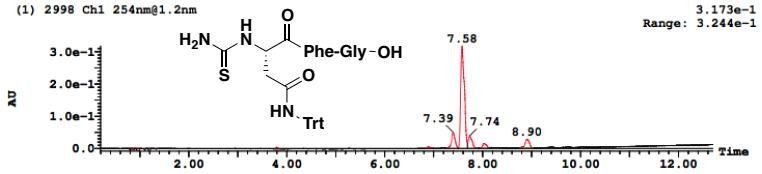

Purity: 76%, $R_f$ = 6.02 min. UPLC-MS (ESI) calcd for $C_{15}H_{21}N_4O_5S$ $[M + H]^+$ 369.1, found 369.3.

**$NH_2CS$-Thr-Phe-Gly-OH**



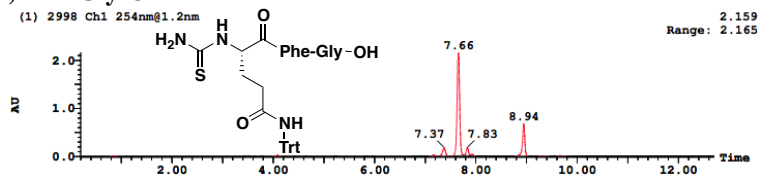

Purity: 83%, $R_f$ = 6.33 min. UPLC-MS (ESI) calcd for $C_{16}H_{23}N_4O_5S$ $[M + H]^+$ 383.1, found 383.3.

**$NH_2CS$-Asn(Trt)-Phe-Gly-OH**



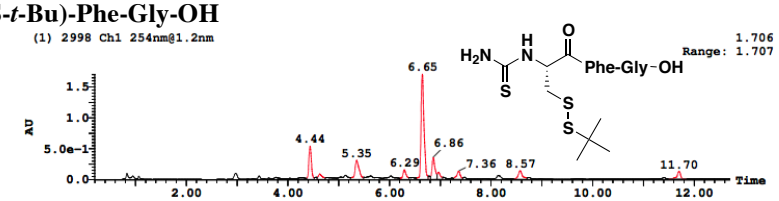

Purity: 94%, $R_f$ = 7.58 min. HRMS (ESI) calcd for $C_{35}H_{36}N_5O_5S$ $[M + H]^+$ 638.2432, found 638.2432.

**$NH_2CS$-Gln(Trt)-Phe-Gly-OH**



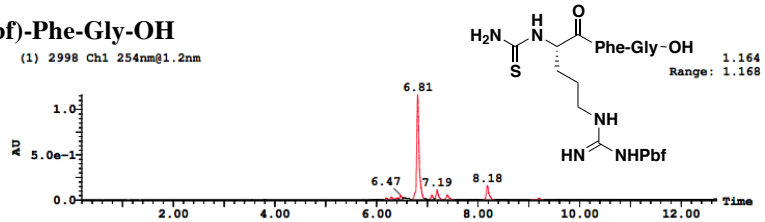

Purity: 72%, $R_f$ = 7.66 min. UPLC-MS (ESI) calcd for $C_{36}H_{38}N_5O_5S$ $[M + H]^+$ 652.3, found 652.3.

**$NH_2CS$-Cys(S-*t*-Bu)-Phe-Gly-OH**



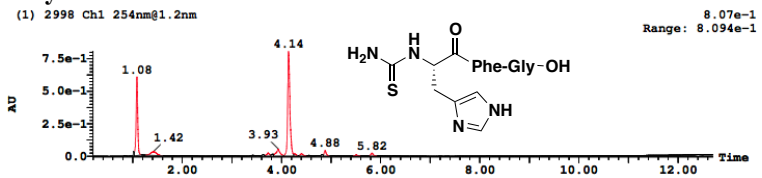

Purity: 71%, $R_f$ = 6.65 min. HRMS (ESI) calcd for $C_{19}H_{29}N_4O_4S_3$ $[M + H]^+$ 473.1345, found 473.1353.

**$NH_2CS$-Arg(Pbf)-Phe-Gly-OH**



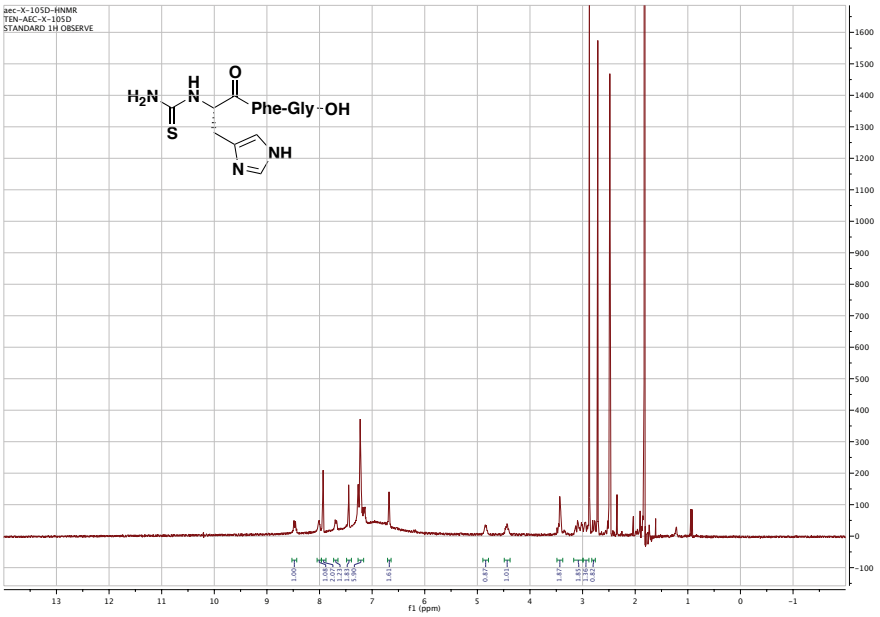

Purity: 78%, $R_f$ = 6.81 min. UPLC-MS (ESI) calcd for $C_{31}H_{44}N_7O_7S_2$ $[M + H]^+$ 690.3, found 690.5.

**$NH_2CS$-His-Phe-Gly-OH**

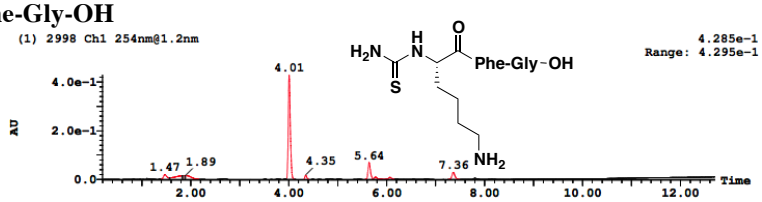



Purity: 83%, $R_f$ = 4.14 min. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 8.45 (1H, d, $J$ = 7.7 Hz), 8.03 (1H, bs), 7.94 (2H, s), 7.65 (1H, d, $J$ = 6.5 Hz), 7.45 (1H, s), 7.30 – 7.10 (5H, m), 6.69 (1H, s), 4.90 – 4.81 (1H, m), 4.48 – 4.42 (1H, m), 3.49 (2H, dd, $J$ = 4.3 Hz), 3.16 – 3.00 (1H, m), 3.00 – 2.91 (2H, m), 2.83 – 2.76 (1H, m). HRMS (ESI) calcd for $C_{18}H_{23}N_6O_4S$ $[M + H]$**+** 419.1496, found 419.1507.

**$^1$H NMR (300 MHz, DMSO-$d_6$)**

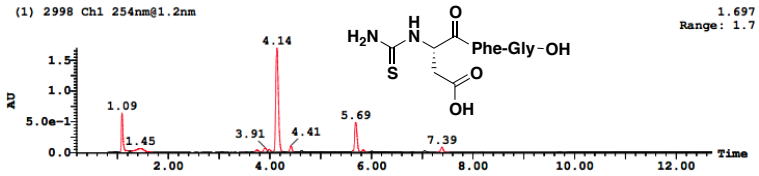



**$NH_2CS$-Lys-Phe-Gly-OH**



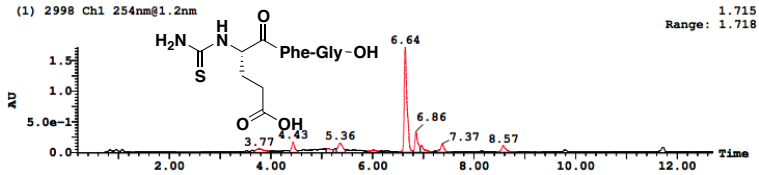

Purity: 90%, $R_f$ = 4.01 min. UPLC-MS (ESI) calcd for $C_{18}H_{28}N_5O_4S$ $[M + H]^+$ 410.2, found 410.4.

**$NH_2CS$-Asp-Phe-Gly-OH**



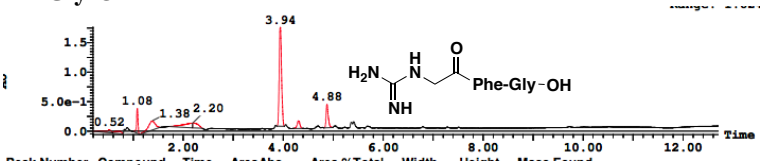

Purity: 76%, $R_f$ = 4.14 min. UPLC-MS (ESI) calcd for $C_{16}H_{21}N_4O_6S$ $[M + H]^+$ 397.1, found 397.3.

**$NH_2CS$-Glu-Phe-Gly-OH**




Purity: 76%, $R_f$ = 6.64 min. UPLC-MS (ESI) calcd for $C_{17}H_{23}N_5O_6$ $[M + H]^+$ 411.1, found 411.3.

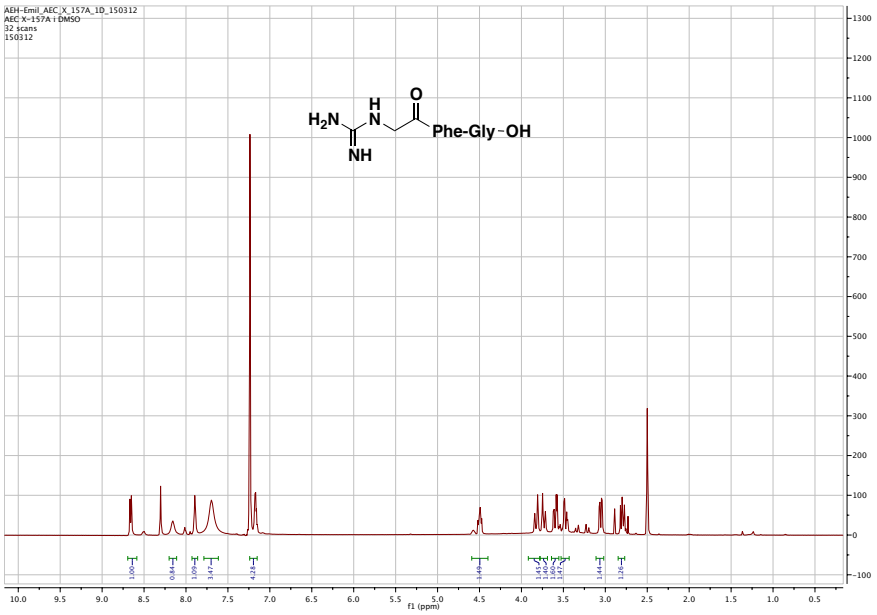
**$NH_2CNH$-Gly-Phe-Gly-OH**



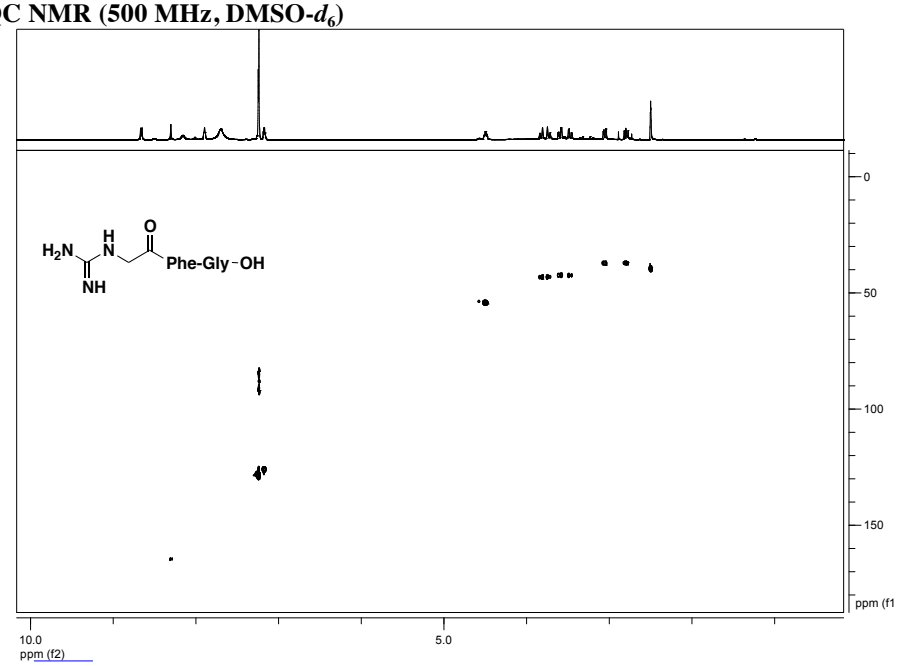

Purity: 83%, Rf = 3.94 min. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 8.66 (1H, d, $J$ = 8.4 Hz), 8.16 (1H , bs), 7.89 (1H, t, $J$ = 4.6 Hz), 7.70 (3H, bs), 7.31 – 7.13 (5H, m), 4.50 (1H, td, $J$ = 4.4 Hz, 9.3 Hz), 3.82 (1H,

d, J = 16.8 Hz), 3.73 (1H, d, *J* = 16.8 Hz), 3.60 (1H, dd, J = 5.4 Hz, 17.1 Hz), 3.47 (1H, dd, *J* = 4.7 Hz, 17.0 Hz), 3.06 (1H, dd, *J* = 4.3 Hz, 13.8 Hz), 2.80 (1H, dd, *J* = 9.9 Hz, 13.7 Hz). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 172.1, 170.4, 167.4, 157.7, 138.0, 129.4 (2C), 127.9 (2C), 126.0, 54.3, 43.2, 42.5, 37.3. HRMS (ESI) calcd for $C_{14}H_{20}N_5O_4$ $[M + H]^+$ 322.1510, found 322.1513.

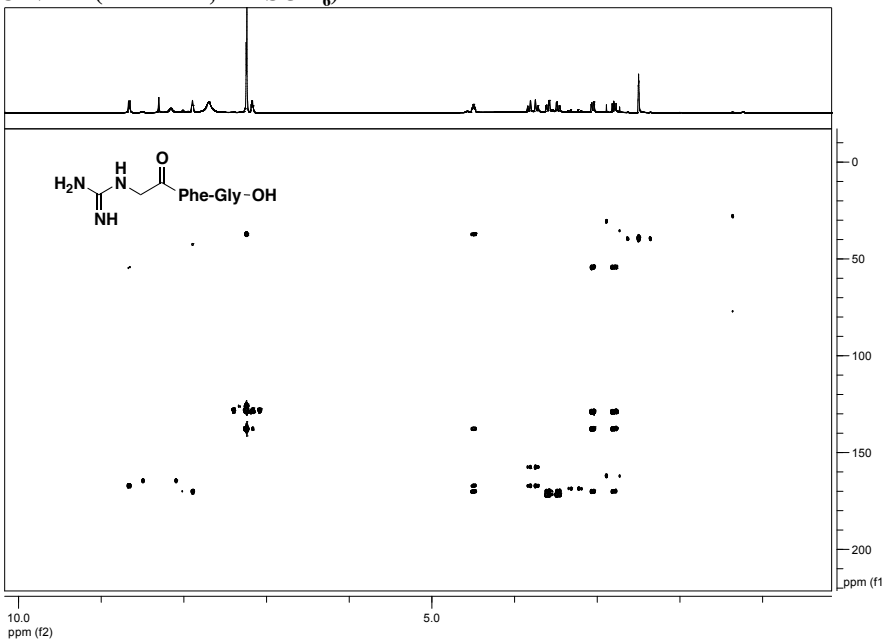
**$^1$H NMR (500 MHz, DMSO-$d_6$)**



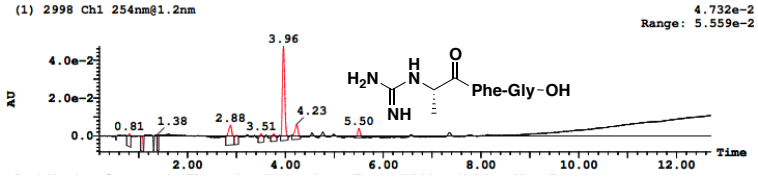

**2D HSQC NMR (500 MHz, DMSO-$d_6$)**



**2D HMBC NMR (500 MHz, DMSO-$d_6$)**

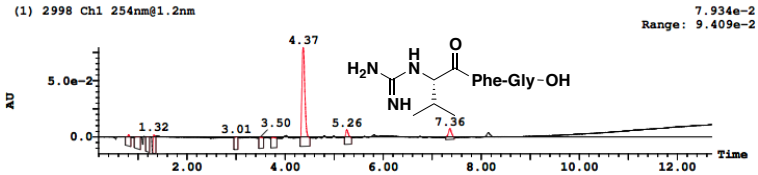



**$NH_2CNH$-Ala-Phe-Gly-OH**



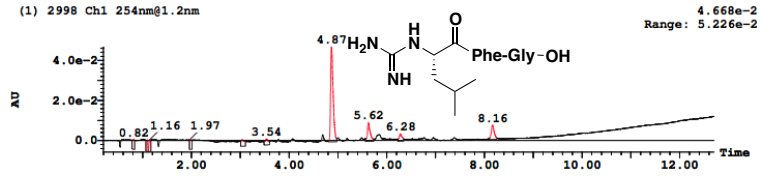

Purity: 74%, $R_f$ = 3.96 min min. UPLCMS (ESI) calcd for $C_{15}H_{22}N_5O_4$ $[M + H]^+$ 336.2, found 336.4.

**$NH_2CNH$-Val-Phe-Gly-OH**



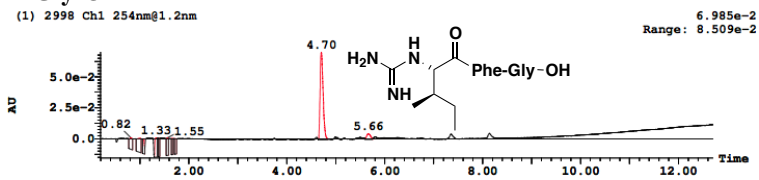

Purity: 76%, $R_f$ = 4.37 min. UPLC-MS (ESI) calcd for $C_{17}H_{26}N_5O_4$ $[M + H]^+$ 364.2, found 364.4.

**$NH_2CNH$-Leu-Phe-Gly-OH**



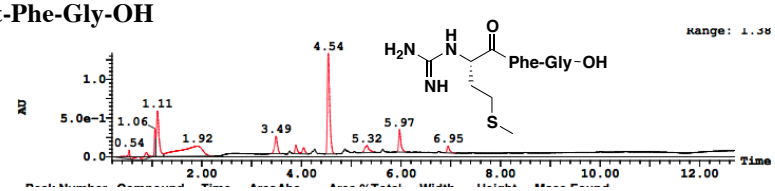

Purity: 84%, $R_f$ = 4.87 min. UPLC-MS (ESI) calcd for $C_{18}H_{28}N_5O_4$ $[M + H]^+$ 378.2, found 378.4.

**$NH_2CNH$-Ile-Phe-Gly-OH**



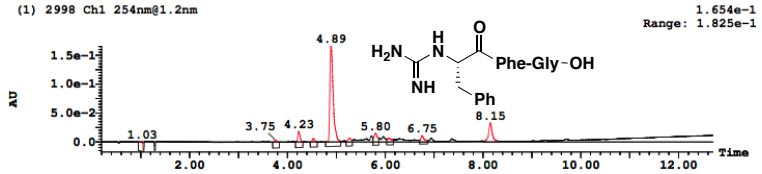

Purity: >95%, $R_f$ = 4.70 min. UPLC-MS (ESI) calcd for $C_{18}H_{28}N_5O_4$ $[M + H]^+$ 378.2, found 378.3.

**$NH_2CNH$-Met-Phe-Gly-OH**



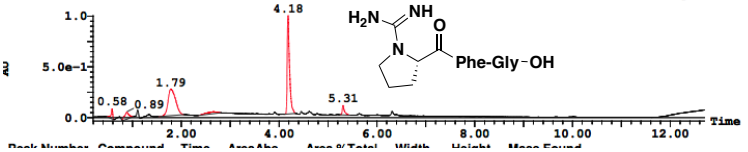

Purity: 71%, $R_f$ = 4.54 min. UPLC-MS (ESI) calcd for $C_{17}H_{26}N_5O_4S$ $[M + H]^+$ 396.2, found 396.4.

**$NH_2CNH$-Phe-Phe-Gly-OH**



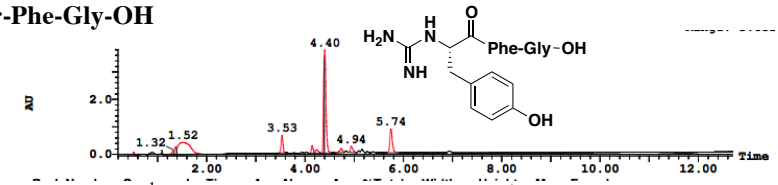

Purity: 75%, $R_f$ = 4.89 min. UPLC-MS (ESI) calcd for $C_{21}H_{26}N_5O_4$ $[M + H]^+$ 412.2, found 412.3.

**$NH_2NH$-Pro-Phe-Gly-OH**



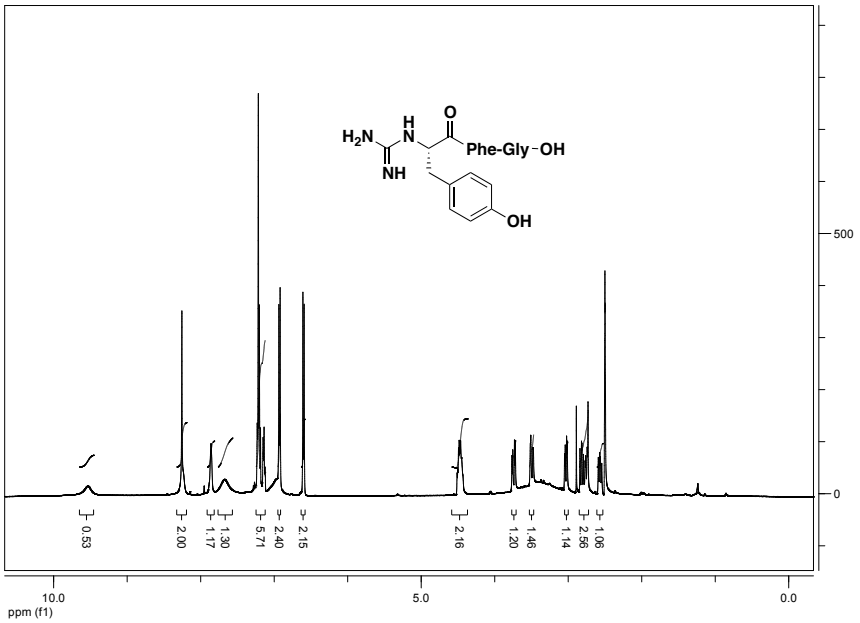

Purity: 69%, $R_f$ = 4.18 min. UPLC-MS (ESI) calcd for $C_{17}H_{24}N_5O_4$ $[M + H]^+$ 362.2, found 362.3.

**$NH_2CNH$-Tyr-Phe-Gly-OH**

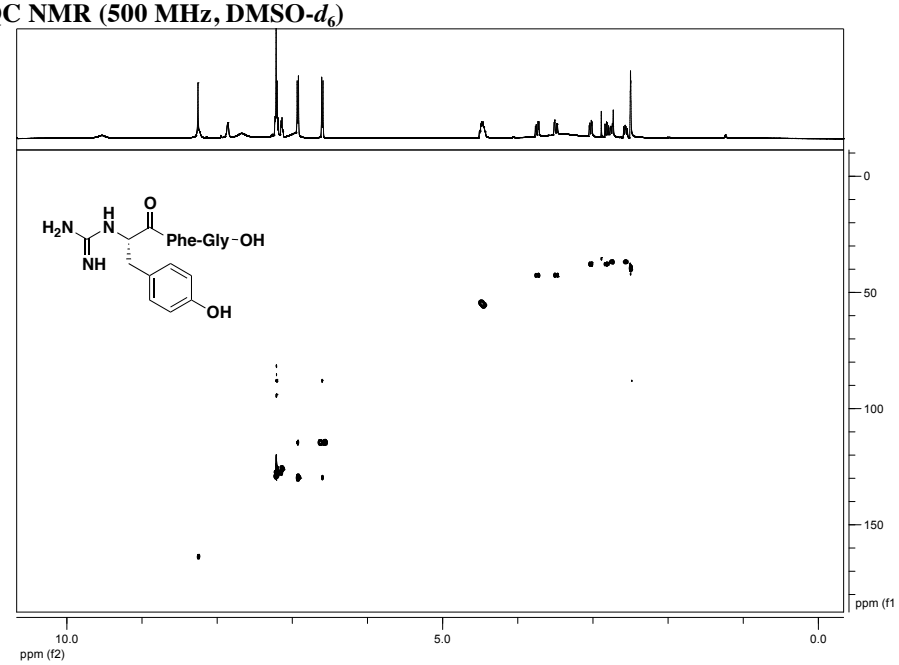



Purity: 65%, $R_f$ = 4.40 min. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 9.54 (1h, bs), 8.30 – 8.07 (2H, m), 7.86 (1H, bs), 7.68 (1H, bs), 7.32 – 7.10 (m, 6H), 7.08 – 6.89 (3H, m), 6.60 (2H, d, $J$ = 8.3 Hz), 4.59 – 4.39 (2H, m), 3.74 (1H, dd, $J$ = 5.8 Hz, 17.2 Hz), 3.49 (1H, dd, $J$ = 2.8 Hz, 16.8 Hz), 3.03 (2H, dd, $J$ = 4.3 Hz, 13.5 Hz), 2.86 – 2.71 (2H, m), 2.57 (1H, dd, $J$ = 9.1 Hz, 13.8 Hz). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 172.1, 170.0, 169.5, 169.0, 155.7, 137.6, 129.7 (2C), 128.2 (2C), 126.4, 127.4 (2C), 125.9, 114.4 (2C), 55.4, 54.4, 42.5, 37.5, 36.7. HRMS (ESI) calcd for $C_{21}H_{26}N_5O_5$ $[M + H]^+$ 428.1928, found 428.1951.

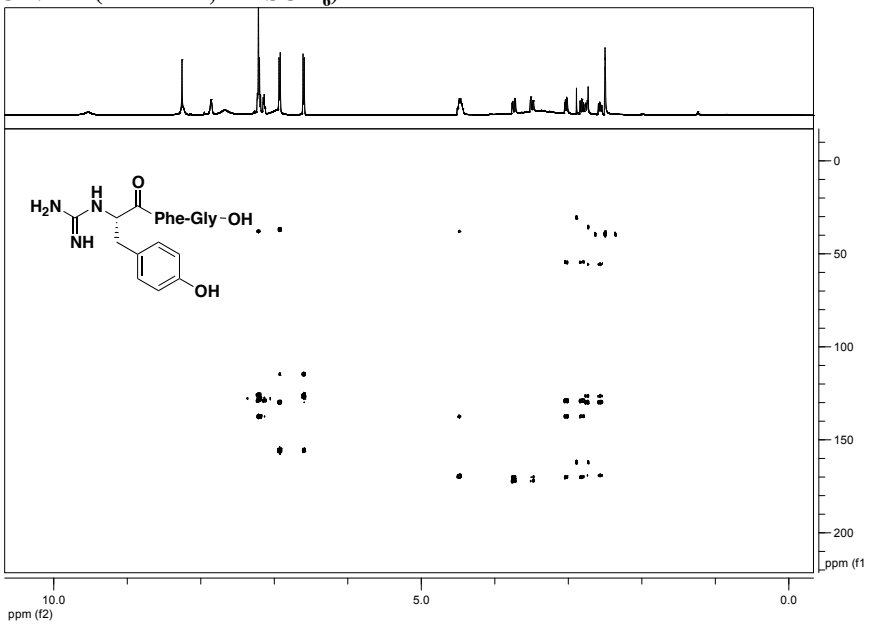
**$^1$H NMR (500 MHz, DMSO-$d_6$)**



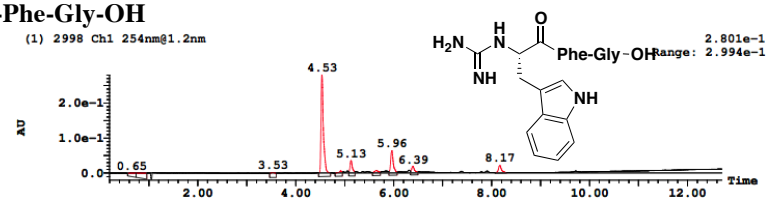

**2D HSQC NMR (500 MHz, DMSO-$d_6$)**



**2D HMBC NMR (500 MHz, DMSO-$d_6$)**

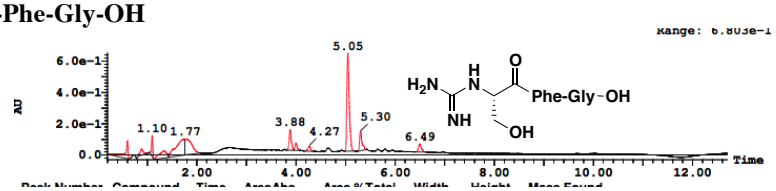



**$NH_2CNH$-Trp-Phe-Gly-OH**



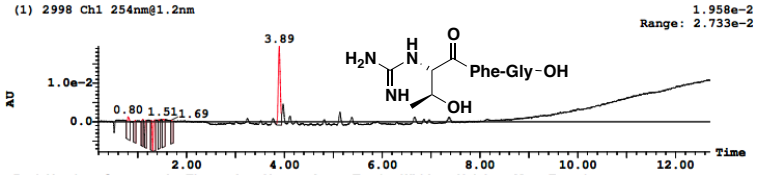

Purity: 72%, $R_f$ = 4.53 min. UPLC-MS (ESI) calcd for $C_{23}H_{27}N_6O_4$ $[M + H]^+$ 451.2, found 451.4.

**$NH_2CNH$-Ser-Phe-Gly-OH**



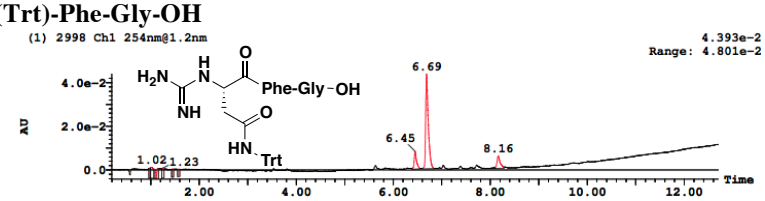

Purity: 72%, $R_f$ = 5.05 min. UPLC-MS (ESI) calcd for $C_{15}H_{22}N_5O_5$ $[M + H]^+$ 352.2, found 352.4.

**$NH_2CNH$-Thr-Phe-Gly-OH**



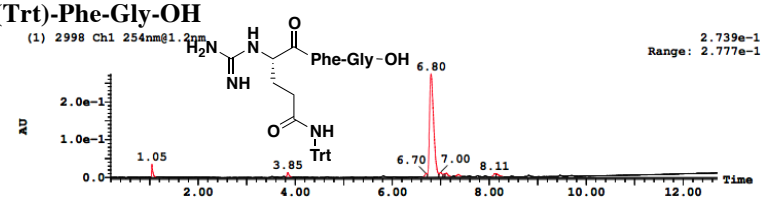

Purity: 90%, $R_f$ = 3.89 min. UPLC-MS (ESI) calcd for $C_{16}H_{24}N_5O_5$ $[M + H]^+$ 366.2, found 366.4.

**$NH_2CNH$-Asn(Trt)-Phe-Gly-OH**



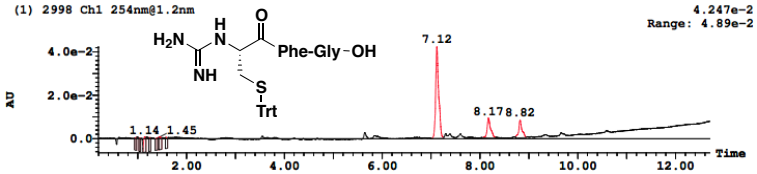

Purity: 85%, $R_f$ = 6.69 min. UPLC-MS (ESI) calcd for $C_{35}H_{37}N_6O_5$ $[M + H]^+$ 621.3, found 621.5.

**$NH_2CNH$-Gln(Trt)-Phe-Gly-OH**



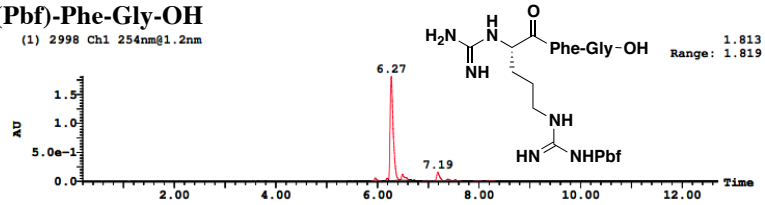

Purity: 85%, $R_f$ = 6.80 min. HRMS (ESI) calcd for $C_{36}H_{39}N_6O_5$ $[M + H]^+$ 635.2976, found 635.2993.

**$NH_2CNH$-Cys(Trt)-Phe-Gly-OH**



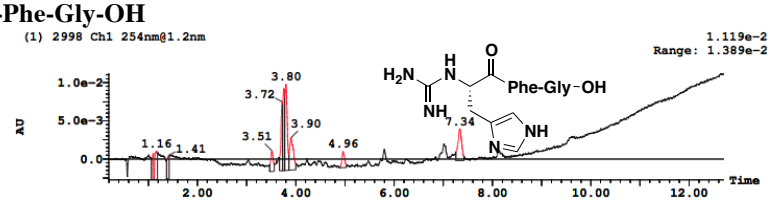

Purity: 89%, $R_f$ = 7.12 min. HRMS (ESI) calcd for $C_{34}H_{36}N_5O_4S$ $[M + H]^+$ 610.2483, found 610.2478.

**$NH_2CNH$-Arg(Pbf)-Phe-Gly-OH**



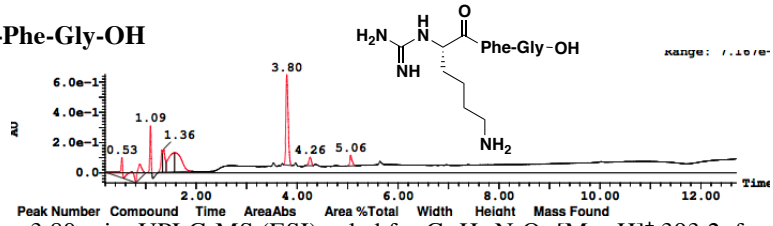

Purity: 92%, $R_f$ = 6.27 min. HRMS (ESI) calcd for $C_{31}H_{45}N_8O_7S$ $[M + H]^+$ 673.3126, found 673.3131.

**$NH_2CNH$-His-Phe-Gly-OH**



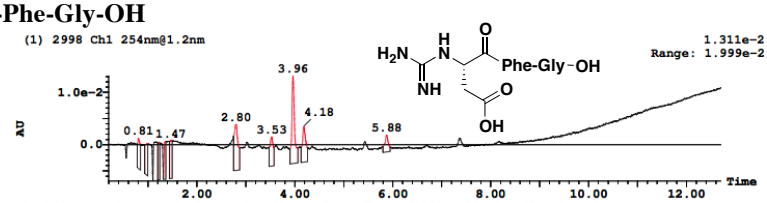

Purity: 73%, $R_f$ = 3.81 min. UPLC-MS (ESI) calcd for $C_{18}H_{24}N_7O_4$ $[M + H]^+$ 402.2, found 402.4.

**$NH_2CNH$-Lys-Phe-Gly-OH**



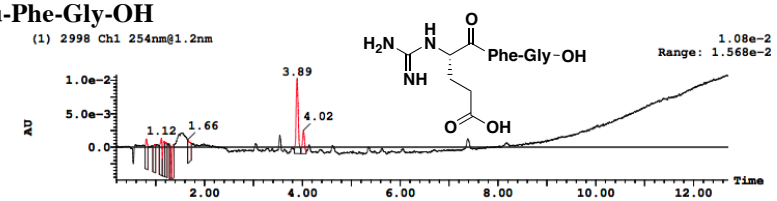

Purity: 82%, $R_f$ = 3.80 min. UPLC-MS (ESI) calcd for $C_{18}H_{29}N_6O_4$ $[M + H]^+$ 393.2, found 393.3.

**$NH_2CNH$-Asp-Phe-Gly-OH**




Purity: 72%, $R_f$ = 3.96 min. UPLC-MS (ESI) calcd for $C_{16}H_{22}N_5O_6$ $[M + H]^+$ 380.2, found 380.4.

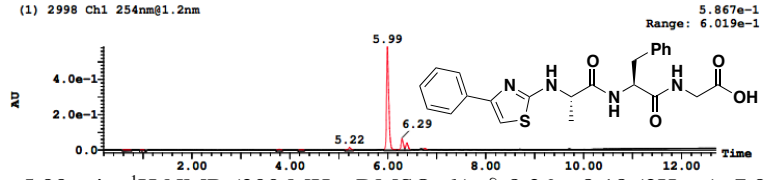
**$NH_2CNH$-Glu-Phe-Gly-OH**




Purity: 88%, $R_f$ = 3.89 min. UPLC-MS (ESI) calcd for $C_{17}H_{24}N_5O_6$ $[M + H]^+$ 394.2, found 394.4

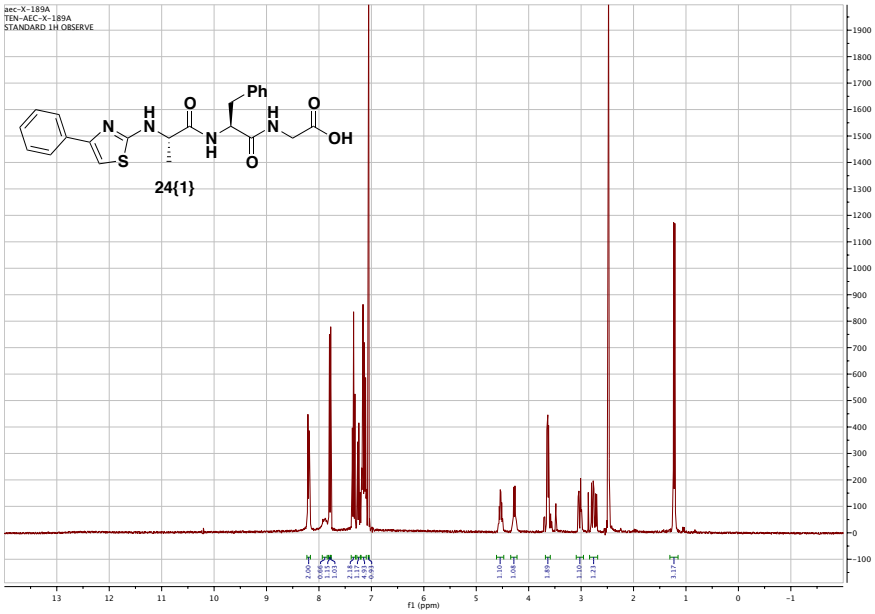
**Synthesis of Thiazoles**

**4-Phenylthiazol-2-yl-Ala-Phe-Gly (24{1})**

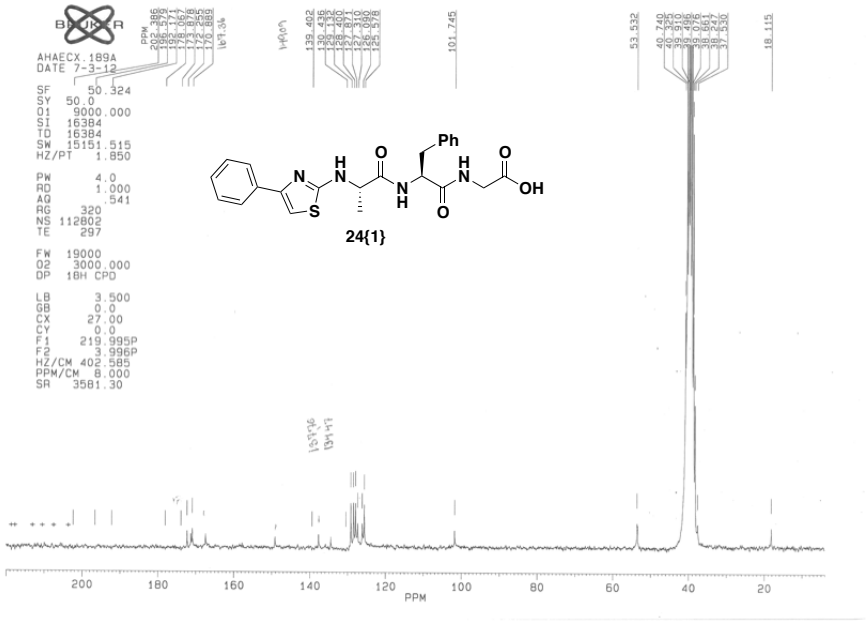



Purity: 92%, $R_f$ = 5.99 min. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.26 – 8.18 (2H, m), 7.90 (1H, bs), 7.81 (2H, dd, *J* = 1.3 Hz, 8.3 Hz), 7.42 – 7.32 (2H, m), 7.27 (1H, tt, *J* = 1.8 Hz, 4.6 Hz), 7.22 – 7.11 (5H, m), 7.07 (1H, s), 4.56 (1H, td, *J* = 4.4 Hz, 9.4 Hz), 4.30 (1H, q, *J* = 6.8 Hz), 3.66 (2H, dd, *J* = 4.3 Hz, 5.7 Hz), 3.05 (1H, dd, *J* = 4.4 Hz, 13.8 Hz), 2.79 (1H, dd, *J* = 9.7 Hz, 13.8 Hz), 1.25 (3H, d, *J* = 7.0 Hz). $^{13}$C NMR (50 MHz, DMSO-$d_6$): δ 172.3, 171.3, 170.9, 167.4, 149.1, 137.8, 134.5, 130.4 (2C), 129.1 (2C), 128.4 (2C), 127.3, 126.1, 125.6 (2C), 101.7, 53.5 (2C), 37.6, 18.1. HRMS (ESI) calcd for $C_{23}H_{25}N_4O_4S$ $[M + H]$**+** 453.1591, found 453.1607.

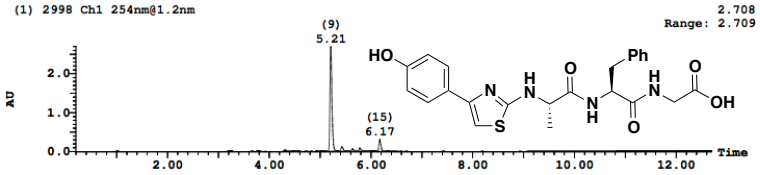
**$^1$H NMR (300 MHz, DMSO-$d_6$)**



**$^{13}$C NMR (50 MHz, DMSO-$d_6$)**

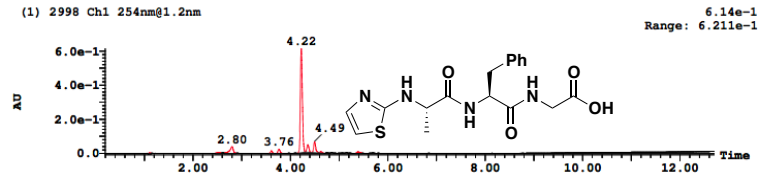



**4-(4-hydroxyphenyl)thiazol-2-yl-Ala-Phe-Gly (24{2})**



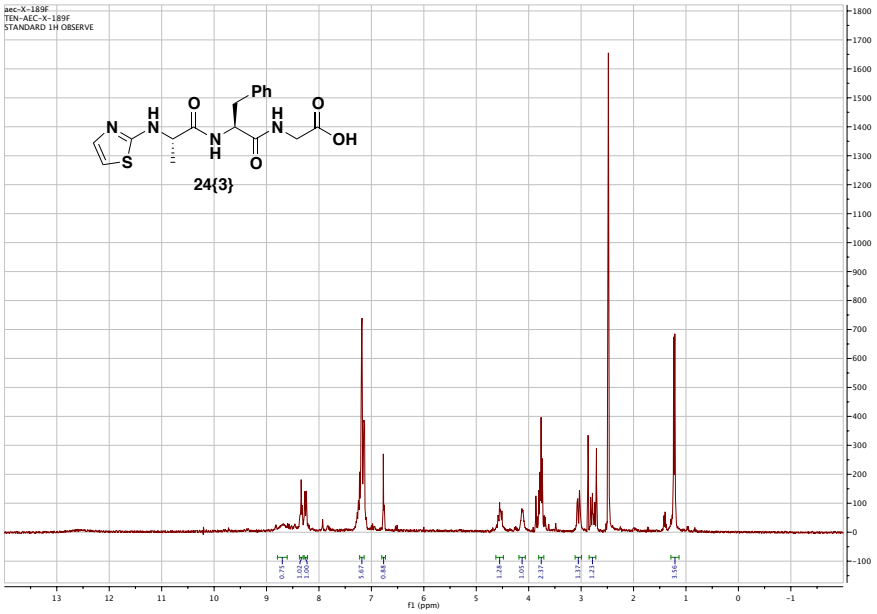

Purity: 90%, $R_f$ = 5.21 min. UPLC-MS (ESI) calcd for $C_{23}H_{25}N_4O_5S$ $[M + H]^+$ 469.2, found 469.2.

**Thiazol-2-yl-Ala-Phe-Gly (24{3})**

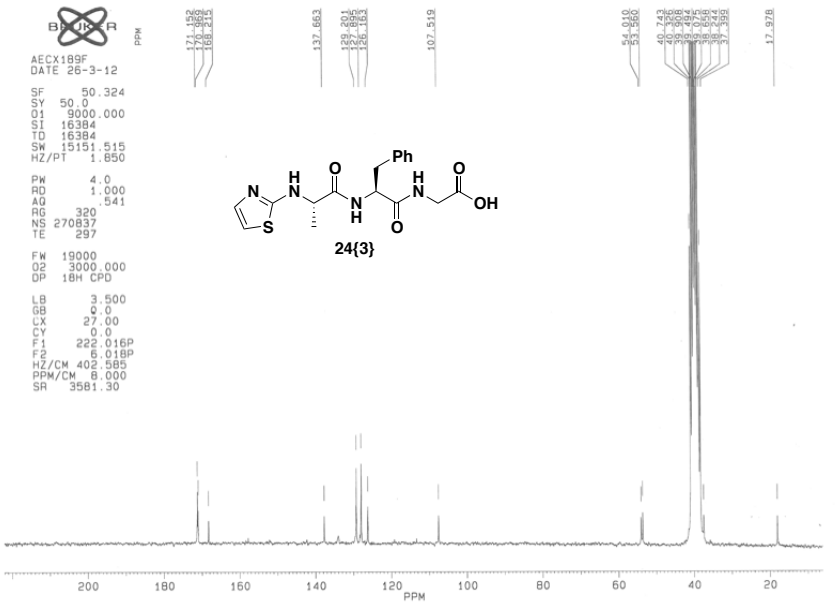



Purity: 87%, $R_f$ = 4.22 min. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.70 (1H, bs), 8.36 (1H, t, $J$ = 5.7 Hz), 8.28 (1H, d, $J$ = 8.3 Hz), 7.37 – 7.08 (5H, m), 6.79 (1H, d, $J$ = 3.9 Hz), 4.57 (1H, td, $J$ = 4.2 Hz, 9.3 Hz), 4.15 (1H, bs), 3.78 (2H, t, $J$ = 6.0 Hz), 3.07 (1H, dd, $J$ = 4.1 Hz, 13.8 Hz), 2.80 (1H, dd, $J$ = 9.9 Hz, 13.8 Hz), 1.24 (3H, d, $J$ = 6.9 Hz). $^{13}$C NMR (50 MHz, DMSO-$d_6$): δ 171.2 (2C), 171.0, 168.2, 137.7, 129.2 (2C), 127.9 (2C), 126.2, 107.5, 54.1, 53.6, 37.4, 18.0. HRMS (ESI) calcd for $C_{17}H_{21}N_4O_4S$ $[M + H]^+$ 377.1278, found 377.1285.

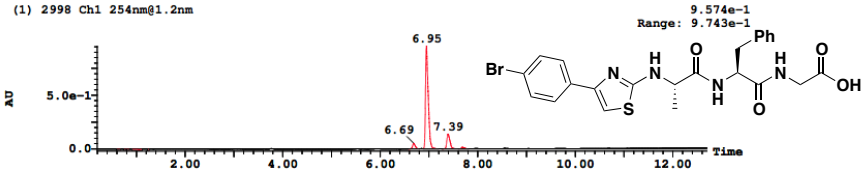
**$^{1}$H NMR (300 MHz, DMSO-$d_6$)**




**$^{13}$C NMR (50 MHz, DMSO-$d_6$)**

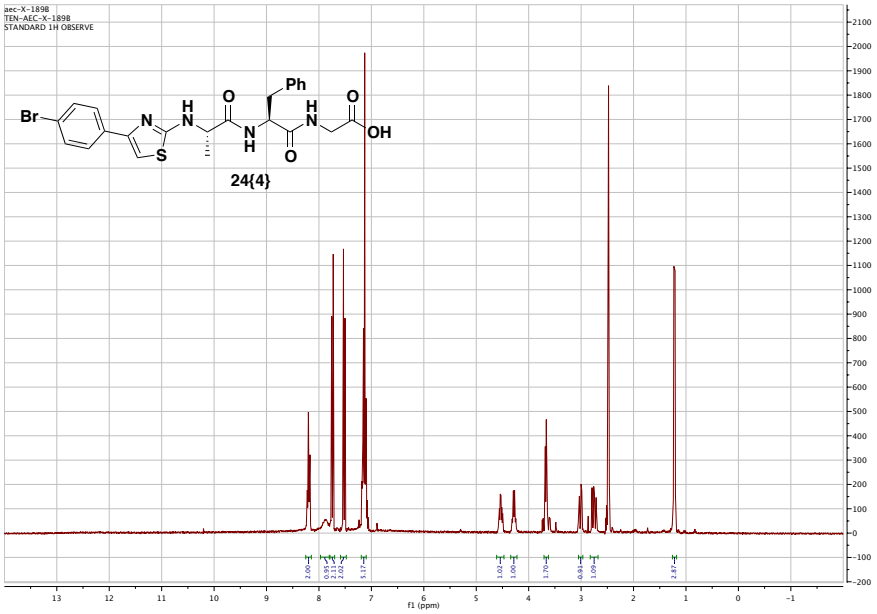



**4-(4-Bromophenyl)thiazol-2-yl-Ala-Phe-Gly (24{4})**

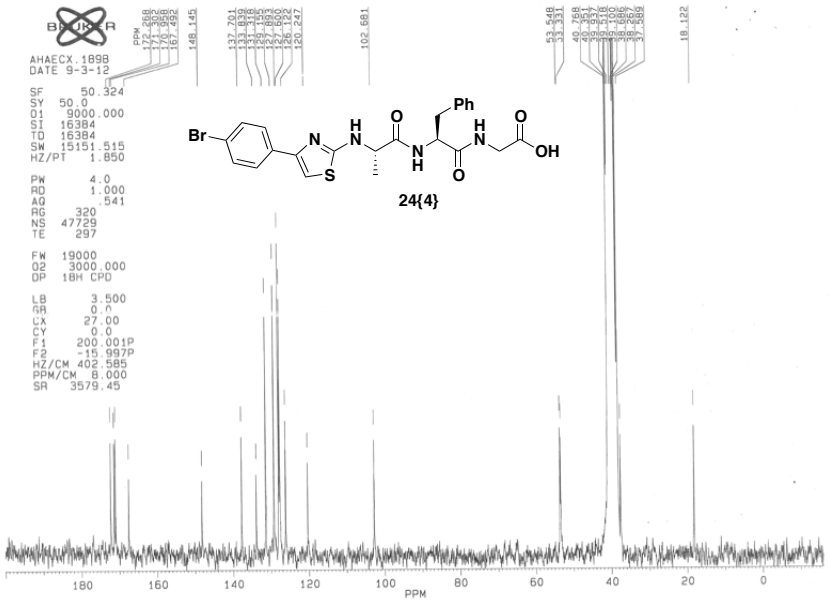



Purity: 87%, $R_f$ = 6.95 min. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 8.26 – 8.18 (2H, m), 7.89 (1H, bs), 7.82 – 7.73 (2H, m), 7.60 – 7.49 (2H, m), 7.25 – 7.10 (5H, m), 4.56 (1H, td, *J* = 4.3 Hz, 9.2 Hz), 4.30 (1H, dd, *J* = 7.0 Hz), 3.69 (2H, dd, *J* = 4.7 Hz, 5.5 Hz), 3.04 (1H, dd, *J* = 4.3 Hz, 13.8 Hz), 2.78 (1H, dd, *J* = 9.7 Hz, 13.8 Hz), 1.24 (3H, d, *J* = 7.0 Hz, 3H). $^{13}$C NMR (50 MHz, DMSO-$d_6$): δ 172.3, 171.3, 171.0, 167.5, 148.1, 137.7, 133.8, 131.3 (2C), 129.2 (2C), 127.9 (2C), 127.6 (2C), 126.1, 120.2, 102.7, 53.5, 53.3, 37.6, 18.1. HRMS (ESI) calcd for $C_{23}H_{24}BrN_4O_4S$ [M + H]**+** 531.0696, found 531.0698.

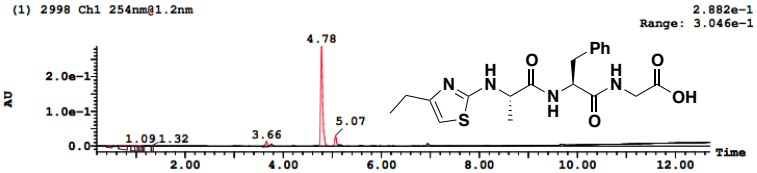
**$^{1}$H NMR (300 MHz, DMSO-$d_6$)**




**$^{13}$C NMR (50 MHz, DMSO-$d_6$)**

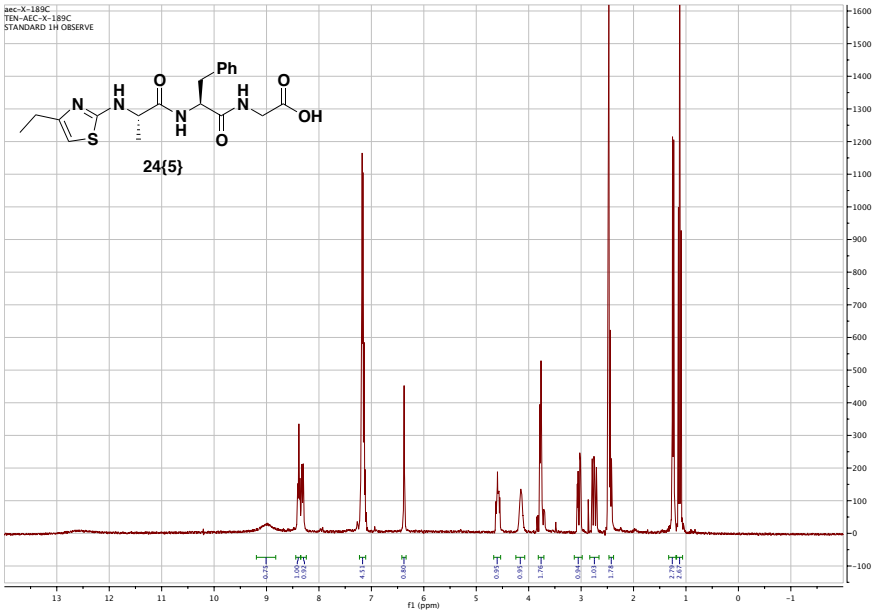



**4-Ethylthiazol-2-yl-Ala-Phe-Gly (24{5})**

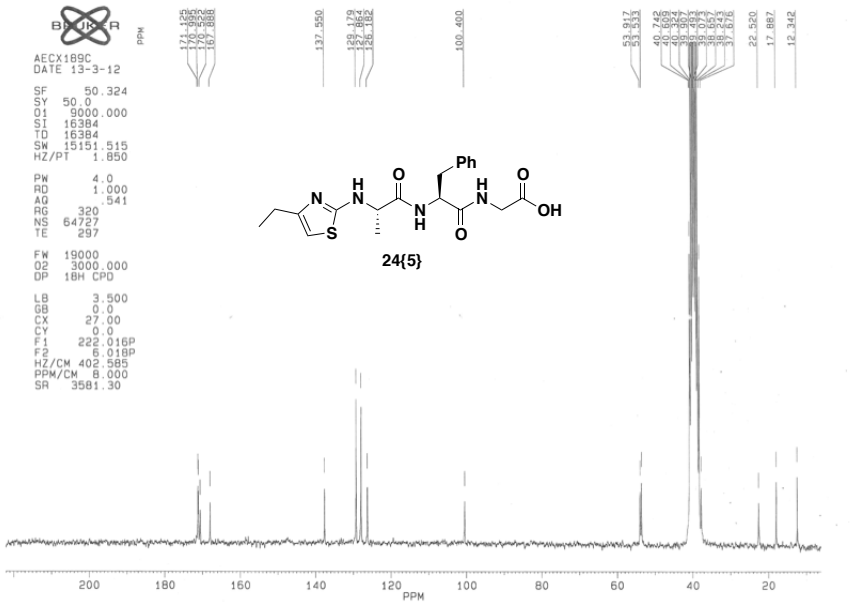



Purity: 93%, $R_f$ = 4.78 min. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 9.02 (1H, bs), 8.41 (1H, t, $J$ = 5.9 Hz), 8.34 (1H, d, $J$ = 8.4 Hz), 7.27 – 7.11 (5H, m), 6.40 (1H, s), 4.61 (1H, td, $J$ = 4.3 Hz, 9.5 Hz), 4.17 (1H, bs, 1H), 3.79 (2H, dd, $J$ = 3.7 Hz, 5.7 Hz), 3.06 (1H, dd, $J$ = 4.2 Hz, 13.8 Hz), 2.77 (1H, dd, $J$ = 10.3 Hz, 14.0 Hz), 2.53 – 2.43 (2H, m), 1.27 (3H, d, $J$ = 6.9 Hz), 1.14 (3H, t, $J$ = 7.5 Hz). $^{13}$C NMR (50 MHz, DMSO-$d_6$): δ 171.1, 171.0, 170.5, 167.9, 137.6, 129.2 (2C), 127.9 (2C), 126.2, 100.4, 53.9, 53.5, 37.7, 22.5, 17.9, 12.3. HRMS (ESI) calcd for $C_{19}H_{25}N_4O_4S$ $[M + H]^+$ 405.1591, found 405.1613.

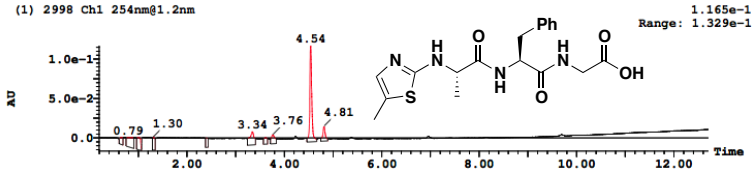
**$^{1}$H NMR (300 MHz, DMSO-$d_6$)**




**$^{13}$C NMR (50 MHz, DMSO-$d_6$)**

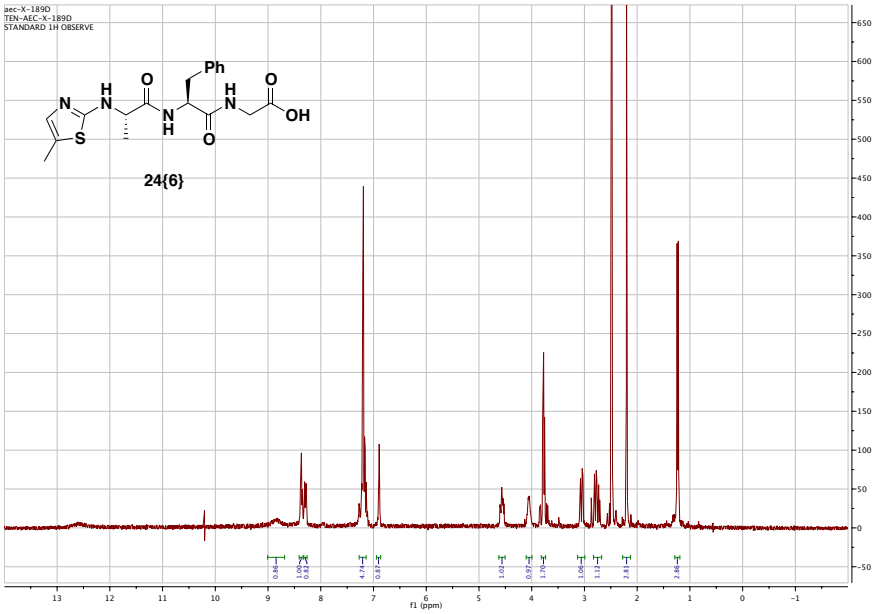



**5-Mehtylthiazol-2-yl-Ala-Phe-Gly (24{6})**

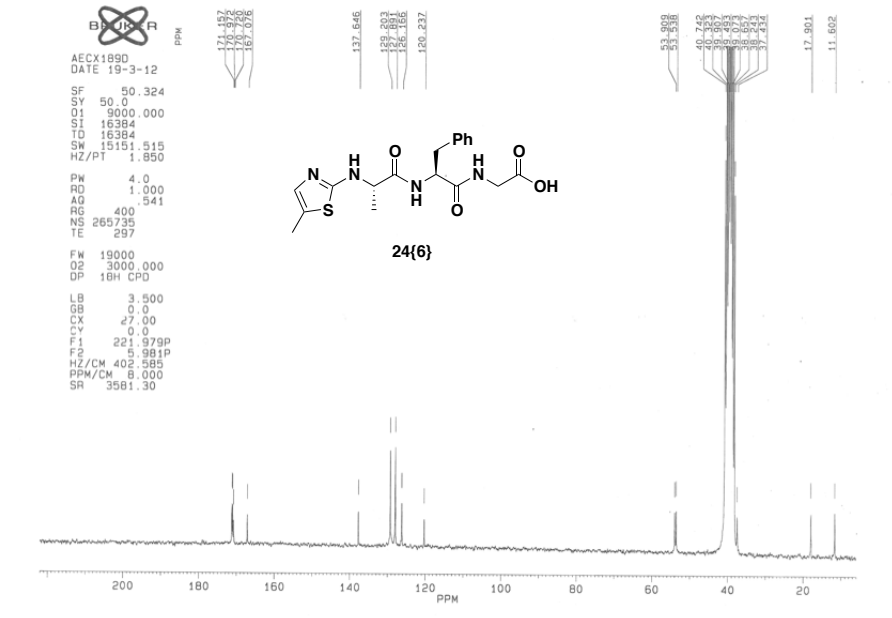



Purity: 84%, $R_f$ = 4.54 min. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 8.85 (1H, bs), 8.38 (1H, t, $J$ = 5.8 Hz), 8.31 (1H, d, $J$ = 8.3 Hz), 7.28 – 7.11 (5H, m), 6.91 (1H, s), 4.58 (1H, td, $J$ = 4.2 Hz, 9.8 Hz), 4.07 (1H, bs), 3.79 (2H, t, $J$ = 5.6 Hz), 3.08 (1H, dd, $J$ = 4.1 Hz, 13.8 Hz), 2.79 (1H, dd, $J$ = 10.1 Hz, 13.9 Hz), 2.22 (3H, d, $J$ = 1.4 Hz), 1.25 (3H, d, $J$ = 6.9 Hz). $^{13}$C NMR (50 MHz, DMSO-$d_6$): δ 171.2, 171.0, 170.7 167.1, 137.6 (2C), 129.2 (2C), 127.9 (2C), 126.2, 120.2, 53.9, 53.5, 37.4, 17.9, 11.6. HRMS (ESI) calcd for $C_{18}H_{23}N_4O_4S$ $[M + H]^+$ 391.1435, found 391.1439.

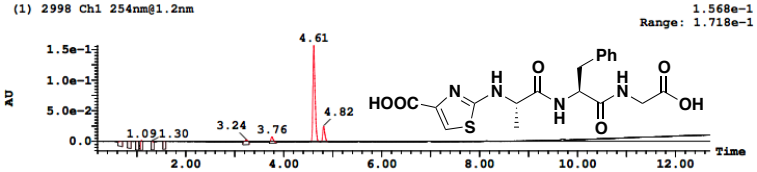
**$^{1}$H NMR (300 MHz, DMSO-$d_6$)**




**$^{13}$C NMR (50 MHz, DMSO-$d_6$)**



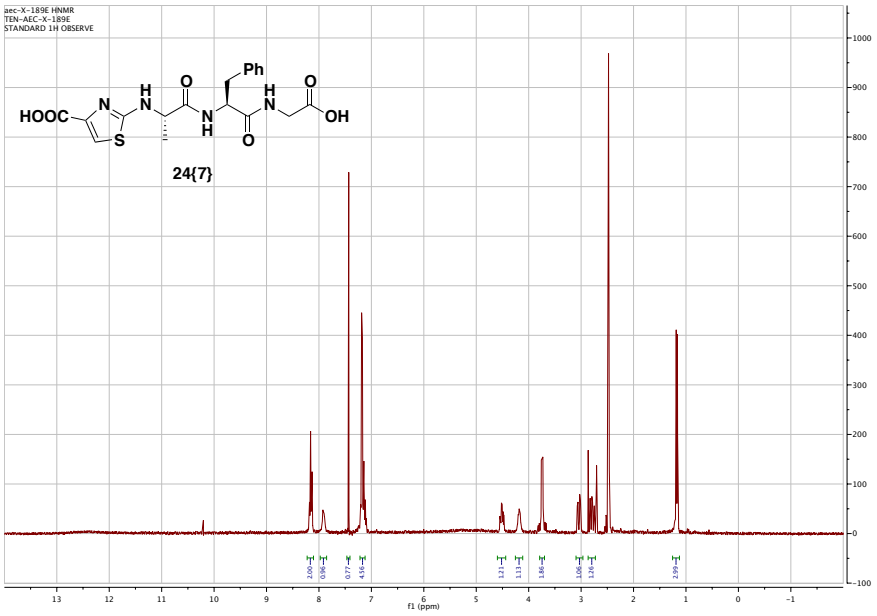

**4-Carboxythiazol-2-yl-Ala-Phe-Gly (24{7})**



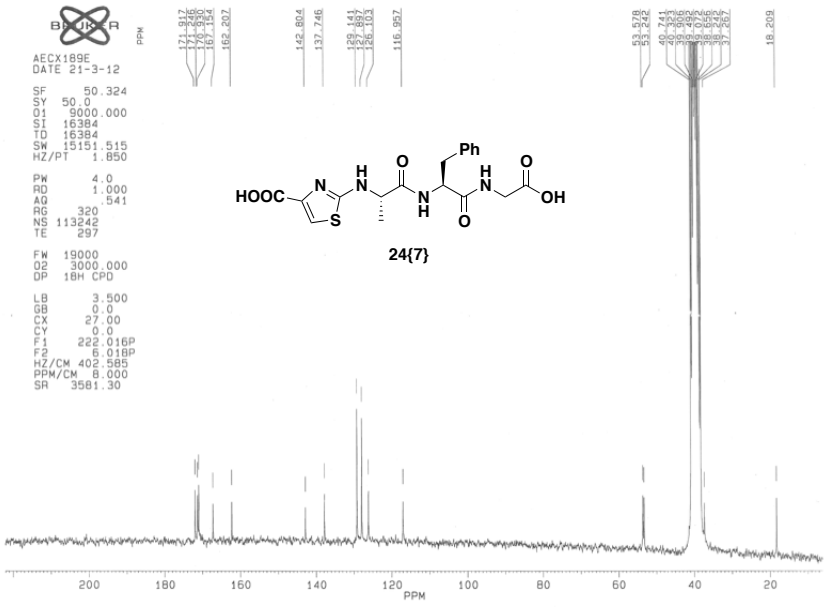

Purity: 88%, $R_f$ = 4.61 min. $^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 8.22 – 8.14 (2H, m), 7.95 (1H, bs), 7.45 (1H, s), 7.28 – 7.10 (5H, m), 4.54 (1H, td, *J* = 4.1 Hz, 9.0 Hz), 4.20 (1H, bs), 3.77 (2H, dd, *J* = 3.3 Hz, 5.7 Hz), 3.07 (1H, dd, *J* = 4.2 Hz, 13.9 Hz), 2.81 (1H, dd, *J* = 9.8 Hz, 13.9 Hz), 1.20 (3H, d, *J* = 7.0 Hz). $^{13}$C NMR (50 MHz, DMSO-*d*6): δ 171.9, 171.2, 170.9, 167.2, 162.2, 142.8, 137.7, 129.1 (2C),

127.9 (2C), 126.1, 117.0, 53.6, 53.2, 37.3, 18.2. HRMS (ESI) calcd for $C_{18}H_{21}N_4O_6S$ $[M + H]^+$ 421.1176, found 421.1171.

**$^1$H NMR (300 MHz, DMSO-$d_6$)**



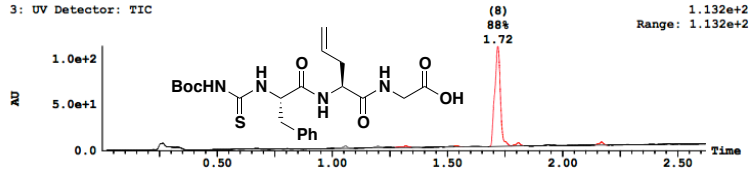

**$^{13}$C NMR (50 MHz, DMSO-$d_6$)**



**Synthesis of Thiazole-Containing Macrocycles**

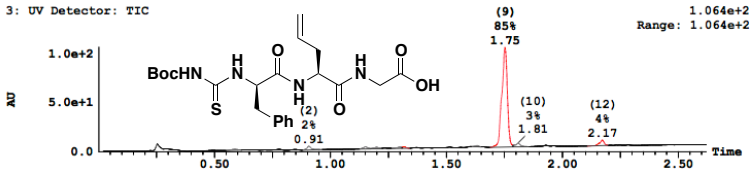
**Precursors**

**BocNHCS-L-Phe-L-Gly(allyl)-Gly-OH**



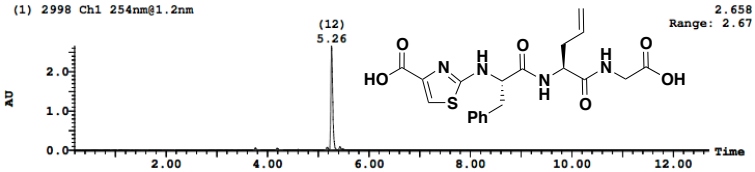

Purity: >95%, $R_f$ = 1.72 min. (LCMS) HRMS (ESI) calcd for $C_{22}H_{31}N_4O_6S$ [M + H]$^+$ 479.1959, found 479.1963.

**BocNHCS-D-Phe-L-Gly(allyl)-Gly-OH**



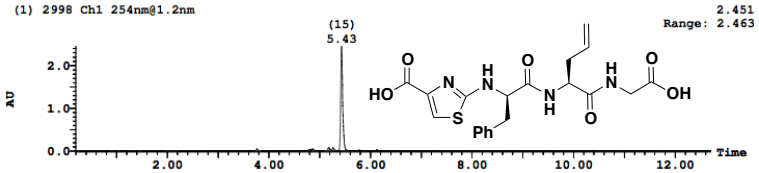

Purity: 91%, $R_f$ = 1.75 min. (LCMS) UPLC-MS (ESI) calcd for $C_{22}H_{31}N_4O_6S$ [M + H]$^+$ 479.2, found 479.3.

**4-Carboxythiazol-2-yl-L-Phe-L-Gly(allyl)-Gly-OH (26{1} (S,S))**



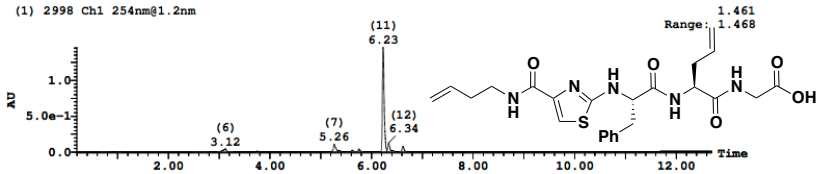

Purity: >95%, $R_f$ = 5.26 min. UPLC-MS (ESI) calcd for $C_{20}H_{23}N_4O_6S$ [M + H]$^+$ 447.1, found 447.2.

**4-Carboxythiazol-2-yl-D-Phe-L-Gly(allyl)-Gly-OH (26{2} (R,S))**



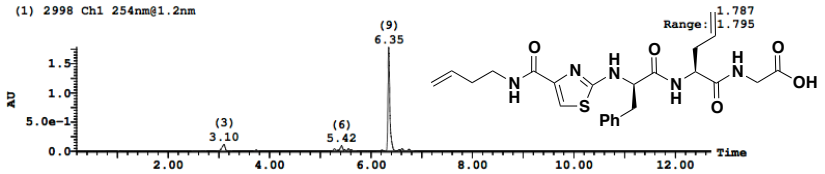

Purity: >95%, $R_f$ = 5.43 min. HRMS (ESI) calcd for $C_{20}H_{23}N_4O_6S$ [M + H]$^+$ 447.1333, found 447.1340.

**(4-(But-3-en-yl)-4-carbamoyl)-thiazol-2-yl-L-Phe-L-Gly(allyl)-Gly-OH**



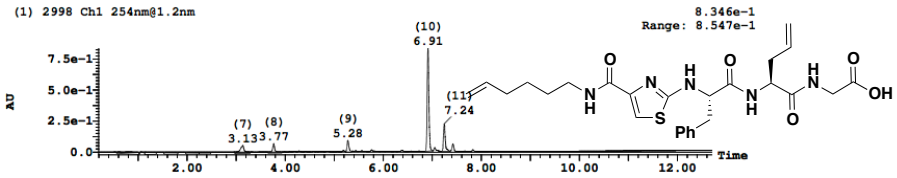

Purity: 78%, $R_f$ = 6.23 min. UPLC-MS (ESI) calcd for $C_{24}H_{30}N_5O_5S$ [M + H]$^+$ 500.2, found 500.3.

**4-(But-3-en-yl)-4-carbamoyl)-thiazol-2-yl-D-Phe-L-Gly(allyl)-Gly-OH**



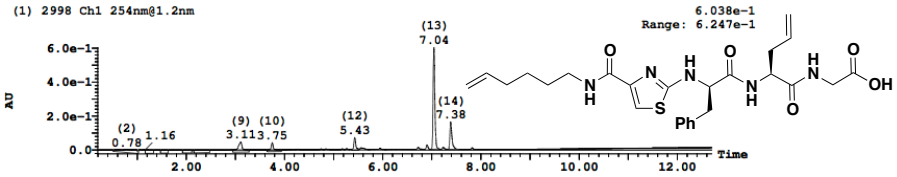

Purity: 83%, $R_f$ = 6.35 min. UPLC-MS (ESI) calcd for $C_{24}H_{30}N_5O_5S$ $[M + H]^+$ 500.2, found 500.3.

**4-(Hex-5-en-yl)-4-carbamoyl)-thiazol-2-yl-L-Phe-L-Gly(allyl)-Gly-OH**



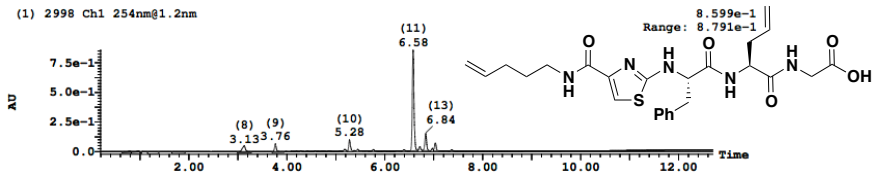

Purity: 63%, $R_f$ = 6.91 min. UPLC-MS (ESI) calcd for $C_{26}H_{34}N_5O_5S$ $[M + H]^+$ 528.2, found 528.3.

**4-(Hex-5-en-yl)-4-carbamoyl)-thiazol-2-yl-D-Phe-L-Gly(allyl)-Gly-OH**



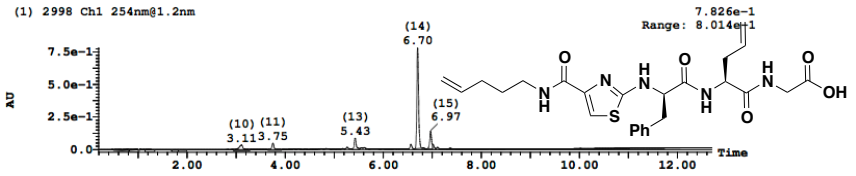

Purity: 60%, $R_f$ = 7.04 min. HRMS (ESI) calcd for $C_{26}H_{34}N_5O_5S$ $[M + H]^+$ 528.2275, found 528.2280.

**4-(Pent-4-en-yl)-4-carbamoyl)-thiazol-2-yl-L-Phe-L-Gly(allyl)-Gly-OH**



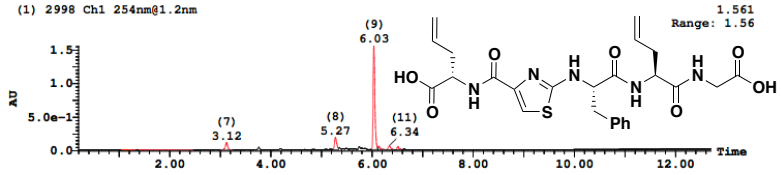

Purity: 70%, $R_f$ = 6.58 min. UPLC-MS (ESI) calcd for $C_{25}H_{32}N_5O_5S$ $[M + H]^+$ 514.2, found 514.3.

**4-(Pent-4-en-yl)-4-carbamoyl)-thiazol-2-yl-D-Phe-L-Gly(allyl)-Gly-OH**



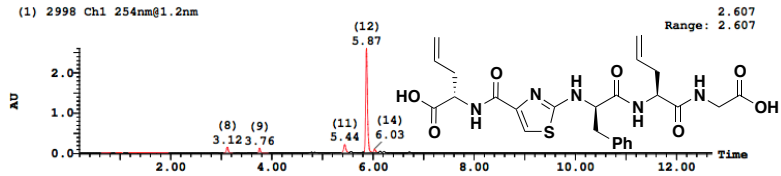

Purity: 68%, $R_f$ = 6.70 min. HRMS (ESI) calcd for $C_{25}H_{32}N_5O_5S$ $[M + H]^+$ 514.2119, found 514.2112.

**L-Gly(allyl)-4-carbamoyl)-thiazol-2-yl-L-Phe-L-Gly(allyl)-Gly-OH**



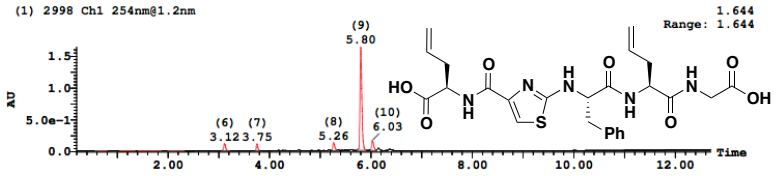

Purity: 83%, $R_f$ = 6.03 min. UPLC-MS (ESI) calcd for $C_{25}H_{30}N_5O_7S$ $[M + H]^+$ 544.2, found 544.3.

**L-Gly(allyl)-4-carbamoyl)-thiazol-2-yl-D-Phe-L-Gly(allyl)-Gly-OH**



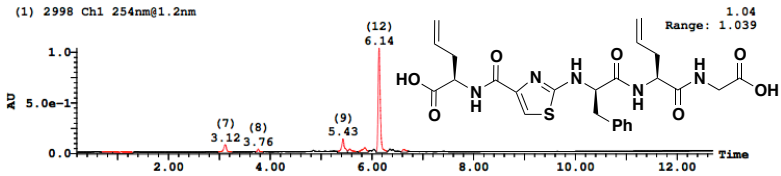

Purity: 88%, $R_f$ = 5.87 min. UPLC-MS (ESI) calcd for $C_{25}H_{30}N_5O_7S$ $[M + H]^+$ 544.2, found 544.3.

**D-Gly(allyl)-4-carbamoyl)-thiazol-2-yl-L-Phe-L-Gly(allyl)-Gly-OH**




Purity: 84%, $R_f$ = 5.80 min. UPLC-MS (ESI) calcd for $C_{25}H_{30}N_5O_7S$ $[M + H]^+$ 544.2, found 544.3.

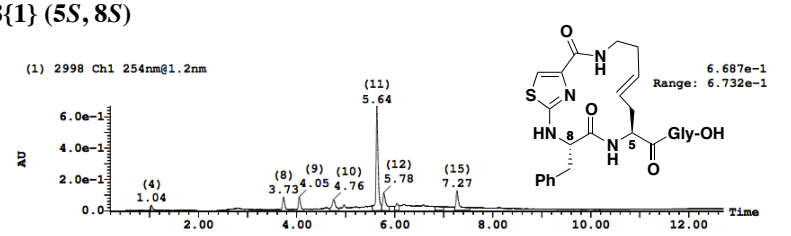
**D-Gly(allyl)-4-carbamoyl)-thiazol-2-yl-D-Phe-L-Gly(allyl)-Gly-OH**




Purity: 87%, $R_f$ = 6.14 min. UPLC-MS (ESI) calcd for $C_{25}H_{30}N_5O_7S$ $[M + H]^+$ 544.2, found 544.3.

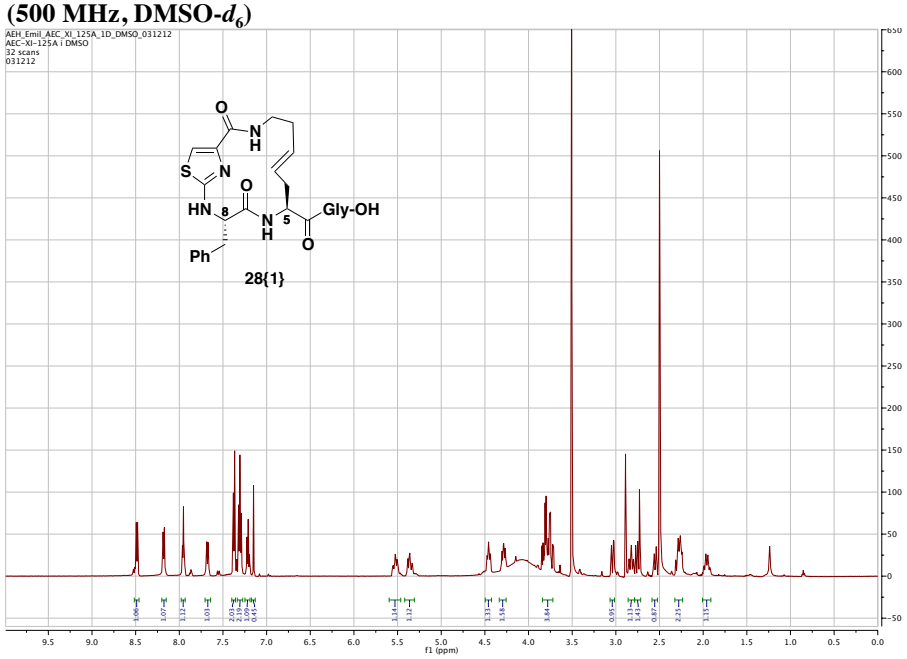
**Macrocycles**

**Macrocycle 28{1} (5*S*, 8*S*)**

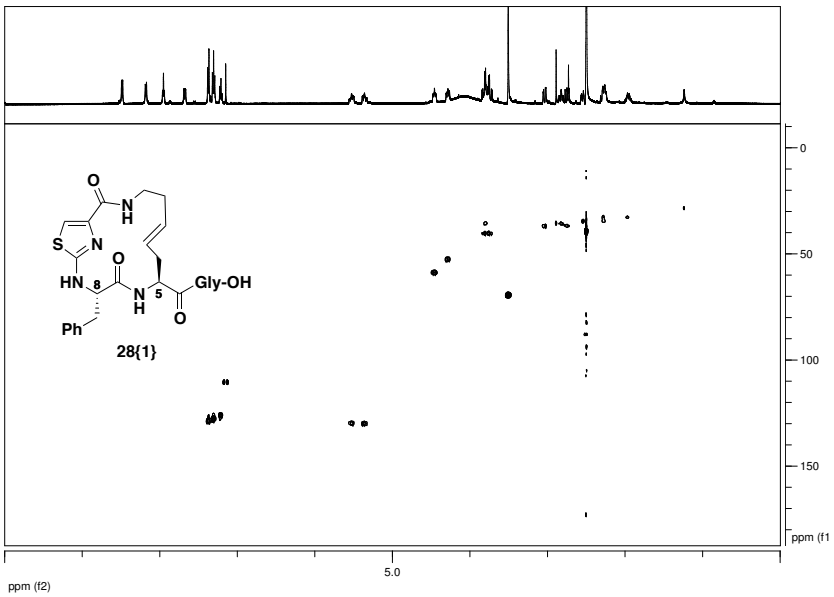



Purity: 71%, $R_f$ = 5.64 min. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 8.49 (1H, d, *J* = 7.4 Hz), 7.95 (1H, t, *J* = 5.8 Hz), 7.68 (1H, dd, *J* = 9.8, 2.1 Hz), 7.37 (2H, d, *J* = 7.3 Hz), 7.31 (2H, t, *J* = 7.6 Hz), 7.21 (1H, t, *J* = 7.3 Hz), 7.15 (1H, s), 5.53 (1H, ddd, *J* = 15.1, 10.0, 2.8 Hz), 5.36 (1H, ddd, *J* = 14.9, 10.0, 2.3 Hz), 4.46 (1H, ddd, *J* = 11.1, 7.6, 2.4 Hz), 4.29 (1H, ddd, *J* = 12.0, 7.4, 2.6 Hz), 3.85-3.70 (3H, m), 3.04 (1H, dd, *J* = 14.2, 2.7 Hz), 2.83 (1H, dd, *J* = 17.7, 7.0 Hz), 2.79 – 2,70 (1H, m), 2.58 – 2.52 (1H, m), 2.33 – 2.22 (2H, m), 2.01 – 1.91 (1H, m). $^{13}$C NMR (125 MHz, DMSO-*d*6): δ 172.8, 171.7, 171.2, 166.2, 159.8, 144.8, 137.9, 129.8, 129.7, 128.6 (2C), 127.6 (2C), 125.8, 110.4, 58.7, 52.7, 40.3, 36.9, 35.6, 34.6, 32.7, HRMS (ESI) calcd for $C_{22}H_{26}N_5O_5S$ $[M + H]^+$ 472.1649, found 472.1650.

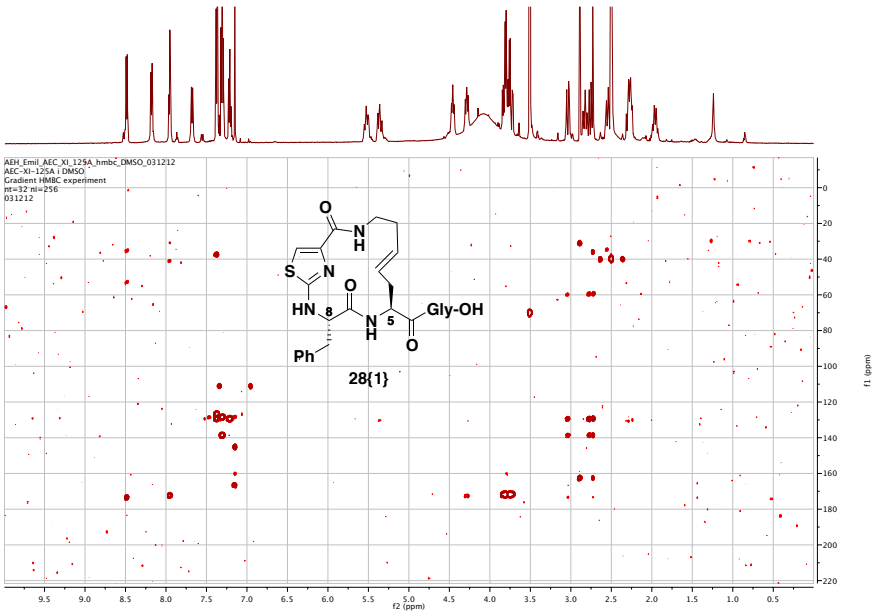
**$^1$H NMR (500 MHz, DMSO-$d_6$)**



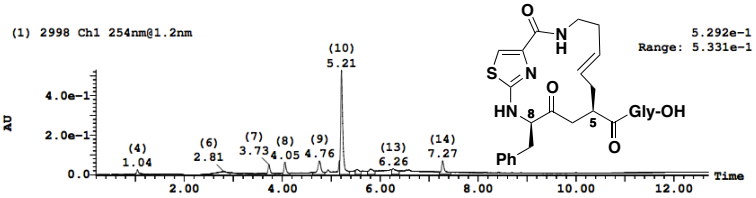

**2D HSQC (500 MHz, DMSO-$d_6$)**



**2D HMBC (500 MHz, DMSO-$d_6$)**

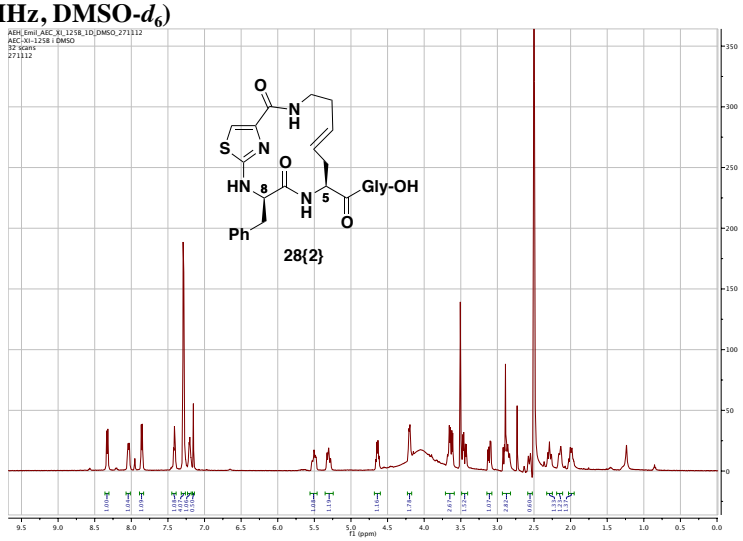



**Macrocycle 28{2} (5*S*, 8*R*)**

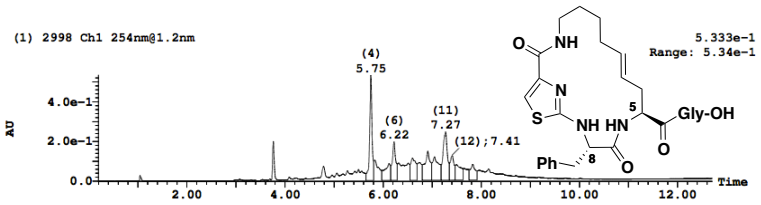



Purity: 74%, $R_f$ = 5.21 min. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 8.33 (1H, d, *J* = 7.6 Hz), 8.04 (1H, dd, *J* = 8.7, 3.7 Hz), 7.86 (1H, d, *J* = 6.9 Hz), 7.41 (1H, t, *J* = 5.8 Hz), 7.29 (4H, d, *J* = 4.2 Hz), 7.24 – 7.18 (1H, m), 7.15 (1H, s), 5.51 (1H, ddd, *J* = 15.0, 10.0, 3.6 Hz), 5.30 (1H, ddd, *J* = 15.0, 9.9, 3.0 Hz), 4.46 (1H, dd, *J* = 14.6, 7.6 Hz), 4.25 – 4.13 (1H, m), 3.72 – 3.60 (2H, m), 3.45 (1H, dd, *J* = 17.5, 5.8 Hz), 3.11 (1H, dd, *J* = 14.0, 6.2 Hz), 2.99 – 2.81 (2H, m), 2.56 (1H, d, *J* = 14.1 Hz), 2.28 (1H, dd, *J* = 17.4, 7.1 Hz), 2.15 (1H, d, *J* = 12.0 Hz), 2.04 – 1.94 (1H, m). UPLC-MS (ESI) calcd for $C_{22}H_{24}N_5O_5S$ [M + H]$^+$ 471.2, found 471.3.

**$^1$H NMR (500 MHz, DMSO-$d_6$)**

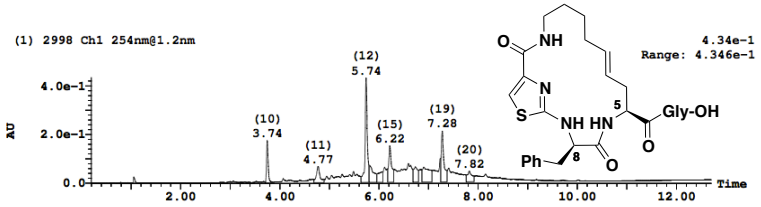


**Macrocycle 34{1} (5*S*, 8*S*)**



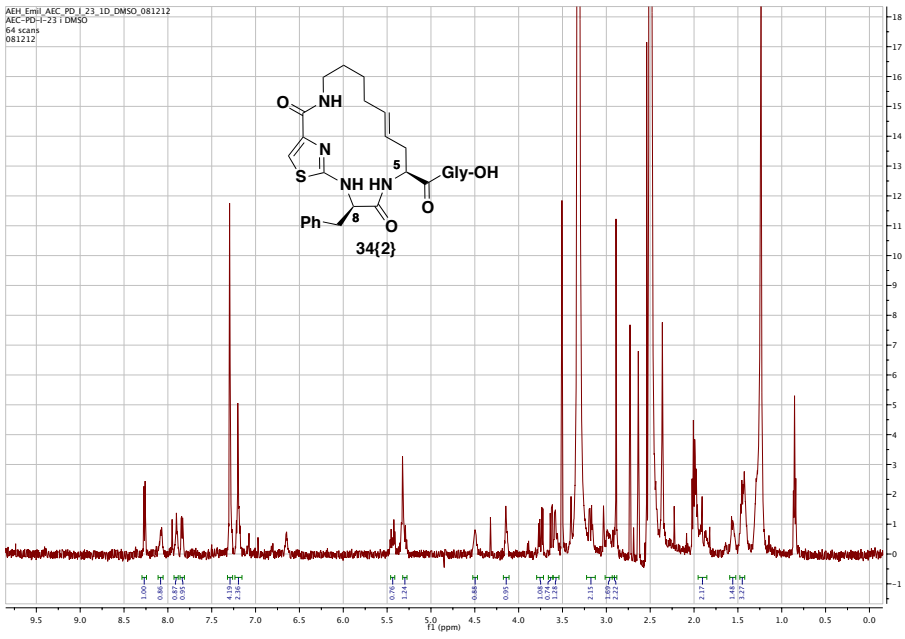

Purity: 51%, $R_f$ = 5.75 min. HRMS (ESI) calcd for $C_{24}H_{30}N_5O_5S$ [M - H]$^-$ 500.1962, found 500.1965.

**Macrocycle 34{2} (5*S*, 8*R*)**

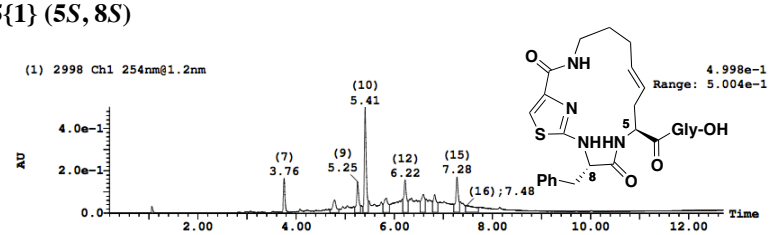



Purity: 65%, $R_f$ = 5.74 min. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 8.27 (1H, d, *J* = 7.1 Hz), 8.10 – 8.06 (1H, m), 7.92 – 7.89 (1H, m), 7.86 – 7.82 (1H, m), 7.33 – 7.25 (4H, m), 7.22 – 7.17 (2H, m), 5.47 – 5.41 (1H, m), 5.34 – 5.27 (1H, m), 4.53 – 4.47 (1H, m), 4.17 – 4.12 (1H, m), 3.75 (1H, dd, *J* = 17.5, 6.0 Hz), 3.60 (1H, dd, *J* = 17.5, 5.5 Hz), 3.60 – 3.53 (1H, m), 3.18 (1H, dd, *J* = 14.1, 5.1 Hz), 3.02 – 2.93 (1H, m), 2.93 – 2.86 (1H, m), 1.96 – 1.81 (2H, m), 1.59 – 1.52 (1H, m), 1.48 – 1.38 (3H, m). UPLC-MS (ESI) calcd for $C_{24}H_{28}N_5O_5S$ [M - H]$^-$ 498.2, found 498.3

**$^1$H NMR (500 MHz, DMSO-$d_6$)**

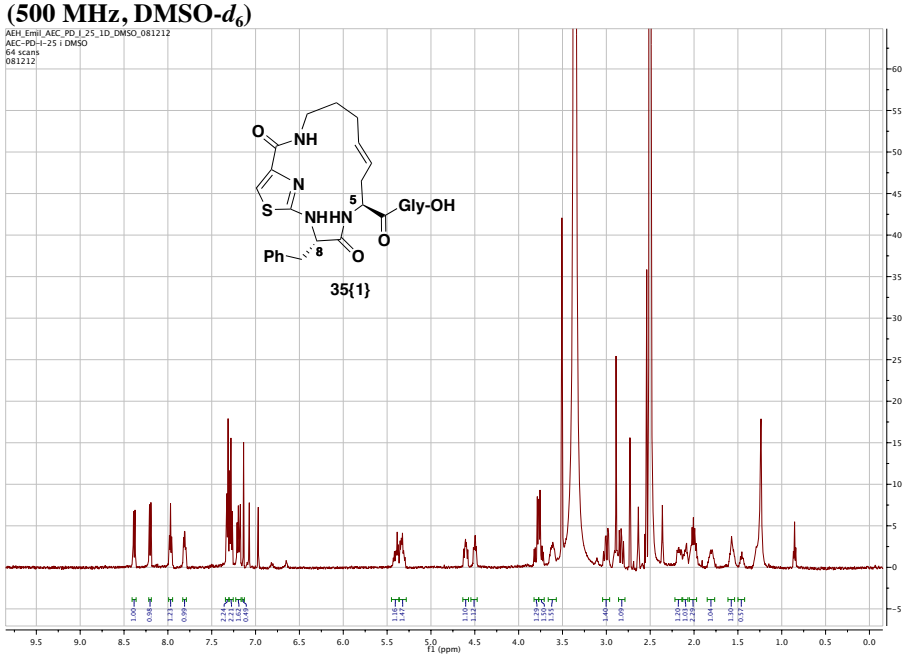


**Macrocycle 35{1} (5*S*, 8*S*)**

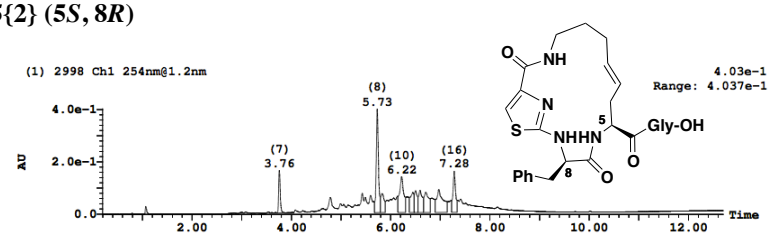



Purity: 69%, $R_f$ = 5.41 min. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 8.38 (1H, d, *J* = 8.5 Hz), 8.20 (1H, d, *J* = 8.0 Hz), 7.97 (1H, t, *J* = 5.9 Hz), 7.81 (1H, dd, *J* = 7.3, 4.8 Hz), 7.34 – 7.25 (4H, m), 7.23 – 7.16 (1H, m), 7.14 (1H, s), 5.44 (1H, dt, *J* = 15.4, 5.8 Hz), 5.31 (1H, dt *J* = 15.4, 6.3 Hz), 4.60 (1H, ddd, *J* = 10.0, 8.0, 4.8 Hz), 4.54 – 4.46 (1H, m), 3.80 (1H, dd, *J* = 17.5, 5.9 Hz), 3.74 (1H, dd, *J* = 17.5, 5.9 Hz), 3.66 – 3.58 (2H, m), 2.99 (1H, dd, *J* = 13.9, 4.5 Hz), 2.83 (1H, dd, *J* = 14.0, 10.1 Hz), 2.22 – 2.13 (1H, m), 2.13 – 2.06 (1H, m), 2.03 – 1.95 (2H, m), 1.85 – 1.74 (1H, m), 1.61 – 1.52 (1H, m), 1.52 – 1.42 (1H, m). UPLC-MS (ESI) calcd for $C_{23}H_{26}N_5O_5S$ [M - H]$^-$ 484.2, found 484.3.

**$^1$H NMR (500 MHz, DMSO-$d_6$)**

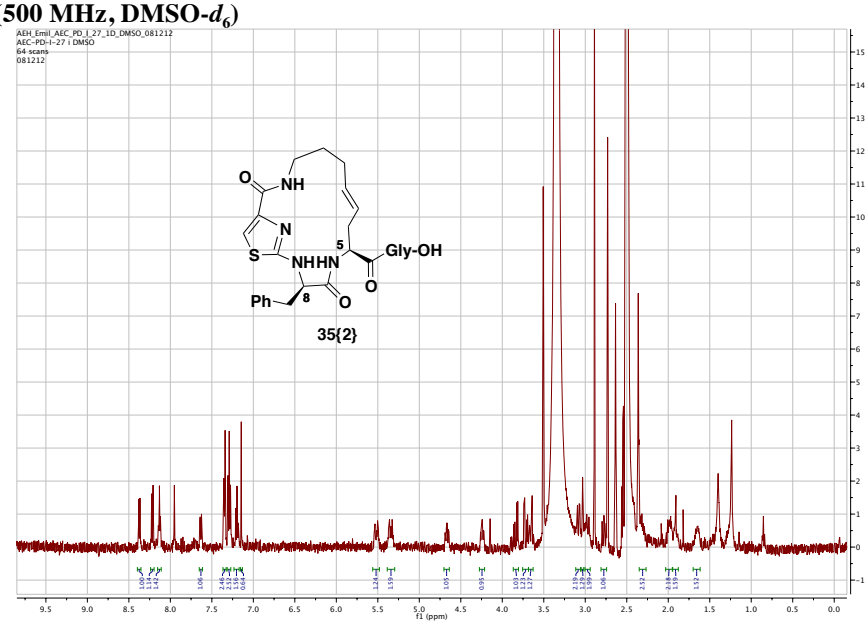



**Macrocycle 35{2} (5*S*, 8*R*)**

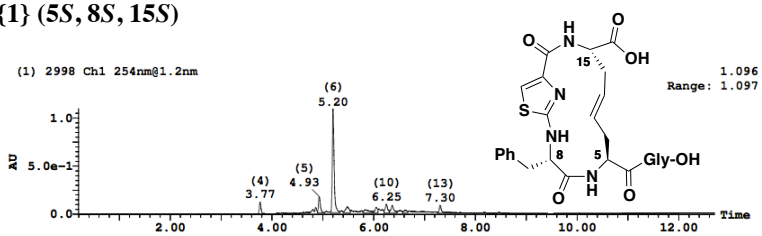



Purity: 71%, $R_f$ = 5.73 min. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 8.37 (1H, d, *J* = 7.2 Hz), 8.22 (1H, d, *J* = 8.6 Hz), 8.13 (1H, t, *J* = 5.8 Hz), 7.63 (1H, d, *J* = 7.8 Hz), 7.35 (2H, d, *J* = 7.4 Hz), 7.29 (2H, t, *J* = 7.6 Hz), 7.20 (1H, t, *J* = 7.3 Hz), 7.15 (1H, s), 5.52 (1H, dt, *J* = 15.4, 5.5 Hz), 5.34 (1H, dt, *J* = 15.3, 6.5 Hz), 4.71 – 4.63 (1H, m), 4.27 – 4.21 (1H, m), 3.84 (1H, dd, *J* = 17.5, 6.1 Hz), 3.72 (1H, dd, *J* = 17.5, 5.5 Hz), 3.69 – 3.63 (1H, m), 3.08 (1H, dd, *J* = 14.0, 4.0 Hz), 3.03 (1H, t, J = 3.2 Hz), 2.99 – 2.95 (1H, m), 2.77 (1H, dd, *J* = 13.9, 10.9 Hz), 2.37 – 2.27 (2H, m), 2.03 – 1.87 (2H, m), 1.70 – 1.60 (1H, m), 1.44 – 1.37 (1H, m). UPLC-MS (ESI) calcd for $C_{23}H_{26}N_5O_5S$ [M - H]$^-$ 484.2, found 484.3.

**$^1$H NMR (500 MHz, DMSO-$d_6$)**

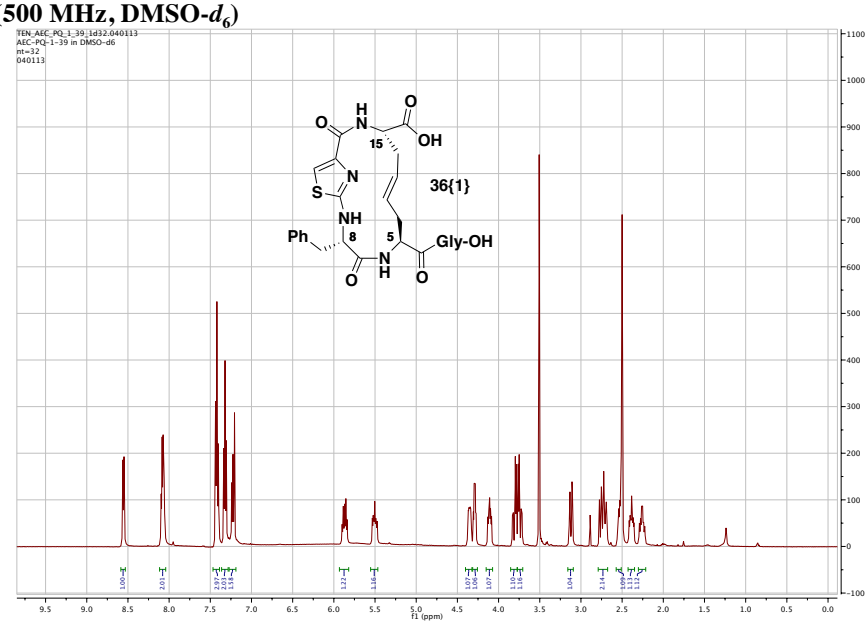



**Macrocycle 36{1} (5*S*, 8*S*, 15*S*)**

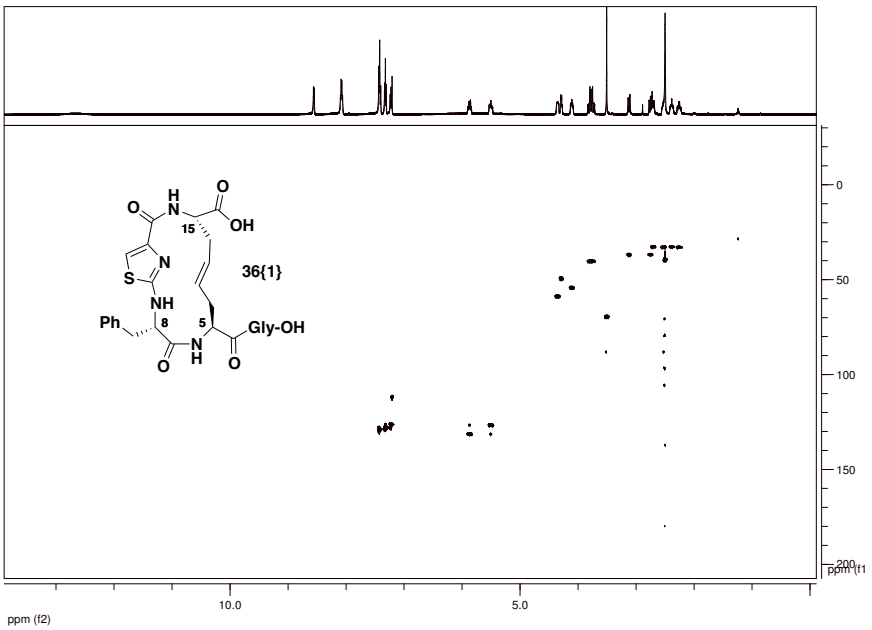



Purity: 76%, $R_f$ = 5.20 min. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 8.58 (1H, d, J = 6.9 Hz), 8.12 (1H, t, J = 5.6 Hz), 8.08 (1H, d, J = 6.9 Hz), 7.42 (3H, t, J = 7.1 Hz) 7.32 (2H, t, J = 7.5 Hz), 7.23 (1H. d, J = 7.4 Hz), 7.21 (1H, s), 5.84 (1H, dt, *J* = 15.4, 7.6 Hz), 5.47 (1H, ddd, *J* = 15.5, 9.6, 4.8 Hz), 4.42 – 4.25 (2H, m), 4.10 (1H, ddd, J = 11.3, 6.6, 4.3 Hz), 3.81 (1H, dd, J = 17.8, 5.3 Hz), 3.73 (1H, dd, J = 17.7, 5.8 Hz), 3,12 (1H, d, J = 12.6 Hz), 2.83 – 2.64 (2H, m), 2.61 – 2.51 (1H, m), 2.43 – 2.32 (1H, m), 2.32 – 2.16 (1H, m). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 172.1, 171.8, 171.5, 171.0, 166.2, 160.0, 144.1, 137.7, 131.2, 128.9 (2C), 127.8 (2C), 126.5, 126.1, 111.7, 58.8, 54.2, 49.4, 40.3, 36.8, 32.8, 32.7. UPLC-MS (ESI) calcd for $C_{23}H_{24}N_5O_7S$ [M - H]$^-$ 514.1, found 514.2.

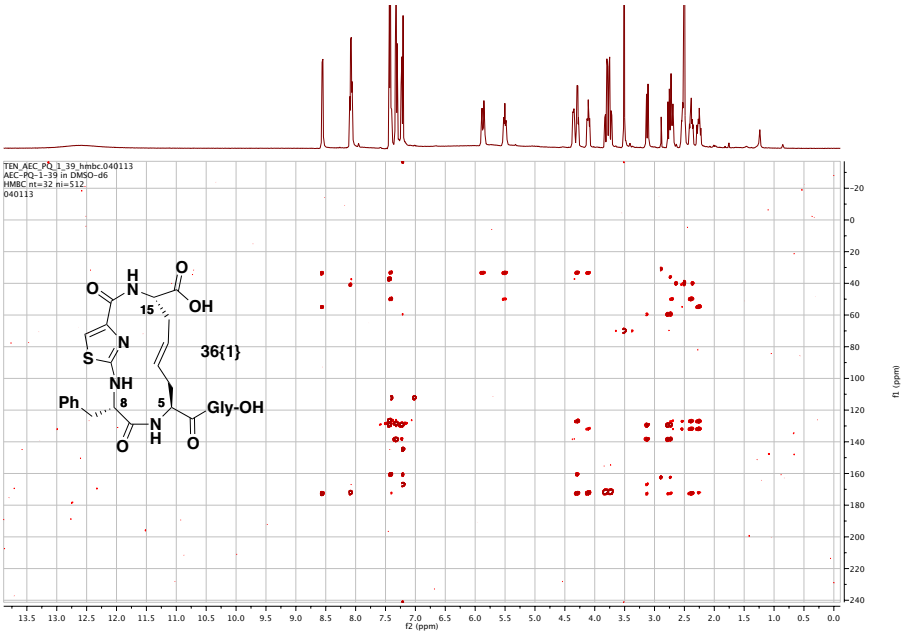
**$^1$H NMR (500 MHz, DMSO-$d_6$)**



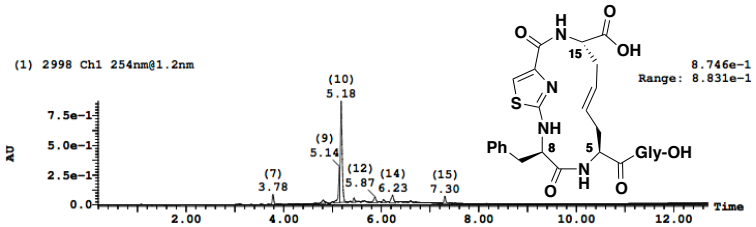
**2D HSQC (500 MHz, DMSO-$d_6$)**




**2D HMBC (500 MHz, DMSO-$d_6$)**

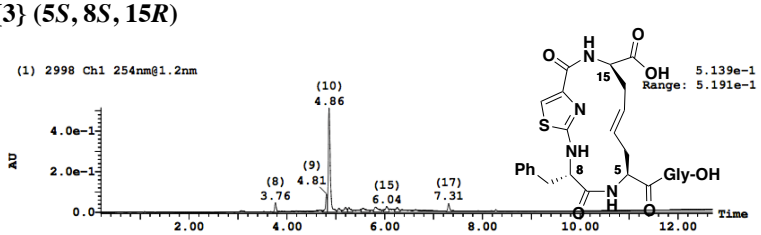



**Macrocycle 36{2} (5*S*, 8*R*, 15*S*)**



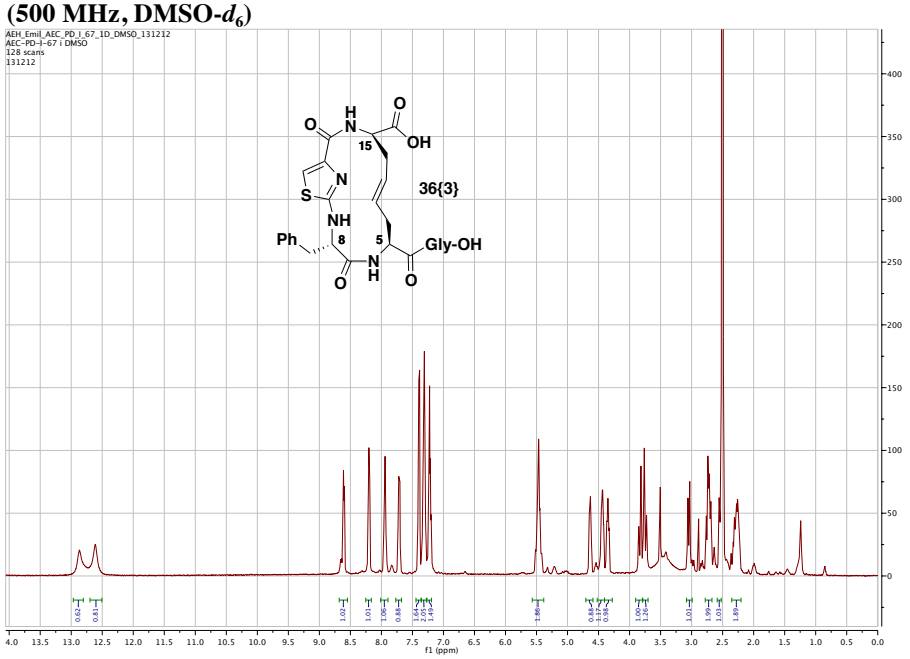

Purity: 86%, $R_f$ = 5.18 min. Olefine isomeric ratio 2/1. UPLC-MS (ESI) calcd for $C_{23}H_{24}N_5O_7S$ [M - H]$^-$ 514.1, found 514.2.

**Macrocycle 36{3} (5*S*, 8*S*, 15*R*)**

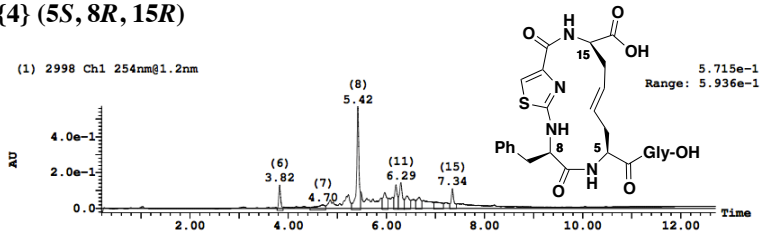



Purity: 86%, $R_f$ = 4.86 min. $^1$H NMR (500 MHz, DMSO-$d_6$): δ 12.87 (1H, bs), 12.61 (1H, bs), 8.60 (1H, d, *J* = 7.6 Hz), 8.20 (1H, d, *J* = 6.9 Hz), 7.99 – 7.91 (1H, m), 7.71 (1H, d, *J* = 9.7 Hz), 7.39 (2H, d, *J* = 6.6 Hz), 7.31 (2H, t, *J* = 6.8 Hz), 7.26 – 7.18 (2H, m), 5.59 – 5.36 (2H, m), 4.64 (1H, dd, *J* = 9.0, 3.9 Hz), 4.51 – 4.41 (1H, m), 4.40 – 4.31 (1H, m), 3.83 (1H, dd, *J* = 17.6, 5.7 Hz), 3.74 (1H, dd, *J* = 17.9, 5.2 Hz), 3.04 (1H, d, *J* = 14.3 Hz), 2.80 – 2.67 (2H, m), 2.55 – 2.45 (1H, m), 2.35 – 2.20 (2H, m). UPLC-MS (ESI) calcd for $C_{23}H_{24}N_5O_7S$ [M - H]$^-$ 514.1, found 514.2.

**$^1$H NMR (500 MHz, DMSO-$d_6$)**




**Macrocycle 36{4} (5*S*, 8*R*, 15*R*)**




Purity: 77%, $R_f$ = 5.42 min. $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.26 (1H, d, *J* = 6.8 Hz), 8.01 (1H, d, *J* = 7.4 Hz), 7.95 (1H, d, *J* = 7.6 Hz), 7.75 – 7.67 (1H, m), 7.33 – 7.16 (6H, m), 5.58 – 5.47 (1H, m), 5.47 – 5.33 (1H, m), 4.49 – 4.39 (1H, m), 4.24 (1H, dd, *J* = 11.8, 5.5 Hz), 4.16 – 4.06 (1H, m), 3.72 (1H, dd, *J* = 17.7, 6.0 Hz), 3.63 (1H, dd, *J* = 17.7, 5.4 Hz), 3.23 – 3.01 (2H, m), 2.56 – 2.45 (2H, m), 2.46 – 2.32 (2H, m). UPLC-MS (ESI) calcd for $C_{23}H_{24}N_5O_7S$ [M - H]$^-$ 514.1, found 514.2.

**$^{1}$H NMR (500 MHz, DMSO-$d_6$)**