Supporting Information

Synthesis and Biological Activity of Analogs of the Antimicrotubule Agent N,β,β-Trimethyl-L-phenylalanyl-N¹[(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N¹,3-dimethyl-L-valinamide (HTI-286).


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Experimentals

Ethyl (E,4S)-4-[(2S)-3,3-dimethyl-2-{[(2S)-3-methyl-2-(methylamino)-3-phenylbutanoyl]amino}butanoyl](methyl)amino]-2,5-dimethyl-2-hexenoate (24). Prepared as described in the literature.\(^7\) Anal. \((C_{26}H_{47}N_3O_4 \cdot 1.5HCl \cdot H_2O)\)

\[\text{N,}\beta,\beta\text{-trimethyl-D-phenylalanyl-N}^1\text{-}[(1S,2E)-3-carboxy-1-isopropyl-2-butenyl]-N^1\text{-}3\text{-dimethyl-L-valinamide (41). Prepared as described in the literature.}\(^7\)\]

\[\text{N,}\beta,\beta\text{-trimethyl-L-phenylalanyl-N}^1\text{-}[(1S,2E)-3-carboxy-1-isopropyl-2-butenyl]-N^1\text{-}3\text{-dimethyl-L-valinamide (42). Prepared by modifications of the methods described in the literature.}\(^7\),\(^6\)\]

\[\text{N,}\beta,\beta\text{-trimethyl-L-phenylalanyl-N}^1\text{-}[(1R,2E)-3-carboxy-1-isopropylbut-2-ynyl]-N^1\text{-}3\text{-dimethyl-L-valinamide (43). Prepared by modifications of the methods described in the literature.}\(^7\),\(^9\)\]

3-Hydroxy-N-methyl-D,L-valyl-N^1\text{-}[(1S,2E)-4-ethoxy-1-isopropyl-3-methyl-4-oxo-2-butenyl]-N^1\text{-}3\text{-dimethyl-L-valinamide (45). To a solution of ethyl 3-hydroxy-L-valyl-N^1\text{-}[(1S,2E)-4-ethoxy-1-isopropyl-3-methyl-4-oxo-2-butenyl]-N^1\text{-}L-valinamide (50 mg, 0.12 mmol) in anhydrous DMF (1 ml) at 0 °C was added iodomethane (0.017 ml, 0.12 mmol). After 30 min diisopropylethylamine (0.042 ml, 0.24 mmol) was added. The reaction mixture was allowed to warm to room temperature. After 2 h water was added and the mixture was acidified by dropwise addition of 1.0M aq citric acid. The acidic mixture was extracted 3X with EtOAc. The combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated in vacuo to give a mixture of ethyl 3-hydroxy-N-methyl-L-valyl-N^1\text{-}[(1S,2E)-4-ethoxy-1-isopropyl-3-methyl-4-oxo-2-butenyl]-N^1\text{-}3\text{-dimethyl-L-valinamide and ethyl-3-hydroxy-N,N-dimethyl-L-valyl-N^1\text{-}[(1S,2E)-4-ethoxy-1-isopropyl-3-methyl-4-oxo-2-butenyl]-N^1\text{-}3\text{-dimethyl-L-valinamide. This material (50 mg) was hydrolyzed according to General Procedure 4 to give the TFA salt of the title compounds as white solids (40 mg, 80 %) after HPLC. A 1:1 mixture of components was present by analytical HPLC/MS: 3-hydroxy-N-methyl-L-valyl-N^1\text{-}[(1S,2E)-4-ethoxy-1-isopropyl-3-methyl-4-oxo-2-butenyl]-N^1\text{-}3\text{-dimethyl-L-valinamide: MS, } m/z: 414.3 \text{ (}\text{M} + \text{H})^+\text{. 3-hydroxy-N,N-dimethyl-L-valyl-N^1\text{-}[(1S,2E)-4-ethoxy-1-isopropyl-3-methyl-4-oxo-2-butenyl]-N^1\text{-}3\text{-dimethyl-L-valinamide: MS, } m/z: 428.4 \text{ (}\text{M} + \text{H})^+\text{.}}\]
(2E,4S)-4-[(2S)-2-[(2S)-3,3-dimethyl-2-(methylamino)octanoyl]amino]-3,3-dimethylbutanoyl]methyl]amino]-2,5-dimethyl-2-hexenoic acid (46). By the method described in General Procedure 3, 3,3-dimethyl-2-(methylamino)-octanoic acid (8 R = CH₃, R₁ = n-pentyl, R₂ = CH₃) (273 mg, 1.36 mmol), 9 (523 mg, 1.5 mmol), Hunig’s base (0.71 mL, 4.1 mmmol) and PyBOP (781 mg, 1.5 mmol) in CH₂Cl₂ (10 mL) gave the ethyl ester of the title compound as a glass (109 mg). As described in General Procedure 4, this material was treated with LiOH (0.39 mmol) in CH₃OH/THF (1 mL)/water (0.5 mL). After 2 days purification by reverse phase HPLC gave the TFA salt of the title compound as a white powder. MS, m/z: 468.2 (M + H)⁺.

3-Cyclohexyl-N-methyl-L-valyl-N-1-[(1S,2E)-3-carboxy-1-isopropyl-2-butene]-N-1,3-dimethyl-L-valinamide (47). According to General Procedure 3, 15 was coupled to 9 and the resulting product treated with TFA in CH₂Cl₂ to give the ethyl ester of the title compound. Following General Procedure 4 this material was hydrolyzed, then purified by reverse phase HPLC to give the TFA salt of the title compound as a white solid. MS, m/z: 480.35 (M + H)⁺. Anal. (C₂₇H₄₃N₅O₄ · 1.5TFA)

N,O,β,β-tetramethyl-L-tyrosyl-N-1-[(1S,2E)-3-carboxy-1-isopropyl-2-butene]-N-1,3-dimethyl-L-valinamide (48). Preparation according to General procedure 3 and 4 and purification by preparative reverse phase HPLC gave the TFA salt of title compound as a white solid. HRMS (ESI) calcd for C₂₈H₄₅N₃O₅ 504.3432(M + H)⁺; found 504.3427. Anal. (C₂₈H₄₅N₃O₄ · 1.5 TFA)

N,3-Dimethyl-4-phenyl-L-valyl-N-1-[(1S,2E)-3-carboxy-1-isopropyl-2-butene]-N-1,3-dimethyl-L-valinamide (50). By the method described in General Procedure 3, 3,3-dimethyl-2-methylamino-4-phenyl-butyric acid (8 R = CH₃, R₁ = Bn, R₂ = CH₃) (300 mg, 1.36 mmol), 9 (523 mg, 1.5 mmol), Hunig’s base (0.71 mL, 4.1 mmmol) and PyBOP (781 mg, 1.5 mmmol) in CH₂Cl₂ (10 mL) gave after purification by reverse phase HPLC the ethyl ester of the title compound as an oil (76 mg). MS, m/z: 516.6 (M + H)⁺. By the method described in General Procedure 4, treatment with LiOH (0.266 mmol) in CH₃OH/THF/water for 4 days gave after purification by reverse phase HPLC, the TFA salt of 50 as a white powder. MS, m/z: 488.6 (M + H)⁺. Anal. (C₂₉H₄₅N₃O₄ · TFA)

(βR)-N, β-dimethyl-L-phenylalananyl-N-1-[(1S,2E)-3-carboxy-1-isopropyl-2-butene]-N-1,3-dimethyl-L-valinamide (51). Following the method used to prepare 52, methyl (βR)-N-(tert-butoxycarbonyl)-N,β-dimethyl-L-phenylalaninate (12a) was converted to the TFA salt of 51.
(βS)-N, β-dimethyl-L-phenylalanyl-N¹-[(1S,2E)-3-carboxy-1-isopropylbut-2-anyl]-N¹,3-dimethyl-L-valinamide (52). Following General Procedure 4, 12b (191 mg, 0.61 mmol) was hydrolyzed with LiOH (1.24 mmol) in CH₃OH/THF/water to give the corresponding acid as a colorless oil after purification by HPLC (122 mg). MS, m/z: 292 (M - H)⁺. Following General Procedure 3, this acid (80 mg, 0.273 mmol), 9 (105 mg, 0.30 mmol), HOBT (45 mg, 0.33 mmol), EDC (68 mg, 0.35 mmol) and diisopropylethylamine in DMF (2 mL) gave, after HPLC, the coupled product as a colorless oil (117 mg). Treatment of this material (108 mg) with TFA (1 mL) in CH₂Cl₂ (5 mL) gave the amine as an oil (127 mg). Following General Procedure 4, treatment with LiOH (0.386 mmol) in CH₃OH/THF/water gave the TFA salt of 52 as a white powder (66 mg). MS, m/z: 458.3 (M - H)⁺. Anal. (C₂₆H₄₁N₅O₄ • 0.6TFA . H₂O)

β,β-diethyl-N-methyl-L-phenylalanyl-N¹-[(1S,2E)-3-carboxy-1-isopropylbut-2-anyl]-N¹,3-dimethyl-L-valinamide (53). General Procedures 1, 2, 3, 4 (using iodoethane in General Procedure 1) gave the TFA salt of the title compound after HPLC. HRMS (ESI) calcd for C₂₉H₄₇N₅O₄: 502.36450 (M + H)⁺; found 502.36402.

(2E,4S)-2,5-dimethyl-4-(methyl(3-methyl-N-[(2S)-2-(methylamino)-2-(1-phenylcyclopentyl)ethanoyl]-L-valyl)amino)-2-hexenoic acid (54). General Procedures 1, 2, 3, 4 (using dibromobutane in General Procedure 1) gave the TFA salt of the title compound as a white glass after HPLC. MS, m/z: 500.6 (M + H)⁺.

(2E,4R)-2,5-dimethyl-4-(methyl(3-methyl-N-[(methylamino)(1-phenylcyclohexyl)acetyl]-L-valyl)amino)-2-hexenoic acid (55). General Procedures 1, 2, 3, 4 (using dibromopentane in General Procedure 1) gave the TFA salt of the title compound as a white glass after HPLC. MS, m/z: 515.15 (M + H)⁺.

(2E,4S)-2,5-dimethyl-4-(methyl(3-methyl-N-[(2R)-2-(methylamino)-2-(1-phenylcyclopropyl)acetyl]-L-valyl)amino)hex-2-enoic acid (56). According to General Procedure 3 compound 11 (465 mg, 2.1 mmol) in CH₂Cl₂ (12 mL) and dimethylformamide (9 mL) in the presence of PyBOP (1.09 g, 2.1 mmol) and diisopropylethylamine (0.81 mL, 4.5 mmol) was coupled to 9 (660 mg, 2.1 mmol). The resulting material was treated according to General Procedure 4 with 1M aq LiOH (10.5 mL, 10.5 mmol) in water (6 mL) and CH₃OH (20 mL), to provide after preparative HPLC the TFA salt of 56 as a white solid (142 mg, contains 4 % of the RSS diastereomer) MS, m/z: 472.3 (M + H)⁺. Anal. (C₂₇H₄₁N₅O₄ • 1.25 TFA-1.5 H₂O)
N-Benzyl-β,β-dimethyl-L-phenylalanyl-N1-[(1S,2E)-3-carboxy-1-isopropylbut-2-etyl]-N1,3-dimethyl-L-valinamide (58). Treatment of 22 (95 mg, 0.181 mmol) in DMF (5 mL) with benzylbromide 0.024 mL, 0.20 mmol) and diisopropylethylamine (66 uL, 0.38 mmol) for 18 h, followed by HPLC gave a solid (40 mg). This material (28 mg) was treated as described in General Procedure 4 to give, after HPLC, the TFA salt of 58 as a white solid (24 mg). MS, m/z: 550.4 (M + H)+. Anal. (C33H47N3O4 • 1.6 TFA)

(2E,4S)-2,5-dimethyl-4-(methyl[3-methyl-N-[(2S)-3-methyl-3-phenyl-2-pyrrolidin-1-ybutanoyl]-L-valyl]amino)hex-2-enolic acid (59). Treatment of 22 (138 mg, 0.264 mmol) in DMF (2 mL) with 1,4-diodobutane (0.04 mL, 0.29 mmol) and diisopropylethylamine (115 uL, 0.66 mmol) for 72 h, followed by HPLC gave a solid (67 mg). This material (43 mg) was treated as described in General Procedure 4 to give, after HPLC, the TFA salt of 59 as a white solid (13 mg). MS, m/z: 514.5 (M + H)+. Anal. (C39H47N3O4 • 2 TFA)

N-(2-hydroxyethyl)-β,β-dimethyl-L-phenylalanyl-N1-[(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N1,3-dimethyl-L-valinamide (60). Treatment of 22 (112 mg, 0.214 mmol) in DMF (3 mL) with 2-bromoethanol (0.02 mL, 0.26 mmol) and diisopropylethylamine (104 uL, 0.60 mmol) for 18 h, followed by HPLC gave an oil (97 mg). This material (85 mg) was treated as described in General Procedure 4 to give, after HPLC, the TFA salt of 60 as a white solid (42 mg). MS, m/z: 504.3 (M + H)+. Anal. (C28H45N3O5 • TFA • H2O)

N-(carboxymethyl)-β,β-dimethyl-L-phenylalanyl-N1-[(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N1,3-dimethyl-L-valinamide (61). Treatment of 22 (385 mg, 0.74 mmol) in DMF (2 mL) with methyl bromoacetate (135 mg, 0.88 mmol) and diisopropylethylamine (385 uL, 2.2 mmol) for 18 h, followed by HPLC purification, gave a solid (193 mg). This material (72 mg) was treated as described in General Procedure 4 (0.64 mmol LiOH) to give, after HPLC, the TFA salt of 61 as a white solid (56 mg). MS, m/z: 518.4 (M + H)+. Anal. (C26H43N3O5 • TFA • H2O)

β,β-dimethyl-N-[2-((methylamino)-2-oxoethyl]-L-phenylalanyl-N1-[(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N1,3-dimethyl-L-valinamide (62). Treatment of 22 (385 mg, 0.74 mmol) in DMF (2 mL) with methyl bromoacetate (135 mg, 0.88 mmol) and diisopropylethylamine (385 uL, 2.2 mmol) for 18h, followed by HPLC purification, gave a solid (193 mg). This material (87 mg, 0.156 mmol) was dissolved in THF (2 mL) and treated with methylamine at 65 °C in a sealed vessel for 7h. Purification by HPLC gave a white
solid (80 mg). This material (77 mg) was treated as described in General Procedure 4 to
give, after HPLC, the TFA salt of 62 as a white solid (28 mg). MS, m/z: 531.5 (M + H)^+.
Anal. (C_{29}H_{46}N_{4}O_{5} . TFA . H_{2}O)

N-methylglycyl-β,β-dimethyl-L-phenylalanyl-N^1-[(1S,2E)-3-carboxy-1- isopropylbut-2-enyl]-N^1,3-dimethyl-L-valinamide (64). Treatment of 22 (140 mg, 0.268 mmol) in DMF (5
mL) with BOC-sarcosine (61 mg, 0.32 mmol), diisopropylethylamine (116 uL, 0.67 mmol),
HOBT (44 mg, 0.32 mmol) and EDC (72 mg, 0.38 mmol) for 18 h, followed by HPLC, gave
a white solid (84 mg). This material (74 mg) was treated with 4N HCl in dioxane (0.7 mL) for
1 h to remove the BOC group. Concentration in vacuo and treatment of the resulting
material as described in General Procedure 4 gave, after HPLC, the TFA salt of 64 as a
white solid (61 mg). MS, m/z: 531.3 (M + H)^+. Anal. (C_{29}H_{46}N_{4}O_{5} . TFA . 2 H_{2}O)

(E,4S)-4-[(2S)-3,3-dimethyl-2-[[3-methyl-2-ethyl-3-
phenylbutanoyl]amino]butanoyl](methyl)amino]-2,5-dimethyl-2-hexenoic acid (66).
Following General Procedures 3 and 4 (using 28 R = Et, in General Procedure 3) gave 66
as a tan foam. MS, m/z: 473.0 (M + H)^+.

(E,4S)-4-[(2S)-3,3-dimethyl-2-[[3-methyl-2-allyl-3-
phenylbutanoyl]amino]butanoyl](methyl)amino]-2,5-dimethyl-2-hexenoic acid (67).
Following General Procedures 3 and 4 (using 28 R = allyl, in General Procedure 3) gave 67
as a powder. MS, m/z: 485.0 (M + H)^+.

(E,4S)-4-[(2S)-3,3-Dimethyl-2-[[3-methyl-2-benzyl-3-
phenylbutanoyl]amino]butanoyl](methyl)amino]-2,5-dimethyl-2-hexenoic acid (68).
Following General Procedures 3 and 4 (using 28 R = Bn, in General Procedure 3) gave 68
as a white foam. MS, m/z: 533.0 (M + H)^+.

(E,4S)-4-[(N-[(2S)-2-methoxy-3-methyl-3-phenylbutanoyl]-3-methyl-L-
valyl](methyl)amino]-2,5-dimethyl-2-hexenoic acid (69). Following General Procedures
3 and 4 (using 35 in General Procedure 3) gave the title compound as a hard white foam.
MS, m/z: 475.0 (M + H)^+.

(E,4S)-4-[(N-[(2S)-2-hydroxy-3-methyl-3-phenylbutanoyl]-3-methyl-L-
valyl](methyl)amino]-2,5-dimethyl-2-hexenoic acid (70). Following General Procedures
3 and 4 (using 32 in General Procedure 3) gave 70 as a white foam. MS, m/z: 461.0 (M + H)<sup>+</sup>. Anal. (C<sub>26</sub>H<sub>40</sub>N<sub>2</sub>O<sub>5</sub>)

(E,4S)-4-[(2S)-3,3-dimethyl-2-[[3-methyl-2-methylsulfanyl-3-phenylbutanoyl]amino]butanoyl](methyl)amino]-2,5-dimethyl-2-hexenoic acid (71). Following General Procedures 3 and 4 (using 30 in General Procedure 3) gave 71 as a light tan powder. MS, m/z: 490.9 (M + H)<sup>+</sup>. Anal. (C<sub>27</sub>H<sub>42</sub>N<sub>2</sub>O<sub>4</sub>S·TFA·H<sub>2</sub>O)

(E,4S)-4-[(2S)-3,3-dimethyl-2-[[3-methyl-2-methylsulfanyl-3-phenylbutanoyl]amino]butanoyl](methyl)amino]-2,5-dimethyl-2-hexenoic acid (72). Following General Procedures 3 and 4 (using 31 in General Procedure 3) gave 72 as a white foam. MS, m/z: 521 (M-H)<sup>-</sup>. Anal. (C<sub>27</sub>H<sub>42</sub>N<sub>2</sub>O<sub>6</sub>S·0.3TFA)

(E,4R)-4-[(2S)-3,3-dimethyl-2-[[3-methyl-3-phenylbutanoyl]amino]butanoyl](methyl)amino]-2,5-dimethyl-2-hexenoic acid (73). Following General Procedures 3 and 4 (using 3,3-dimethyl-3-phenyl propionic acid in General Procedure 3) gave 73.

2,5-Dimethyl-4-(methyl-[2-(3-methyl-2-methylamino-3-phenyl-butryrlyamino)-propionyl]-amino)-hex-2-enoic acid (74). Prepared by modifications of the methods described in the literature. 7. 9a

(2E,4S)-2,5-dimethyl-4-(methyl[(2S)-2-[[N,\beta,\beta-trimethyl-L-phenylalanylamino]butanoyl]amino]hex-2-enoic acid (75). Prepared by modifications of the methods described in the literature. 7. 9a

N,\beta,\beta-trimethyl-L-phenylalanyl-N<sup>1</sup>-(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N<sup>1</sup>-methyl-L-norvalinamide (76). Prepared by modifications of the methods described in the literature. 7. 9a

N,\beta,\beta-trimethyl-L-phenylalanyl-N<sup>1</sup>-(1S,2E)-3-carboxy-1-isopropyl-2-butenyl]-N<sup>1</sup>-methyl-L-valinamide (77). Prepared by modifications of the methods described in the literature. 7. 9a

(E,4S)-2,5-Dimethyl-4-[methyl[(2S)-2-[[2S)-3-methyl-2-(methylamino)-3-phenylbutanoyl]amino]-3-phenylpropanoyl]amino]-2-hexenoic acid (78). Prepared
by modifications of the methods described in the literature\(\textsuperscript{7,9a}\) as a white solid. MS, \(m/z\): 507.9 (M + H\(^+\)). Anal. (C\(_{30}\)H\(_{41}\)N\(_3\)O\(_4\) . HCl . 2H\(_2\)O . 0.5C\(_4\)H\(_6\)O\(_2\))

\(\text{N,}\beta,\beta\text{-trimethyl-L-phenylalanine-N-}[(1S,2E)-3-carboxy-1-isopropyl-2-butenyl]-\text{N,O,}\beta,\beta\text{-tetramethyl-L-tyrosinamide (79).\) Prepared by modifications of the methods described in the literature\(\textsuperscript{7,9a}\) as a white solid. HRMS (ESI) calcd for C\(_{33}\)H\(_{47}\)N\(_3\)O\(_5\): 566.3589 (M + H\(^+\)); found 566.3584. Anal. (C\(_{30}\)H\(_{41}\)N\(_3\)O\(_4\) . 2HCl . H\(_2\)O . 0.5C\(_4\)H\(_6\)O\(_2\))

\((E,4S)-2,5\text{-dimethyl-4-}[(methyl][(2R)-3-methyl-2-][(2S)-3-methyl-2-(methylamino)-3-phenylbutanoyl][amino]-3-(methylsulfanyl)butanoyl][amino]-2-hexenoic acid (80).\) Prepared by modifications of the methods described in the literature\(\textsuperscript{7,9a}\) as a white solid. HRMS (ESI) calcd for C\(_{27}\)H\(_{43}\)N\(_3\)O\(_4\)S 506.3047 (M + H\(^+\)); found 506.3044.

\(\text{N,}\beta,\beta\text{-Trimethyl-L-phenylalanine-N'-(1S,2E)-3-carboxy-1-isopropyl-2-pentenyl]-N',3-dimethyl-L-valinamide (81).\) Prepared by modifications of the methods described in the literature\(\textsuperscript{7,9a}\) as a white solid. MS, \(m/z\): 486.5 (M - H\(^-\)). IR cm\(^{-1}\): 2966, 2877, 1677, 1645. Anal. (C\(_{28}\)H\(_{45}\)N\(_3\)O\(_4\) . 1.5 TFA . H\(_2\)O)

\(\text{N,}\beta,\beta\text{-Trimethyl-L-phenylalanine-N'-(1S,2E)-1-butyl-3-carboxybut-2-enyl]-N',3-dimethyl-L-valinamide (82).\) Prepared by modifications of the methods described in the literature\(\textsuperscript{7,9a}\) as a white powder. MS, \(m/z\): 488.6 (M + H\(^+\)). IR cm\(^{-1}\): 3402, 2962, 2873, 1680, 1649. Anal. (C\(_{28}\)H\(_{45}\)N\(_3\)O\(_4\) . HCl . 2.2 H\(_2\)O)

\((E,4S)-4-[(2S)-3,3\text{-dimethyl-2-}[(2S)-3-methyl-2-(methylamino)-3-phenylbutanoyl][amino]butanoyl](methyl)amino]-2-methyl-5-phenyl-2-pentenoic acid (83).\) Prepared by modifications of the methods described in the literature\(\textsuperscript{7,9a}\)

\(\text{N,}\beta,\beta\text{-trimethyl-L-phenylalanine-N'-}(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-3-methyl-L-valinamide (84).\) Prepared as described in the literature\(\textsuperscript{7}\)

\(\text{N,}\beta,\beta\text{-trimethyl-L-phenylalanine-N'-}(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N'-ethyl-3-methyl-L-valinamide (85).\) Prepared by modifications of the methods described in the literature\(\textsuperscript{7,9a}\)

\(\text{N,}\beta,\beta\text{-trimethyl-L-phenylalanine-N-1-}(1S,2E)-1-isopropyl-3-methyl-4-oxo-4-[2-phenylethyl]amino]but-2-enyl]-N-1'-3-dimethyl-L-valinamide (88).\) Following General
Procedure 5, 2 (238 mg, 0.504 mmol) and phenethylamine (73 mg, 0.605 mmol) were coupled to give, after HPLC, the TFA salt of 88 as white crystals (62 mg). MS, m/z: 575.4 (M - H)^+. Anal. (C_{38}H_{52}N_{10}O_{3} \cdot 1.1\ TFA \cdot 1.5\ H_{2}O)

N,β,β-trimethyl-L-phenylalanyl-N-1-[(1S,2E)-4-[(1,1'-biphenyl-4-ylmethyl)amino]-1-isopropyl-3-methyl-4-oxobut-2-etyl]-N',3-dimethyl-L-valinamide (89). Following General Procedure 5, 2 (256 mg, 0.542 mmol) and 4-phenylbenzylamine (119 mg, 0.65 mmol) were coupled to give 89 as a yellow oil (83 mg). MS, m/z: 639.4 (M + H)^+. Anal. (C_{40}H_{54}N_{10}O_{3} \cdot 0.1\ H_{2}O)

(2S)-N-[(1S,2E)-1-isopropyl-3-methyl-4-(4-morpholinyl)-4-oxo-2-butenyl]-N,3,3-trimethyl-2-[(2S)-3-methyl-2-(methylamino)-3-phenylbutanoyl]amino)butanamide (90). As described in General Procedure 5, 2 (30 mg) and morpholine (0.022 mL, 0.25 mmol) were coupled to give, after HPLC, the TFA salt of 90 as a white powder (37 mg). MS, m/z: 543.6 (M + H)^+. Anal. (C_{31}H_{52}N_{10}O_{4} \cdot 1.5\ TFA)

N,β,β-trimethyl-L-phenylalanyl-N-1-[(1S,2E)-4-(4-benzylpiperazin-1-yl)-1-isopropyl-3-methyl-4-oxobut-2-etyl]-N',3-dimethyl-L-valinamide (91). Following General Procedure 5, 2 (0.239 g, 0.505 mmol) and 1-benzylpiperazine (0.107 g, 0.606 mmol) were coupled to give, after HPLC, the TFA salt of 91 as white crystals (0.378 g). MS, m/z: 632.5 (M + H)^+. Anal. (C_{39}H_{57}N_{10}O_{3} \cdot 2.5\ TFA \cdot 2\ H_{2}O)

N,β,β-trimethyl-L-phenylalanyl-N-1-[(1S,2E)-1-isopropyl-3-methyl-4-(4-methyl-1-piperazinyl)-4-oxo-2-butenyl]-N',3-dimethyl-L-valinamide (92). Following General Procedure 5, 2 (50 mg) and N-methylpiperazine (0.047 mL, 0.42 mmol) were coupled to give, after HPLC, the TFA salt of 92 as a white powder (58 mg). HRMS (ESI) calcd for C_{32}H_{53}N_{10}O_{3}: 556.42290 (M + H)^+; found 556.42137. Anal. (C_{32}H_{53}N_{10}O_{3} \cdot 3\ TFA \cdot 1.5\ H_{2}O)

N,β,β-trimethyl-L-phenylalanyl-N-1-[(1R,2E)-4-[(4-(benzyloxy)benzyl]oxy]-1-isopropyl-3-methyl-4-oxobut-2-etyl]-N',3-dimethyl-L-valinamide (95). Following General Procedure 6, 2 (287 mg, 0.607 mmol) and 4-(benzyloxy)benzyl alcohol (137 mg, 0.638 mmol) gave, after HPLC, the TFA salt of 95 as a white gum (208 mg). MS, m/z: 670.4 (M + H)^+. Anal. (C_{41}H_{58}N_{10}O_{5} \cdot 0.1\ H_{2}O)

N,β,β-trimethyl-L-phenylalanyl-N-1-[(1S,2E)-1-isopropyl-3-methyl-4-oxo-4-(thien-2-ylmethoxy)but-2-enyl]-N',3-dimethyl-L-valinamide (96). Following General Procedure
6, 2 (287 mg, 0.607 mmol) and 2-thiophenemethanol (83 mg, 0.728 mmol) gave, after HPLC, the TFA salt of 96 as a light yellow gum (187 mg). MS, m/z: 570.3 (M + H)^+.

\(^1\)H NMR Data

(Methylamino)(1-phenylcyclopropyl)acetic acid (11). \(^1\)H NMR ((CD\(_3\))\(_2\)SO) δ 0.94 - 1.0 (m, 2H), 1.23 (s, 2H), 2.57 (s, 3H), 3.64 (s, 1H), 7.31 - 7.35 (m, 5H), 8.79 (bs, 1H), 9.00 (bs, 1H).

Adamantan-1-yl-methylamino-acetic acid (17). \(^1\)H NMR ((CD\(_3\))\(_2\)SO + TFA) δ 1.60 (6H, d, J = 12 Hz), 1.70 (6H, d, J = 12 Hz), 2.01 (3H, s), 2.58 (3H, s), 3.56 (1H, d, J = 9.9 Hz), 8.45 (1H, bd s), 8.81 (1H, bd s). MS, m/z: 224.2 (M + 1)^+.

(2E,4S)-4-[[N-[[2S]-2-(1-adamantyl)-2-(methylamino)ethanoyl]-3-methyl-L-valyl](methyl)amino]-2,5-dimethyl-2-hexenoic acid (18). \(^1\)H NMR ((CD\(_3\))\(_2\)SO) δ 0.74 (d, 3H, J = 7.6 Hz), 0.80 (d, 3H, J = 6.4 Hz), 0.93 (s, 9H), 1.38 (d, 3H, J = 12 Hz), 1.52 (d, 3H, J = 11.6 Hz), 1.65 (d, 3H, J = 10.8 Hz), 1.76 (s, 2H), 1.78 (s, 4H), 1.92 (s, 3H), 1.95 - 2.03 (m, 1H), 2.42 (t, 3H, J = 4.4 Hz), 2.97 (s, 3H), 3.66 (d, 1H, J = 8.4 Hz), 4.78 (d, 1H, J = 8.8 Hz), 4.95 (t, 1H, J = 10 Hz), 6.64 (d, 1H, J = 7.6 Hz), 8.54 (bs, 1H), 8.57 (d, 1H, J = 8.8 Hz), 8.66 (bs, 1H).

(2E,4S)-2,5-dimethyl-4-(methyl[3-methyl-N-[2,2,4-trimethylthiomorpholin-3-yl]carbonyl]-L-valyl)amino)hex-2-enoic acid (20). \(^1\)H NMR ((CD\(_3\))\(_2\)SO) δ 0.73 - 0.76 (m, 3H), 0.80 (d, 3H, J = 5.6 Hz), 0.96 (s, 9H), 1.32 (d, 3H, J = 14 Hz), 1.46 (d, 3H, J = 38 Hz), 1.77 (d, 3H, J = 0.8 Hz), 1.94 - 2.04 (m, 1H), 2.69 (d, 3H, J = 48 Hz), 2.85 - 2.9 (m, 1H), 3.0 (s, 3H), 3.05 - 3.24 (m, 2H), 3.71 (t, 1H, J = 13.2 Hz), 4.26 (bs, 1H), 4.61 - 4.66 (m, 1H), 4.92 (t, 1H, J = 9.6 Hz), 6.65 (d, 1H, J = 9.6 Hz), 8.68 (d, 1H, J = 6.4 Hz), 8.92 (d, 1H, J = 7.6 Hz), 9.91 (bs, 1H), 11.6 (bs, 1H).

Ethyl (E,4S)-4-[[[(2S)-3,3-dimethyl-2-[[[2S)-3-methyl-2-(methylamino)-3-phenylbutanoyl]amino]butanoyl](methyl)amino]-2,5-dimethyl-2-hexenoate (24). \(^1\)H NMR ((CD\(_3\))\(_2\)SO) δ 0.79 (t, 6H, J = 6.7 Hz), 0.99 (s, 9H), 1.21 (t, 3H, J = 7.1 Hz), 1.25 (s, 3H), 1.39 (s, 3H), 1.83 (d, 3H, J = 1.3 Hz), 2.01 - 2.08 (m, 1H), 2.28 (s, 3H), 3.02 (s, 3H), 4.12 - 4.19 (q, 2H), 4.5 (bs, 1H), 4.73 (d, 1H, J = 7.9 Hz), 4.92 (t, 1H, J = 10.1 Hz), 6.69 (dd, 1H, J = 1.4 Hz, J = 9.5 Hz), 7.3 (t, 1H, J = 7.2 Hz), 7.4 (t, 2H, J = 7.4 Hz), 7.51 (d, 2H, J = 7.5 Hz), 7.96 (bs, 1H), 8.78 (d, 2H, J = 7 Hz).
N-(2-hydroxyethyl)-N,β,β-trimethyl-L-phenylalaninyl-N\textsuperscript{1}[(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N\textsuperscript{1},3-dimethyl-L-valinamide (25). \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \textdelta 0.91 (d, 3H, J = 2.8 Hz), 0.93 (d, 3H, J = 2.8 Hz), 0.99 (s, 9H), 1.56 (s, 3H), 1.58 (s, 3H), 1.96 (d, 3H, J = 0.8 Hz), 1.96 - 2.00 (m, 1H), 2.96 (s, 3H), 3.09 (s, 3H), 3.33 (m, 2H), 3.77 (d, 1H, J = 13.2 Hz), 4.04 (m, 1H), 4.74 (d, 1H, J = 8 Hz), 5.04 (s, 1H), 5.18 (t, 1H, J = 10.4 Hz), 6.82 (d, 1H, J = 9.6 Hz), 7.26 - 7.47 (m, 5H), 7.87 (d, 1H, J = 7.2 Hz).

N,N,β,β-Tetramethyl-L-phenylalaninyl-N\textsuperscript{1}[(1S,2E)-3-carboxy-1-isopropyl-2-butenyl]-N\textsuperscript{1},3-dimethyl-L-valinamide (26). \textsuperscript{1}H NMR ((CD\textsubscript{3})\textsubscript{2}SO) \textdelta 0.73 (d, 3H, J = 6.5 Hz), 0.78 (d, 3H, J = 6.5 Hz), 1.00 (s, 9H), 1.08 (s, 3H), 1.56 (s, 3H), 1.79 (d, 3H, J = 1.1 Hz), 1.98 - 2.02 (m, 1H), 2.14 (s, 3H), 2.70 (s, 3H), 3.03 (s, 3H), 4.6 (d, 1H, J = 8.8 Hz), 4.8 (d, 1H, J = 8.1 Hz), 4.89 (t, 1H, J = 10.2 Hz), 6.66 (d, 1H, J = 9.6 Hz), 7.29 (t, 1H, J = 7.3 Hz), 7.42 (t, 2H, J = 7.7 Hz), 7.64 (d, 2H, J = 8 Hz), 9.12 (d, 1H, J = 8 Hz), 9.64 (bs, 1H), 12.4 (bs, 1H).

(2S)-2,3-Dimethyl-3-phenylbutanoic acid (28, R = CH\textsubscript{3}). \textsuperscript{1}H NMR ((CD\textsubscript{3})\textsubscript{2}SO) \textdelta 0.83 (d, 3H, J = 7 Hz), 1.3 (s, 3H), 1.34 (s, 3H), 2.69 (q, 1H, J = 7 Hz), 7.17 (t, 1H, J = 7 Hz), 7.29 (t, 2H, J = 7.3 Hz), 7.36 (d, 2H, J = 7.3 Hz), 12 (bs, 1H).

2-Benzyl-3-methyl-3-phenylbutanoic acid (28, R = Bn). \textsuperscript{1}H NMR (CD\textsubscript{3} CN) \textdelta 1.43 (s, 3H), 1.5 (s, 3H), 2.45 (dd, 1H, J = 2.4 Hz, J = 13.3 Hz), 2.79 (t, 1H, J = 13.2 Hz), 2.98 (dd, 1H, J = 2.5 Hz, J = 12 Hz), 7.02 (d, 2H, J = 7 Hz), 7.17 - 7.28 (m, 4H), 7.37 - 7.41 (m, 2H), 7.52 (d, 2H, J = 8 Hz), 8.88 (bs, 1H).

2-Ethyl-3-methyl-3-phenylbutanoic acid (28, R = Et). \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \textdelta 0.81 (t, 3H, J = 7.3 Hz), 1.17 - 1.25 (m, 1H), 1.4 (s, 3H), 1.42 (s, 3H), 1.57 - 1.65 (m, 1H), 2.59 (dd, 1H, J = 2.8 Hz, J = 11.9 Hz), 7.18 - 7.22 (m, 1H), 7.31 (t, 2H, J = 8 Hz), 7.36 - 7.38 (m, 2H), 10 (bs, 1H).

2-Allyl-3-methyl-3-phenylbutanoic acid (28, R = allyl). \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \textdelta 1.41 (s, 3H), 1.44 (s, 3H), 1.87 - 1.92 (m, 1H), 2.27 - 2.35 (m, 1H), 2.77 (dd, 1H, J = 2.8 Hz, J = 12 Hz), 4.95 (t, 2H, J = 13Hz), 5.56 - 5.67 (m, 1H), 7.19 - 7.23 (m, 1H), 7.32 (t, 2H, J = 7 Hz), 7.37 - 7.39 (m, 2H), 10.17 (bs, 1H).
3-Methyl-2-(methylsulfanyl)-3-phenylbutanoic acid (30). $^1$H NMR ((CD$_3$)$_2$SO) $\delta$ 1.43 (s, 3H), 1.45 (s, 3H), 1.99 (s, 3H), 3.54 (s, 1H), 7.16 - 7.20 (m, 1H), 7.27 - 7.31 (m, 2H), 7.43 (d, 2H, J = 6.3 Hz), 12.15 (bs, 1H).

3-methyl-2-(methylsulfonyl)-3-phenylbutanoic acid (31). $^1$H NMR ((CD$_3$)$_2$SO) $\delta$ 1.61 (s, 3H), 1.63 (s, 3H), 2.67 (s, 3H), 4.65 (s, 1H), 7.21 - 7.26 (m, 1H), 7.28 - 7.38 (m, 2H), 7.48 (d, 2H, J = 8 Hz), 13.1 (bs, 1H).

2-Hydroxy-3-methyl-3-phenylbutanoic acid (32). $^1$H NMR ((CD$_3$)$_2$SO) $\delta$ 1.28 (s, 3H), 1.32 (s, 3H), 3.32 (bs, 1H), 4.07 (s, 1H), 7.15 (t, 1H, J = 7.2 Hz), 7.26 (t, 2H, J = 7.2 Hz), 7.36 (d, 2H, J = 7.2 Hz).

2-Methoxy-3-methyl-3-phenylbutanoic acid (35). $^1$H NMR ((CD$_3$)$_2$SO) $\delta$ 1.28 (s, 3H), 1.33 (s, 3H), 3.15 (s, 3H), 3.81 (s, 1H), 7.17 (t, 1H, J = 7.2 Hz), 7.27 (t, 2H, J = 7.9 Hz), 7.37 (d, 2H, J = 1.3 Hz, J = 8.6 Hz), 12.45 (bs, 1H).

N,β,β-trimethyl-L-phenylalanyl-N$^1$-[(1R,3S)-3-carboxy-1-isopropylbutyl]-N$^1$,3-dimethyl-L-valinamide (36). $^1$H NMR ((CD$_3$)$_2$SO) $\delta$ 0.68 (d, 3H, J = 6.6 Hz), 0.9 (d, 3H, J = 6.5 Hz), 1.04 (s, 9H), 1.09 (d, 3H, J = 7 Hz), 1.2 (s, 3H), 1.38 (s, 3H), 1.64 (m, 1H), 1.87 - 1.92 (m, 1H), 2.13 - 2.18 (m, 1H), 2.29 (t, 3H, J = 4.5 Hz), 2.93 (s, 3H), 4.15 (bs, 1H), 4.4 (d, 1H, J = 10 Hz), 4.82 (t, 1H, J = 8.5 Hz), 7.31 (t, 1H, J = 7.1 Hz), 7.41 (t, 2H, J = 7.2 Hz), 7.49 (d, 2H, J = 7.6 Hz), 7.86 (bs, 1H), 8.69 (d, 1H, J = 8.5 Hz), 8.77 (bs, 1H), 12.4 (bs, 1H).

N,β,β-trimethyl-L-phenylalanyl-N$^1$-[(1R,3R)-3-carboxy-1-isopropylbutyl]-N$^1$,3-dimethyl-L-valinamide (37). $^1$H NMR (CD$_3$CN) $\delta$ 0.78 (d, 3H, J = 8.8 Hz), 0.97 (d, 3H, J = 8.7 Hz), 1.05 (s, 9H), 1.13 (d, 3H, J = 9.1 Hz), 1.39 (s, 3H), 1.42 (s, 3H), 1.66 - 1.76 (m, 2H), 1.86 - 1.90 (m, 1H), 2.19 - 2.22 (m, 1H), 2.48 (s, 3H), 2.99 (s, 3H), 4.26 (s, 1H), 4.35 (t, 1H, J = 13.5 Hz), 4.96 (d, 3H, J = 11.9 Hz), 7.32 - 7.61 (m, 5H).

N,β,β-trimethyl-L-phenylalanyl-N$^1$-[(1S,2E)-3-carboxy-1-isopropyl-2-butenyl]-N$^1$,N$^2$,3-trimethyl-L-valinamide (38). $^1$H NMR (CD$_3$CO CD$_3$) $\delta$ 0.87 (d, 3H, J = 6.6 Hz), 0.91 (d, 3H, J = 6.6 Hz), 1.07 (s, 9H), 1.55 (s, 3H), 1.65 (s, 3H), 1.89 (s, 3H), 1.96 (s, 1H), 2.53 (s, 1H), 2.71 (s, 3H), 3.04 (s, 3H), 3.29 (s, 3H), 4.97 (s, 1H), 5.04 (t, 1H, J = 10.2 Hz), 6.78 (d, 1H, J = 9.5 Hz), 7.3 (t, 1H, J = 7.3 Hz), 7.38 (t, 2H, J = 7.2 Hz), 7.57 (d, 2H, J = 7.4 Hz).
N,β,β-trimethyl-D-phenylalanyl-N1-[(1S,2E)-3-carboxy-1-isopropyl-2-buteny]-N1,3-dimethyl-L-valinamide (41). 1H NMR (CD3OD) δ 0.89 (d, 3H, J = 4.8 Hz), 0.91 (d, 3H, J = 5.6 Hz), 0.92 (s, 9H), 1.31 (s, 3H), 1.39 (d, 3H, J = 8 Hz), 1.48 (s, 3H), 1.55 (s, 3H), 1.89 (d, 3H, J = 0.9 Hz), 1.93 (s, 3H), 2.0 - 2.10 (m, 1H), 2.17 (s, 3H), 2.48 (s, 3H), 2.52 (s, 3H), 3.12 (s, 3H), 4.95 (s, 1H), 5.05 (t, 1H, J = 9 Hz), 6.76 (d, 1H, J = 9 Hz), 7.33 (t, 1H, J = 9 Hz), 7.46 (t, 2H, J = 6 Hz), 7.53 (d, 2H, J = 9 Hz).

N,β,β-trimethyl-L-phenylalanyl-N1-[(1S,2E)-3-carboxy-1-isopropyl-2-buteny]-N1,3-dimethyl-D-valinamide (42). 1H NMR ((CD3)2SO) δ 0.80 (d, 3H, J = 6.5 Hz), 0.83 (d, 3H, J = 6.5 Hz), 0.87 (s, 9H), 1.35 (s, 3H), 1.42 (s, 3H), 1.75 (d, 3H, J = 1.2 Hz), 1.93 - 2.01 (m, 1H), 2.13 (t, 3H, J = 4.6 Hz), 3.04 (s, 3H), 4.41 (d, 1H, J = 10.5 Hz), 4.66 (d, 1H, J = 9.2 Hz), 4.85 (t, 1H, J = 10.2 Hz), 6.56 (dd, 1H, J = 1.4 Hz, J = 10 Hz), 7.27 (t, 1H, J = 7.2 Hz), 7.38 (t, 2H, J = 7.4 Hz), 7.46 (d, 2H, J = 7.4 Hz), 8.12 (bs, 1H), 8.68 (d, 1H, J = 9.2 Hz), 8.84 (bs, 1H), 12.4 (bs, 1H). Anal. (C27H43N3O4 • 1.4TFA • H2O)

N,β,β-trimethyl-L-phenylalanyl-N1-[(1R,2E)-3-carboxy-1-isopropylbut-2-enyl]-N1,3-dimethyl-L-valinamide (43). 1H NMR (CD3COCD3) δ 0.91 (d, 3H, J = 6 Hz), 0.96 (d, 3H, J = 7.2 Hz), 1.08 (s, 9H), 1.42 (s, 3H), 1.47 (s, 3H), 1.92 (d, 3H, J = 1.6 Hz), 2.08 - 2.15 (m, 1H), 2.63 (s, 3H), 3.19 (s, 3H), 4.52 (bs, 1H), 4.95 (s, 1H), 5.05 (t, 1H, J = 10.8 Hz), 6.78 (d, 1H, J = 8 Hz), 7.25 (t, 1H, J = 8 Hz), 7.33 (t, 2H, J = 6.4 Hz), 7.48 (d, 2H, J = 8 Hz).

3-Hydroxy-N-methyl-D,L-valyl-N1-[(1S,2E)-4-ethoxy-1-isopropyl-3-methyl-4-oxo-2-buteny]-N1,3-dimethyl-L-valinamide (45). 1H NMR (CD3COCD3) δ 0.84- 0.89 (m, 12H), 1.0 (d, 9H, J = 5 Hz), 1.03 (s, 9H), 1.18 - 1.23 (m, 6H), 1.33 - 1.4 (m, 6H), 1.9 (s, 6H), 2.08 (m, 2H), 2.36 (s, 1H), 2.57 (s, 3H), 2.85 (s, 3H), 3.05 - 3.15 (m, 9H), 3.39 (s, 1H), 3.51 (s, 1H), 4.25 (s, 1H), 4.31 (s, 1H), 4.83 (s, 1H), 4.91 (d, 1H, J = 13.1 Hz), 5.08 - 5.13 (m, 2H), 6.78 (d, 2H, J = 8.6 Hz), 7.43 (bs, 1H).

(2E,4S)-4-[(2S)-2-[[2S]-3,3-dimethyl-2-(methylamino)octanoyl]amino]-3,3-dimethylbutanoyl](methyl)amino]-2,5-dimethyl-2-hexenoic acid (46). 1H NMR ((CD3)2SO) δ 0.73 (d, 3H, J = 6.5 Hz), 0.79 (d, 3H, J = 6.5 Hz), 0.86 (q, 3H, J = 4.6 Hz), 0.84 - 0.99 (m, 6H), 0.94 (s, 9H), 0.99 (m, 2H), 1.21 (bs, 3H), 1.29 (d, 3H, J = 6.2 Hz), 1.78 (d, 3H, J = 1.2 Hz), 1.95 - 2.01 (m, 1H), 2.43 (t, 3H, J = 4.7 Hz), 2.98 (s, 3H), 3.82 (d, 1H, J = 10.6 Hz), 4.73 (d, 1H, J = 8.3 Hz), 4.92 (t, 1H, J = 10.2 Hz), 6.64 (dd, 1H, J = 1.4 Hz, J = 9.6 Hz), 8.41 (bs, 1H), 8.52 (d, 1H, J = 8.3 Hz), 8.7 (bs, 1H), 12.4 (bs, 1H).
3-Cyclohexyl-N-methyl-L-valyl-N-1-[(1S,2E)-3-carboxy-1-isopropyl-2-butenyl]-N-1,3-dimethyl-L-valinamide (47). 1H NMR (DMSO-d6, d): 12.43 (1H, vbr), 8.64 (1H, br), 8.53 (1H, d, J=8.3 Hz), 8.37 (1H, br), 6.64 (1H, dd, J=9.6, 1.4 Hz), 4.91 (1H, t, J=10.1 Hz), 4.74 (1H, d, J=8.3 Hz), 4.01 (1H, d, J=9.7 Hz), 2.98 (3H, s), 2.44 (3H, br t, J=4.7 Hz) 1.92-2.05 (1H, m), 1.78 (3H, d, J=1.1 Hz) over lap with 1.59-1.8 (5H, m), 0.95 (9H, s, t-Bu) and 0.93 (3H, s, Me) overlap with 0.89-1.43 (5H, m), 0.79 (3H, d, J=6.6 Hz), 0.73 (3H, d, J=6.6 Hz), 0.71 (3H, s).

N,O,β,β-tetramethyl-L-tyrosyl-N1-[(1S,2E)-3-carboxy-1-isopropyl-2-butenyl]-N1,3-dimethyl-L-valinamide (48). 1H NMR ((CD3)2SO) δ 0.72 (d, 3H, J = 6.4 Hz), 0.79 (d, 3H, J = 6.4 Hz), 0.91 (s, 9H), 1.19 (s, 3H), 1.26 (s, 3H), 1.77 (s, 3H), 1.94 - 2.00 (m, 1H), 1.97 (s, 3H), 2.97 (s, 3H), 3.16 (s, 1H), 3.32 (bs, 1H), 3.72 (s, 3H), 4.68 (d, 3H, J = 9.2 Hz), 4.91 (t, 1H, J = 10.4 Hz), 6.63 (dd, 1H, J = 1.2 Hz, J = 9.6 Hz), 6.84 (d, 2H, J = 8.8 Hz), 7.31 (d, 3H, J = 8.8 Hz), 7.83 (d, 1H, J = 9.2 Hz).

4-Phenyl-N,β,β-trimethyl-L-phenylalanyl-N1-[(1S,2E)-3-carboxy-1-isopropyl-2-butenyl]-N1,3-dimethyl-L-valinamide (49). 1H NMR ((CD3)2SO) δ 0.78 (d, 3H, J = 6.8 Hz), 0.80 (d, 3H, J = 6 Hz), 0.99 (s, 9H), 1.27 (s, 3H), 1.8 (d, 3H, J = 1.6 Hz), 1.97 - 2.05 (m, 1H), 2.32 (s, 3H), 4.44 (d, 1H, J = 9.6 Hz), 4.78 (d, 1H, J = 7.2 Hz), 4.93 (t, 1H, J = 11.2 Hz), 6.67 (d, 1H, J = 9.6 Hz), 7.38 (t, 1H, J = 7.2 Hz), 7.48 (t, 2H, J = 7.2 Hz), 7.58 (d, 1H, J = 9.6 Hz), 7.64 - 7.73 (m, 5H), 7.94 (bs, 1H), 8.74 (d, 1H, J = 8 Hz), 8.81 (bs, 1H), 12.43 (bs, 1H).

N,3-Dimethyl-4-phenyl-L-valyl-N1-[(1S,2E)-3-carboxy-1-isopropyl-2-butenyl]-N1,3-dimethyl-L-valinamide (50). 1H NMR ((CD3)2SO) δ 0.69 (d, 3H, J = 6.5 Hz), 0.76 (d, 3H, J = 6.5 Hz), 0.82 (s, 3H), 0.86 (s, 3H), 0.95 (s, 9H), 0.98 (dd, 2H, J = 5.5 Hz, J = 13.4 Hz), 1.76 (d, 3H, J = 1.2 Hz), 1.94 - 2.00 (m, 1H), 2.51 (t, 3H, J = 3.5 Hz), 3.89 (d, 1H, J = 10.3 Hz), 4.78 (d, 1H, J = 8.4 Hz), 4.91 (t, 1H, J = 10.1 Hz), 6.64 (dd, 1H, J = 1.4 Hz, J = 9.6 Hz), 7.08 (d, 2H, J = 6.9 Hz), 7.23 - 7.33 (m, 3H), 8.69 (m, 1H), 8.9 (bs, 1H), 12.4 (bs, 1H).

(βR)-N,β-dimethyl-L-phenylalanyl-N1-[(1S,2E)-3-carboxy-1-isopropylbut-2-eny]-N1,3-dimethyl-L-valinamide (51). 1H NMR (CD3CO CD3) δ 0.90 (d, 3H, J = 4 Hz), 0.93 (d, 3H, J = 3.6 Hz), 1.03 (s, 9H), 1.47 (T, 3H, J = 4.1 Hz), 1.82 (t, 3H, J = 2.6 Hz), 2.05 - 2.08 (m, 1H), 2.69 (d, 3H, J = 4 Hz), 3.11 (d, 3H, J = 4 Hz), 3.67 (bs, 1H), 4.45 (d, 1H, J = 5.4 Hz), 4.88 (d, 1H, J = 4 Hz), 5.15 (t, 1H, J = 10.2 Hz), 6.81 (d, 1H, J = 9.8 Hz), 7.27 (d, 5H, J = 4.1 Hz).
(βS)-N,β-dimethyl-L-phenylalanoyl-N'-(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N',3-dimethyl-L-valinamide (52). $^1$H NMR ((CD$_3$)$_2$SO) δ 0.74 (d, 3H, J = 6.4 Hz), 0.80 (d, 3H, J = 6.8 Hz), 0.94 (s, 9H), 1.09 (d, 3H, J = 6.8 Hz), 1.79 (d, 3H, J = 1.2 Hz), 1.97 - 2.03 (m, 1H), 2.21 (s, 3H), 2.62 (d, 1H, J = 15.6 Hz), 2.92 (m, 1H), 3.00 (s, 3H), 4.79 (d, 1H, J = 8.8 Hz), 4.91 (t, 1H, J = 10 Hz), 6.66 (dd, 1H, J = 1.6 Hz, J = 9.6 Hz), 7.26 - 7.36 (m, 5H), 8.48 (bs, 1H).

β,β-diethyl-N-methyl-L-phenylalanoyl-N'-(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N',3-dimethyl-L-valinamide (53). $^1$H NMR (CD$_3$OD) δ 0.8 (t, 3H, J = 7.2 Hz), 0.92 (t, 3H, J = 7.2 Hz), 0.95 (d, 3H, J = 6.8 Hz), 0.99 (d, 3H, J = 6.4 Hz), 1.04 (s, 9H), 1.86 (m, 1H), 1.94 (d, 3H, J = 1.2 Hz), 1.93 - 1.98 (m, 2H), 2.09 - 2.16 (m, 2H), 2.54 (s, 3H), 3.32 (d, 3H, J = 1.6 Hz), 3.33 (t, 1H, J = 1.6 Hz), 4.95 (s, 1H), 5.14 (t, 1H, J = 10.4 Hz), 6.8 (d, 1H, J = 8 Hz), 7.32 - 7.43 (m, 5H).

(2E,4S)-2,5-dimethyl-4-(methyl{3-methyl-N-[(2S)-2-(methylamino)-2-(1-phenylcyclopentyl)ethanoyl]-L-valyl]amino)-2-hexenoic acid (54). $^1$H NMR ((CD$_3$)$_2$SO) δ 0.70 (d, 3H, J = 4 Hz), 0.78 (d, 3H, J = 4 Hz), 0.83 (d, 6H, J = 4 Hz), 0.92 (s, 9H), 0.95 (s, 9H), 1.06 - 1.2 (m, 8H), 1.35 - 1.52 (m, 8H), 1.77 (s, 3H), 1.81 (s, 3H), 1.9 - 1.98 (m, 1H), 1.99 - 2.12 (m, 1H), 2.27 (m, 3H), 2.28 (m, 3H), 2.97 (s, 3H), 3.01 (s, 3H), 4.04 (d, 1H, J = 10 Hz), 4.33 (d, 1H, J = 10 Hz), 4.63 (d, 1H, J = 8 Hz), 4.77 (d, 1H, J = 8 Hz), 4.88 (t, 1H, J = 8 Hz), 5.01 (t, 1H, J = 10.4 Hz), 6.62 (s, 1H), 6.67 (d, 1H, J = 10.4 Hz), 7.26 - 7.32 (m, 5H), 7.33 - 7.44 (m, 5H), 7.85 (bs, 1H), 8.30 (bs, 1H), 8.42 (bs, 1H), 8.66 (d, 1H, J = 7.6 Hz), 8.72 (d, 1H, J = 5.6 Hz).

(2E,4R)-2,5-dimethyl-4-(methyl{3-methyl-N-[(methylamino)(1-phenylcyclohexyl)acetyl]-L-valyl]amino)-2-hexenoic acid (55). $^1$H NMR ((CD$_3$)$_2$SO) δ 0.66 - 0.73 (m, 4H), 0.77 - 0.83 (m, 3H), 0.86 - 0.92 (m, 3H), 0.89 (s, 9H), 0.92 - 0.97 (m, 4H), 1.39 - 1.51 (m, 2H), 1.71 - 1.75 (m, 3H), 2.0 - 2.04 (m, 1H), 2.56 (s, 3H), 2.91 - 2.98 (m, 3H), 3.01 - 3.05 (m, 1H), 4.72 - 4.78 (m, 1H), 4.84 - 4.95 (m, 1H), 6.43 - 6.5 (bs, 1H), 7.16 - 7.35 (m, 5H), 7.65 - 7.7 (m, 1H).

(2E,4S)-2,5-dimethyl-4-(methyl{3-methyl-N-[(2R)-2-(methylamino)-2-(1-phenylcyclopropyl)acetyl]-L-valyl]amino)hex-2-enoic acid (56). $^1$H NMR (CD$_3$OD) δ 0.78 (d, 3H, J = 6.4 Hz), 0.86 (d, 3H, J = 6.4 Hz), 1.02 - 1.16 (m, 3H), 1.12 (s, 9H), 1.4 - 1.45 (m, 1H), 1.87 (d, 3H, J = 1.2 Hz), 1.93 - 2.01 (m, 1H), 2.46 (s, 3H), 3.07 (s, 3H), 3.65
N-ethyl-\(\beta,\beta\)-dimethyl-L-phenylalanyl-N¹-[(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N¹,3-dimethyl-L-valinamide (57). \(^1\)H NMR (D\(_2\)OD) \(\delta\) 0.84 (d, 3H, J = 6.8 Hz), 0.89 (d, 3H, J = 6.4 Hz), 0.98 (t, 3H), 1.03 (d, 9H, J = 2 Hz), 1.36 (s, 3H), 1.44 (s, 3H), 1.89 (m, 1H), 1.98 (m, 2H), 3.10 (d, 3H, J = 2.4 Hz), 3.3 (d, 1H, J = 1.2 Hz), 4.84 (d, 1H, J = 1.6 Hz), 5.03 (t, 1H), 6.7 (d, 1H), 7.28 (t, 1H), 7.39 (t, 2H), 7.49 (d, 2H).

N-Benzyl-\(\beta,\beta\)-dimethyl-L-phenylalanyl-N¹-[(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N¹,3-dimethyl-L-valinamide (58). \(^1\)H NMR (D\(_2\)OD) \(\delta\) 0.88 (s, 3H), 0.90 (s, 3H), 1.06 (d, 9H, J = 2.8 Hz), 1.1 (s, 1H), 1.31 (d, 3H, J = 2.4 Hz), 1.46 (d, 3H, J = 2.4 Hz), 1.88 (d, 3H, J = 1.6 Hz), 2.02 (m, 2H), 3.16 (d, 3H, J = 2.8 Hz), 3.83 (d, 1H, J = 14 Hz), 4.94 (m, 1H), 5.03 (t, 1H, J = 10.4 Hz), 6.76 (d, 1H, J = 9.6 Hz), 7.10 (d, 2H, J = 5.2 Hz), 7.34 – 7.46 (m, 8H).

(2E,4S)-2,5-dimethyl-4-(methyl[3-methyl-N-[(2S)-3-methyl-3-phenyl-2-pyrrolidin-1-ybutanoyl]-L-valyl]amino)hex-2-enoic acid (59). \(^1\)H NMR (D\(_2\)OD) \(\delta\) 0.84 (d, 3H, J = 3.2 Hz), 0.88 (d, 3H, J = 3.2 Hz), 0.84- 0.89 (m, 2H), 1.01 (d, 3H, J = 3.6 Hz), 1.03 – 1.07 (m, 2H), 1.08 (d, 9H, J = 3.2 Hz), 1.22 (d, 3H, J = 2.8 Hz), 1.82 (m, 2H), 1.90 (d, 3H, J = 2 Hz), 1.90 (m, 1H), 2.05 (m, 2H), 2.95 (d, 1H, J = 3.6 Hz), 3.14 (d, 3H, J = 3.2 Hz), 3.61 (bs, 1H), 4.93 (d, 1H, J = 3.2 Hz), 5.02 (t, 1H, J = 10 Hz), 6.76 (d, 1H, J = 10 Hz), 7.32 (d, 1H), 7.43 (d, 2H), 7.61(d, 2H, J = 8 Hz).

N-(2-hydroxyethyl)-\(\beta,\beta\)-dimethyl-L-phenylalanyl-N¹-[(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N¹,3-dimethyl-L-valinamide (60). \(^1\)H NMR (D\(_2\)OD) \(\delta\) 0.89 (d, 3H, J = 3.2 Hz), 0.9 (d, 3H, J = 3.6 Hz), 1.05 (d, 9H, J = 3.2 Hz), 1.41 (d, 3H, J = 2.8 Hz), 1.46 (s, 3H), 1.9 (d, 3H, J = 1.6 Hz), 2.02 (m, 2H), 2.81 (bs, 1H), 2.98 (bs, 1H), 3.13 (d, 3H, J = 2.8 Hz), 3.34 (d, 1H, J = 3.2 Hz), 3.60 – 3.64 (m, 2H), 4.9 (d, 1H, J = 2.8 Hz), 5.04 (t, 1H, J = 10 Hz), 6.76 (d, 1H, J = 9.6 Hz), 7.34 (d, 1H), 7.43 (d, 2H, J = 8 Hz), 7.55 (d, 2H, J = 8 Hz).

N-(carboxymethyl)-\(\beta,\beta\)-dimethyl-L-phenylalanyl-N¹-[(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N¹,3-dimethyl-L-valinamide (61). \(^1\)H NMR (D\(_2\)OD) \(\delta\) 0.89 (d, 3H, J = 2 Hz), 0.90 (s, 3H), 1.04 (d, 9H, J = 4 Hz), 1.41(d, 3H, J = 3.2 Hz), 1.486 (s, 3H), 1.89 (d, 3H, J = 2.4 Hz), 2.02 - 2.08 (m, 2H), 3.13 (dd, 1H, J = 3.6 Hz, J = 17.2 Hz), 3.62 (dd, 1H, J = 4 Hz, J = 17.2 Hz), 4.65 (d, 1H, J = 4 Hz), 4.88 (d, 1H, J = 4 Hz), 5.04 (d, 1H, J = 10.4 Hz).
Hz), 6.76 (d, 1H, J = 9.2 Hz), 7.34 (d, 1H, J = 7.2 Hz), 7.43 (t, 2H, J = 8 Hz), 7.56 (d, 2H, J = 8 Hz).

\( \beta,\beta\)-dimethyl-N-[2-(methylamino)-2-oxoethyl]-L-phenylalanyl-N1-[(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N1,3-dimethyl-L-valinamide (62). \(^1\)H NMR (CD\(_2\)OD) \( \delta \) 0.88 (d, 3H, J = 4.4 Hz), 0.90 (d, 3H, J = 4.4 Hz), 1.04 (s, 9H), 1.38 (s, 3H), 1.44 (s, 3H), 1.9 (d, 3H, J = 1.6 Hz), 2.02 – 2.08 (m, 2H), 2.59 (s, 3H), 3.13 (s, 3H), 3.47 (m, 1H), 4.88 (s, 1H), 5.04 (t, 1H, J = 10.4 Hz), 6.76 (d, 3H, J = 9.6 Hz), 7.32 (t, 1H, J = 7.2 Hz), 7.43 (t, 2H, J = 7.2 Hz), 7.55 (d, 2H, J = 7.6 Hz).

\( \beta,\beta\)-Dimethyl-L-phenylalanyl-N\(^1\)-[(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N\(^1\),3-dimethyl-L-valinamide (63). \(^1\)H NMR (CD\(_2\)OD) \( \delta \) 0.91 (s, 3H), 0.91 (s, 3H), 1.04 (s, 9H), 1.42 (s, 3H), 1.46 (s, 3H), 1.92 (d, 3H, J = 0.9 Hz), 1.94 - 2.2 (m, 1H), 3.14 (s, 3H), 3.67 (s, 1H), 4.40 (s, 1H), 4.81 (s, 1H), 5.0 (t, 1H, J = 2.4 Hz), 6.77 (d, 1H, J = 15 Hz), 7.35 (t, 1H, J = 6 Hz), 7.45 (t, 2H, J = 6 Hz), 7.55 (d, 2H, J = 6 Hz).

N-methylglycyl-\( \beta,\beta\)-dimethyl-L-phenylalanyl-N\(^1\)-[(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N\(^1\),3-dimethyl-L-valinamide (64). \(^1\)H NMR (CD\(_2\)OD) \( \delta \) 0.87 (d, 3H, J = 3.6 Hz), 0.90 (d, 3H, J = 3.6 Hz), 0.93 (d, 9H, J = 3.6 Hz), 1.37 (d, 3H, J = 3.2 Hz), 1.40 (d, 3H, J = 3.2 Hz), 1.88 (d, 3H, J = 2.4 Hz), 2.00 (m, 2H), 2.51 (d, 3H, J = 3.6 Hz), 3.08 (d, 3H, J = 3.6 Hz), 3.51 (dd, 1H, J = 3.6 Hz, J = 16 Hz), 3.71 (dd, 1H, J = 3.6 Hz, J = 16 Hz), 4.77 (dd, 1H, J = 3.6 Hz, J = 8.4 Hz), 5.00 – 5.05 (m, 1H), 6.75 (d, 1H, J = 10 Hz), 7.18 (s, 1H), 7.43 (t, 2H, J = 7.6 Hz), 7.48 (d, 2H, J = 7.6 Hz), 7.79 (d, 1H, J = 8.8 Hz).

(E,4S)-4-[(2S)-2-[(2S)-2,3-dimethyl-3-phenylbutanoyl]amino]-3,3-dimethylbutanoyl](methyl)amino]-2,5-dimethyl-2-hexenoic acid (65). \(^1\)H NMR (CD\(_3\)SO) \( \delta \) 0.65 (d, 3H, J = 6.8 Hz), 0.76 (d, 3H, J = 6.5 Hz), 0.79 (d, 3H, J = 6.5 Hz), 0.92 (s, 9H), 1.17 (s, 3H), 1.27 (s, 3H), 1.78 (d, 3H, J = 1.08 Hz), 1.92 - 2.0 (m, 1H), 2.96 (s, 3H), 2.99 (s, 1H), 4.69 (d, 1H, J = 8.9 Hz), 4.92 (t, 1H, J = 10 Hz), 6.64 (dd, 1H, J = 1.28 Hz, J = 9.4 Hz), 7.16 (t, 1H, J = 7.2 Hz), 7.29 (t, 2H, J = 7.5 Hz), 7.43 (d, 2H, J = 7.5 Hz), 7.95 (d, 1H, J = 8.8 Hz), 12.35 (bs, 1H).

(E,4S)-4-[(2S)-3,3-dimethyl-2-[(3-methyl-2-ethyl-3-phenylbutanoyl)amino]butanoyl](methyl)amino]-2,5-dimethyl-2-hexenoic acid (66). \(^1\)H NMR (CD\(_3\)SO) \( \delta \) 0.52 (t, 3H, J = 6.9 Hz), 0.6 (t, 3H, J = 6.9 Hz), 0.69 (d, 3H, J = 3.7 Hz), 0.71 (d, 3H, J = 2.9 Hz), 0.76 (d, 3H, J = 6.6 Hz), 0.79 (d, 3H, J = 6.1 Hz), 0.9 (s, 9H), 0.95.
(E,4S)-4-[(2S)-3,3-dimethyl-2-[[3-methyl-2-allyl-3-phenylbutanoyl]amino]butanoyl]((methyl)amino)-2,5-dimethyl-2-hexenoic acid (67). \(^1\)H NMR ((CD\(_3\))\(_2\)SO) \(\delta\) 0.73 (d, 3H, J = 6.5 Hz), 0.76 (d, 3H, J = 6.5 Hz), 0.78 (d, 3H, J = 2.3 Hz), 0.8 (d, 3H, J = 2.3 Hz), 0.9 (s, 9H), 0.92 (s, 9H), 1.28 (s, 3H), 1.31 (s, 3H), 1.32 (s, 3H), 1.34 (s, 3H), 1.39 - 1.49 (m, 3H), 1.77 (d, 3H, J = 1.2 Hz), 1.78 (d, 3H, J = 1.2 Hz), 1.9 - 1.99 (m, 2H), 2.19 - 2.24 (m, 3H), 2.93 (s, 3H), 3.00 (s, 3H), 4.66 - 4.94 (m, 8H), 5.35 - 5.63 (m, 2H), 6.64 (t, 2H, J = 7.9 Hz), 7.15 - 7.21 (m, 2H), 7.28 - 7.33 (m, 4H), 7.38 (d, 1H, J = 7.2 Hz), 7.47 - 7.5 (m, 3H), 8.05 - 8.11 (m, 2H), 12.3 (bs, 2H).

(E,4S)-4-[(2S)-3,3-Dimethyl-2-[[3-methyl-2-benzyl-3-phenylbutanoyl]amino]butanoyl]((methyl)amino)-2,5-dimethyl-2-hexenoic acid (68). \(^1\)H NMR ((CD\(_3\))\(_2\)SO) \(\delta\) 0.64 (s, 9H), 0.75 - 0.79 (m, 12H), 0.9 (s, 9H), 1.35 (d, 12H, J = 11Hz), 1.75 (dd, 6H, J = 1.2Hz, J = 4.7Hz), 1.9 (m, 1H), 1.98 - 2.01 (m, 2H), 2.3 (dd, 1H, J = 1.8Hz, J = 13.2 Hz), 2.69 - 2.78 (m, 1H), 2.82 (s, 3H), 2.86 - 2.91 (m, 1H), 2.98 (s, 3H), 3.21 - 3.27 (m, 2H), 4.56 (d, 1H, J = 8.8 Hz), 4.71 (d, 1H, J = 8.9 Hz), 4.8 - 4.92 (m, 2H), 6.57 - 6.61 (m, 1H), 6.71 (d, 1H, J = 1.5 Hz, J = 8 Hz), 6.89 (d, 1H, J = 7 Hz), 6.96 (d, 1H, J = 1.3 Hz, J = 8.3 Hz), 7.04 - 7.12 (m, 4H), 7.18 - 7.23 (m, 4H), 7.34 - 7.38 (m, 5H), 7.48 (d, 2H, J = 1.2 Hz, J = 8.5 Hz), 7.6 (d, 3H, J = 8 Hz), 7.85 (d, 1H, J = 8.8 Hz), 8.06 (d, 1H, J = 8.9 Hz), 12.25 (bs, 2H).

(E,4S)-4-[(N-(2S)-2-methoxy-3-methyl-3-phenylbutanoyl]-3-methyl-L-valyl]((methyl)amino)-2,5-dimethyl-2-hexenoic acid (69). \(^1\)H NMR ((CD\(_3\))\(_2\)SO) \(\delta\) 0.73 (d, 3H, J = 6.5 Hz), 0.79 (d, 3H, J = 6.5Hz), 0.84 (s, 9H), 1.23 (s, 3H), 1.25 (s, 3H), 1.77 (d, 3H, J = 1.2 Hz), 1.93 - 2.02 (m, 1H), 2.96 (s, 3H), 3.04 (s, 3H), 4.01 (s, 1H), 4.68 (d, 1H, J = 9.2 Hz), 4.91 (t, 1H, J = 10.1 Hz), 6.63 (dd, 1H, J = 1.4 Hz, J = 9.4 Hz), 7.15 (t, 1H, J = 7.2 Hz), 7.27 (t, 2H, J = 7.4 Hz), 7.4 (d, 2H, J = 1.2 Hz, J = 8.5 Hz), 7.56 (d, 1H, J = 9.2 Hz), 12.4 (bs, 1H).

(E,4S)-4-[(2S)-3,3-dimethyl-2-[[3-methyl-2-methylsulfanyl-3-phenylbutanoyl]amino]butanoyl]((methyl)amino)-2,5-dimethyl-2-hexenoic acid (71). \(^1\)H
NMR ((CD$_3$)$_2$SO) δ 0.73 (d, 6H, J = 6.5 Hz), 0.76 (s, 9H), 0.79 (dd, 6H, J = 2.3 Hz, J = 6.5 Hz), 0.93 (s, 9H), 1.39 - 1.43 (t, 12H, J = 8 Hz), 1.72 (s, 3H), 1.75 (d, 3H, J = 1.2 Hz), 1.77 (s, 9H), 1.93 - 1.99 (m, 2H), 2.91 (d, 6H, J = 2.3 Hz), 3.92 (s, 1H), 4.0 (s, 1H), 4.61 (d, 1H, J = 9.3 Hz), 4.67 (d, 1H, J = 9 Hz), 4.9 (q, 2H, J = 9.8 Hz), 6.61 - 6.65 (m, 2H), 7.17 (q, 2H, J = 7.3 Hz), 7.28 (q, 4H, J = 7.4 Hz), 7.45 (d, 4H, J = 1.3 Hz, J = 8.2 Hz), 7.98 (d, 1H, J = 9.3 Hz), 8.14 (d, 1H, J = 9 Hz), 12.4 (bs, 2H).

(E,4S)-4-[(2S)-3,3-dimethyl-2-[[3-methyl-2-methylsulfonyl-3-phenylbutanoyl]amino]butanoyl](methyl)amino]-2,5-dimethyl-2-hexenoic acid (72). $^1$H NMR ((CD$_3$)$_2$SO) δ 0.71 (d, 6 H, J = 6.5 Hz), 0.75 (s, 9H), 0.76 - 0.83 (m, 6H), 0.95 (s, 9H), 1.35 (s, 3H), 1.56 (s, 3H), 1.63 (d, 6 H, J = 10.3 Hz), 1.75 (d, 3H, J = 1.2 Hz), 1.78 (d, 3H, J = 1.2 Hz), 1.98 - 2.02 (m, 2H), 2.25 (s, 3H), 2.56 (s, 3H), 2.9 (s, 3H), 2.97 (s, 3H), 4.53 (d, 1H, J = 8.9 Hz), 4.73 (d, 1H, J = 8.8 Hz), 4.86 - 4.94 (m, 4H), 6.61 (dd, 1H, J = 1.4 Hz, J = 9.5 Hz), 6.65 (dd, 1H, J = 1.4 Hz, J = 9.4 Hz), 7.18 (t, 1H, J = 7.2 Hz), 7.23 (t, 1H, J = 7.2 Hz), 7.28 - 7.36 (m, 4H), 7.48 (d, 2H, J = 7.4 Hz), 7.53 (d, 2H, J = 7.4 Hz), 8.3 (d, 1H, J = 8.8 Hz), 8.53 (d, 1H, J = 8.8 Hz), 12.4 (bs, 2H).

(E,4R)-4-[(2S)-3,3-dimethyl-2-[[3-methyl-3-phenylbutanoyl]amino]butanoyl](methyl)amino]-2,5-dimethyl-2-hexenoic acid (73). $^1$H NMR (CDCl$_3$) δ 0.70 (s, 9H), 0.80 (d, 3H, J = 6.56 Hz), 0.87 (d, 3H, J = 6.56 Hz), 1.38 (s, 3H), 1.46 (s, 3H), 1.88 (d, 3H, J = 1.24 Hz), 2.52 (d, 1H, J = 9.2 Hz), 2.57 (d, 1H, J = 8.6 Hz), 2.97 (s, 3H), 4.70 (d, 1H, J = 9.44 Hz), 5.01 (t, 1H, J = 9.92 Hz) 6.18 (d, 1H, J = 9.04 Hz), 6.75 (d, 1H, J = 9.4 Hz) 7.19 (t, 1H, J = 7.2 Hz), 7.33 (t, 2H, J = 7.48 Hz, J = 8.08 Hz), 7.19 (d, 2H, J = 0.88 Hz, J = 1.32 Hz)

2,5-Dimethyl-4-[(methyl-2-[3-methyl-2-methylamino-3-phenyl-butyryl]amino)-propionyl]-amino]-hex-2-enoic acid (74). $^1$H NMR ((CD$_3$)$_2$SO) δ 0.75 (d, 3H , J = 5.7 Hz), 0.77 (d, 3H , J = 5.7 Hz), 0.81 (t, 3H, J = 1.47 Hz), 1.23 (s, 3H), 1.36 (s, 3H), 1.73 (s, 3H), 1.85 (s, 1H), 2.37 (s, 3H), 2.60 (s, 1H), 2.88 (s, 3H), 3.92 - 3.98 (m, 1H), 4.70 - 4.72 (m, 1H), 4.78 - 4.84 (m, 1H), 6.60 - 6.63 (m, 1H), 7.12 - 7.46 (m, 5H).

(2E,4S)-2,5-dimethyl-4-[(methyl(2S)-2-[(N,β,β-trimethyl-L-phenylalanyl)amino]butanoyl]amino]-hex-2-enoic acid (75). $^1$H NMR ((CD$_3$)$_2$SO) δ 0.79 (d, 3H, J = 6.4 Hz), 0.82 (d, 3H, J = 6.6 Hz), 0.88 (t, 3H, J = 7.8 Hz), 1.32 (s, 3H), 1.40 (s, 3H), 1.54 - 1.65 (m, 1H), 1.67 - 1.78 (m, 1H), 1.74 (s, 3H), 1.94 - 2.02 (m, 1H), 2.32 (s, 3H), 2.38 - 2.47 (m, 1H), 2.93 (s, 3H), 4.15 - 4.22 (m, 1H), 4.65 (d, 1H, J = 11.4 Hz), 4.85 (t, 1H,
J = 10.1 Hz), 6.64 (d, 1H, J = 8.8 Hz), 7.30 (t, 1H, J = 10 Hz), 7.38 (t, 2H, J = 10 Hz), 7.45 (d, 2H, J = 10 Hz), 7.92 (bs, 1H), 8.75 (bs, 1H), 8.88 (bs, 1H).

N,β,β-trimethyl-L-phenylalanyl-N\(^{-1}[-(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N\(^{-1}\)-methyl-L-norvalinamide (76). \(^{1}\)H NMR ((CD\(_3\))\(_2\)SO) δ 0.79 (d, 3H, J = 6.56 Hz), 0.82 (d, 3H, J = 6.6 Hz), 0.89 (t, 3H, J = 6.8 Hz), 1.25 - 1.37 (m, 2H), 1.33 (s, 3H), 1.40 (s, 3H), 1.54 - 1.64 (m, 2H), 1.74 (s, 3H), 2.25 - 2.32 (m, 1H), 2.32 (s, 3H), 2.93 (s, 3H), 4.11 - 4.20 (m, 1H), 4.69 - 4.75 (m, 1H), 4.80 - 4.87 (m, 1H), 6.65 (d, 1H, J = 10 Hz), 7.25 - 7.35 (m, 1H), 7.35 - 7.47 (m, 4H), 7.9 (bs, 1H), 8.72 (bs, 1H), 8.92 (bs, 1H).

N,β,β-trimethyl-L-phenylalanyl-N\(^{-1}[-(1S,2E)-3-carboxy-1-isopropyl-2-buteny]-N\(^{-1}\)-methyl-L-valinamide (77). \(^{1}\)H NMR ((CD\(_3\))\(_2\)SO) δ 0.80 (d, 3H, J = 9.1 Hz), 0.81 (d, 3H, J = 11.4 Hz), 0.86 (d, 3H, J = 11.4 Hz), 0.94 (d, 3H, J = 13.7 Hz), 1.25 (s, 3H), 1.38 (s, 3H), 1.78 (s, 3H), 2.32 (s, 3H), 2.37 - 2.44 (m, 1H), 2.66 (m, 1H), 3.00 (s, 3H), 4.25 (d, 1H, J = 8.5 Hz), 4.54 - 4.6 (m, 1H), 4.88 (t, 1H, J = 11.4 Hz), 6.66 (d, 1H, J = 12.5 Hz), 7.25 - 7.35 (m, 1H), 7.36 - 7.43 (m, 2H), 7.43 - 7.48 (m, 2H), 8.77 (bs, 1H).

(E,4S)-2,5-Dimethyl-4-[methyl[(2S)-2-[[2S]-3-methyl-2-(methylamino)-3-phenylbutanoyl]amino]-3-phenylpropanoyl]amino]-2-hexenoic acid (78). \(^{1}\)H NMR ((CD\(_3\))\(_2\)SO) δ 0.76 (d, 3H, J = 6.4 Hz), 0.79 (d, 3H, J = 6.8 Hz), 1.29 (s, 3H), 1.37 (s, 3H), 1.77 (s, 3H), 1.77 - 1.96 (m, 1H), 1.96 (s, 3H), 2.76 (s, 3H), 2.85 - 2.93 (m, 1H), 2.97 - 3.04 (m, 1H), 4.11 (d, 1H, J = 8 Hz), 4.87 (t, 1H, J = 8 Hz), 4.98 - 5.15 (m, 1H), 6.51 (d, 1H, J = 8 Hz), 7.2 - 7.43 (m, 10H), 7.89 - 7.98 (bs, 1H), 8.6 - 8.8 (bs, 1H), 9.3 (d, 1H, J = 4 Hz), 12.4 - 12.6 (bs, 1H).

N,β,β-trimethyl-L-phenylalanyl-N\(^{-1}[-(1S,2E)-3-carboxy-1-isopropyl-2-buteny]-N,O,β-tetramethyl-L-tyrosinamide (79). \(^{1}\)H NMR (CD\(_3\))\(_2\)OD δ 0.70 (d, 3H, J = 6.8 Hz), 0.78 (d, 3H, J = 6.5 Hz), 1.32 (s, 3H), 1.43 (s, 3H), 1.48 (d, 6H, J = 2.5 Hz), 1.83 - 1.89 (m, 1H), 1.97 (d, 3H, J = 1.3 Hz), 2.21 (s, 3H), 2.54 (s, 3H), 3.73 (s, 3H), 4.27 (s, 1H), 5.01 (t, 1H, J = 10.4 Hz), 5.23 (s, 1H), 6.48 (dd, 1H, J = 1.4 Hz, J = 10.2 Hz), 6.79 (d, 1H, J = 1.3 Hz), 7.33 (dd, 2H, J = 1.6 Hz, J = 8.3 Hz), 7.44 (t, 3H, J = 7.4 Hz), 7.51 - 7.58 (m, 3H).

(E,4S)-2,5-dimethyl-4-[methyl[(2R)-3-methyl-2-[[2S]-3-methyl-2-(methylamino)-3-phenylbutanoyl]amino]-3-(methylsulfanyl)butanoyl]amino]-2-hexenoic acid (80). \(^{1}\)H NMR (CD\(_3\))\(_2\)OD δ 0.89 (t, 6H, J = 6.8 Hz), 1.34 (s, 3H), 1.41 (d, 6H, J = 3.2 Hz), 1.48 (s, 3H), 1.90 (d, 3H, J = 1.3 Hz), 2.01 - 2.07 (m, 1H), 2.08 (s, 3H), 2.57 (s, 3H), 3.17 (s, 3H), 4.34 (s, 3H).
\[ \text{N}_3\beta,\beta\text{-Trimethyl-L-phenylalanyl-N}^1\text{[1S,2E]-3-carboxy-1-isopropyl-2-pentenyl-N}^1,3\text{-dimethyl-L-valinamide (81).} \]

\[ ^1\text{H NMR} ((\text{CD}_3)_2\text{SO} \delta 0.78 \text{ (d, 3H, } J = 5.6 \text{ Hz), 0.83 (d, 3H, } J = 5.6 \text{ Hz), 0.94 (t, 3H, } J = 8.4 \text{ Hz), 0.98 (s, 9H), 1.27 (s, 3H), 1.39 (s, 3H), 1.93 - 2.04 (m, 1H), 2.22 - 2.32 (m, 2H), 3.06 (s, 3H), 3.56 (s, 3H), 3.56 (s, 1H), 4.73 (d, 1H, } J = 8.4 \text{ Hz), 4.97 (t, 1H, } J = 10.8 \text{ Hz), 6.61 (d, 1H, } J = 8 \text{ Hz), 7.3 (t, 1H, } J = 4 \text{ Hz), 7.42 (t, 2H, } J = 4 \text{ Hz), 7.51 (d, 2H, } J = 8 \text{ Hz), 7.92 (bs, 1H), 8.75 (d, 1H, } J = 8 \text{ Hz), 8.78 (bs, 1H), 12.4 (bs, 1H).} \]

\[ \text{N}_3\beta,\beta\text{-Trimethyl-L-phenylalanyl-N}^1\text{[1S,2E]-1-butyty-3-carboxybut-2-etyl-N}^1,3\text{-dimethyl-L-valinamide (82).} \]

\[ ^1\text{H NMR} ((\text{CD}_3)_2\text{SO} \delta 0.81 \text{ (t, 3H, } J = 6.8 \text{ Hz), 0.859 - 0.927 (m, 4H), 0.95 - 1.02(m, 2H), 1.15 (s, 9H), 1.23 (d, 3H, } J = 2 \text{ Hz), 1.25 (d, 3H, } J = 3.6 \text{ Hz), 1.77 (d, 3H, } J = 1.2 \text{ Hz), 2.98 (s, 3H), 3.55 (s, 1H), 3.56 (s, 3H), 5.1 (d, 1H, } J = 4 \text{ Hz), 5.40 (t, 1H, } J = 8.4 \text{ Hz), 6.61 (d, 1H, } J = 9.6 \text{ Hz), 7.31 (t, 1H, } J = 6 \text{ Hz), 7.51(d, 2H, } J = 8 \text{ Hz), 7.64 (d, 2H, } J = 7.6 \text{ Hz), 8.08 (bs, 1H), 8.62 - 8.72 (bs, 1H), 10.0 (bs, 1H).} \]

\[ \text{(E,4S)-4-[[2S]-3,3-dimethyl-2-[[2S]-3-methyl-2-(methylamino)-3-phenylbutanoyl]amino]butanoyl(methyl)amino]-2-methyl-5-phenyl-2-pentenoic acid (83).} \]

\[ ^1\text{H NMR} ((\text{CD}_3)_2\text{SO} \delta 0.98 (d, 9H, } J = 8 \text{ Hz), 1.46 (d, 3H, } J = 12 \text{ Hz), 1.4 (d, 3H, } J = 8 \text{ Hz), 2.3 (s, 3H), 2.42 (m, 1H), 2.64 (m, 1H), 3.03 (s, 3H), 3.67 (s, 1H), 4.72 (d, 1H, } J = 8 \text{ Hz), 5.49 (t, 1H, } J = 8 \text{ Hz), 6.73 (d, 1H, } J = 8 \text{ Hz), 7.17 - 7.66 (m, 10 H), 8.12 (bs, 1H), 8.74 (d, 1H, } J = 8 \text{ Hz), 9.04 (bs, 1H), 12.5 (bs, 1H).} \]

\[ \text{N}_3\beta,\beta\text{-trimethyl-L-phenylalanyl-N}^1\text{[1S,2E]-3-carboxy-1-isopropylbut-2-enyl-3-methyl-L-valinamide (84).} \]

\[ ^1\text{H NMR} ((\text{CD}_3)_2\text{SO} \delta 0.82 (d, 3H, } J = 6.6 \text{ Hz), 0.88 (d, 3H, } J = 6.5 \text{ Hz), 0.94 (s, 9H), 1.31 (s, 3H), 1.43 (s, 3H), 1.79 (s, 3H), 2.04 - 2.09 (m, 1H), 2.25 - 2.35 (m, 1H), 2.47 (s, 3H), 3.50 (s, 1H), 4.30 - 4.35 (m, 1H), 4.55 (d, 1H, } J = 10.7 \text{ Hz), 6.45 (d, 1H, } J = 9.8 \text{ Hz), 7.28 (t, 1H, } J = 7.2 \text{ Hz), 7.37 (t, 2H, } J = 7.6 \text{ Hz), 7.53 (d, 2H, } J = 7.7 \text{ Hz), 8.16 (bs, 1H), 8.26 (bs, 1H), 8.31 (d, 1H, } J = 8.6 \text{ Hz), 8.41 (d, 1H, } J = 8.6 \text{ Hz).} \]

\[ \text{N}_3\beta,\beta\text{-trimethyl-L-phenylalanyl-N}^1\text{[1S,2E]-3-carboxy-1-isopropylbut-2-enyl-N}^1\text{-ethyl-3-methyl-L-valinamide (85).} \]

\[ ^1\text{H NMR} ((\text{CD}_3)_2\text{SO} \delta 0.77 (t, 3H, } J = 8 \text{ Hz), 0.85 (t, 3H, } J = 7.48 \text{ Hz), 0.98 (s, 9H), 1.24 (t, 3H, } J = 7.48 \text{ Hz), 1.44 (s, 3H), 1.53 (s, 3H), 1.79 (s, 3H), 2.27 - 2.32 (m, 2H), 2.36 (s, 1H), 2.99 (s, 3H), 4.38 - 4.43 (m, 1H), 4.65 (d, 1H, } J = 11.4 \text{ Hz), 5.17 (q, 1H, } J = 8.8 \text{ Hz), 6.46 (d, 1H, } J = 9.2 \text{ Hz), 7.31 (t, 1H, } J = 7.04 \text{ Hz), 7.37 (t,} \]
2H, J = 7.4 Hz), 7.43 (d, 2H, J = 7.4 Hz), 7.96 (bs, 1H), 8.55 (bs, 1H), 8.75 (d, 1H, J = 10.8 Hz), 8.81 (bs, 1H).

(E,E4S)-4-[(2S)-3,3-dimethyl-2-[(2S)-3-methyl-2-(methylamino)-3-phenylbutanoyl]amino]butanoyl](methyl)amino]-2,5-dimethyl-2-hexenamide (86). 1H NMR ((CD₃)₂SO) δ 0.76 (d, 3H, J = 6.5 Hz), 0.82 (d, 3H, J = 6.5 Hz), 0.98 (s, 9H), 1.24 (s, 3H), 1.39 (s, 3H), 1.77 (d, 3H, J = 1 Hz), 1.89 - 1.95 (m, 1H), 2.28 (d, 3H, J = 4.8 Hz), 2.99 (s, 3H), 4.4 (d, 1H, J = 10 Hz), 4.77 (d, 1H, J = 8.2 Hz), 4.94 (t, 1H, J = 10 Hz), 6.32 (dd, 1H, J = 1.2 Hz, J = 7.9 Hz), 7.0 (s, 3H), 7.31 (t, 1H, J = 7.2 Hz), 7.41 (t, 2H, J = 7.4 Hz), 7.4 (d, 2H, J = 7.5 Hz), 7.88 (bs, 1H), 8.6 (d, 1H, J = 8.1 Hz), 8.76 (bs, 1H).

(E,E4S)-4-[(2S)-3,3-dimethyl-2-[(2S)-3-methyl-2-(methylamino)-3-phenylbutanoyl]amino]butanoyl](methyl)amino]-N,2,5-trimethyl-2-hexenamide (87). 1H NMR ((CD₃)₂SO) δ 0.76 (d, 3H, J = 6.5 Hz), 0.82 (d, 3H, J = 6.5 Hz), 0.98 (s, 9H), 1.24 (s, 3H), 1.39 (s, 3H), 1.79 (d, 3H, J = 1.1 Hz), 1.9 - 1.95 (m, 1H), 2.29 (t, 3H, J = 4.6 Hz), 2.63 (d, 3H, J = 4.5 Hz), 2.98 (s, 3H), 4.4 (d, 1H, J = 10.4 Hz), 4.77 (d, 1H, J = 8.2 Hz), 4.94 (t, 1H, J = 10 Hz), 6.25 (dd, 1H, J = 1.3 Hz, J = 9.2 Hz), 7.31 (t, 1H, J = 7.2 Hz), 7.41 (t, 2H, J = 7.4 Hz), 7.4 (d, 2H, J = 7.4 Hz), 7.83 (d, 1H, J = 4.6 Hz), 7.84 (bs, 1H), 8.7 (d, 1H, J = 8.1 Hz), 8.77 (bs, 1H).

N,β,β-trimethyl-L-phenylalanil-N-1-[(1S,2E)-1-isopropyl-3-methyl-4-oxo-4-[(2-phenylethyl)amino]but-2-enyl]-N-1,3-dimethyl-L-valinamide (88). 1H NMR (CD₃OD) δ 0.9 (t, 6H, J = 9 Hz), 1.07 (s, 9H), 1.39 (s, 3H), 1.48 (s, 3H), 1.95 (s, 3H), 1.97 - 2.03 (m, 1H), 2.51 (s, 3H), 2.83 - 2.9 (m, 2H, J = 13.4), 3.12 (s, 3H), 3.32 - 3.33 (m, 1H), 3.48 (t, 2H, J = 6.9 Hz), 4.38 (s, 1H), 4.92 (d, 1H, J = 5.34), 5.05 (t, 1H, J = 9.9 Hz), 6.27 (d, 1H, J = 9.4), 7.18 - 7.31(m, 5H), 7.36 (t, 1H, J = 7.1), 7.46 (t, 2H, J = 7.3), 7.55 (d, 2H, J = 7.5).

N,β,β-trimethyl-L-phenylalanil-N-1-[(1S,2E)-4-[(1,1'-biphenyl-4-ylmethyl)amino]-1-isopropyl-3-methyl-4-oxobut-2-enyl]-N₁,3-dimethyl-L-valinamide (89). 1H NMR (CDCl₃) δ 0.79 (d, 3H, J = 6.5 Hz), 0.86 (d, 3H, J = 6.5 Hz), 1.01 (s, 9H), 1.40 (s, 3H), 1.41 (s, 3H), 1.58 (bs, 1H), 1.87 - 1.92 (m, 1H), 1.96 (d, 3H, J = 1.1 Hz), 2.03 (s, 3H), 3.05 (s, 3H), 3.11 (s, 1H), 4.55 (d, 2H, J = 5.6 Hz), 4.84 (d, 1H, J = 9.7 Hz), 5.07 (t, 1H, J = 9.7 Hz), 6.04 (bs, 1H), 6.49 (d, 1H, J = 9.3 Hz), 7.31 - 7.46 (m, 10H), 7.57 (d, 4H, J = 6.7 Hz), 7.88 (d, 1H, J = 9.7 Hz).
(2S)-N-[(1S,2E)-1-isopropyl-3-methyl-4-(4-morpholinyl)-4-oxo-2-butenyl]-N,3,3-
trimethyl-2-[[2S)-3-methyl-2-(methylamino)-3-phenylbutanoyl]amino]butanamide
(90). $^1$H NMR ((CD$_3$)$_2$SO) $\delta$ 0.75 (d, 3H, J = 6.4 Hz), 0.82 (d, 3H, J = 6.4 Hz), 0.98 (s, 9H),
1.24 (s, 3H), 1.39 (s, 3H), 1.79 (d, 3H, J = 1.2 Hz), 1.86 - 1.95 (m, 1H), 2.28 (d, 3H, J = 4.4
Hz), 2.98 (s, 3H), 3.41 (s, 4H), 3.55 (d, 4H, J = 4.4 Hz), 4.4 (d, 1H, J = 10 Hz), 4.76 (d, 1H, J = 8 Hz), 4.93 (t, 1H, J = 10.4 Hz), 5.58 (dd, 1H, J = 1.6 Hz, J = 9.6 Hz), 7.31 (t, 1H, J = 7.2 Hz), 7.41 (t, 2H, J = 7.6 Hz), 7.49 (d, 2H, J = 8 Hz), 7.88 (bs, 1H), 8.69 (d, 1H, J = 8.4 Hz), 8.76 (bs, 1H).

N,β,β-trimethyl-L-phenylalanyl-N$^1$-[(1S,2E)-4-(4-benzylpiperazin-1-yl)-1-isopropyl-3-
methyl-4-oxobut-2-enyl]-N$^1$-3-dimethyl-L-valinamide (91). $^1$H NMR (CDCl$_3$) $\delta$ 0.85 (d,
3H, J = 6.4 Hz), 0.87 (d, 3H, J = 6.8 Hz), 0.9 (s, 9H), 1.43 (s, 3H), 1.5 (s, 3H), 1.89 (d, 3H, J = 1.2 Hz), 1.98 (bs, 1H), 2.63 (s, 3H), 2.82 (d, 1H, J = 6.8 Hz), 2.98 (s, 3H), 3.16-3.5 (bs, 2H), 3.5 - 3.83 (bs, 4H), 4.16 - 4.24 (m, 4H), 4.68 (d, 1H, J = 8 Hz), 4.82 (bs, 1H), 5.59 (d, 1H, J = 9.2 Hz), 6.91 (d, 1H, J = 7.6 Hz), 7.28 - 7.52 (m, 10H).

N,β,β-trimethyl-L-phenylalanyl-N$^1$-[(1S,2E)-1-isopropyl-3-methyl-4-(4-methyl-1-
piperazinyl)-4-oxo-2-butenyl]-N$^1$-3-dimethyl-L-valinamide (92). $^1$H NMR ((CD$_3$)$_2$SO) $\delta$
0.76 (d, 3H, J = 6.4 Hz), 0.83 (d, 3H, J = 6.4 Hz), 1.00 (s, 9H), 1.24 (s, 3H), 1.39 (s, 3H),
1.81 (d, 3H, J = 1.2 Hz), 1.86 - 1.93 (m, 1H), 2.29 (s, 3H), 2.81 (s, 3H), 2.99 (s, 3H), 2.99
(bs, 2H), 3.43 (bs, 2H), 3.43 - 4.42 (bs, 4H), 4.42 (d, 1H, J = 9.6 Hz), 4.77 (d, 1H, J = 8 Hz),
4.95 (t, 1H, J = 10 Hz), 5.68 (dd, 1H, J = 4 Hz, J = 8 Hz), 7.32 (t, 1H, J = 4 Hz), 7.42 (t, 2H,
J = 4 Hz), 7.5 (d, 2H, J = 8 Hz), 7.91 (bs, 1H), 8.72 (d, 1H, J = 8 Hz), 8.73 (bs, 1H), 10.1
(bs, 1H).

(E,4S)-4-[[2S)-3,3-dimethyl-2-[[2S)-3-methyl-2-(methylamino)-3-
phenylbutanoyl]amino]butanoyl](methyl)amino]-N-hydroxy-2,5-dimethyl-2-
hexanamide (93). $^1$H NMR ((CD$_3$)$_2$SO) $\delta$ 0.75 (d, 3H, J = 6.5 Hz), 0.81 (d, 3H, J = 6.5 Hz),
0.98 (s, 9H), 1.24 (s, 3H), 1.39 (s, 3H), 1.77 (d, 3H, J = 1.2 Hz), 1.89 - 1.96 (m, 1H), 2.29 (t,
3H, J = 4.6 Hz), 2.98 (s, 3H), 4.4 (d, 1H, J = 10.2 Hz), 4.77 (d, 1H, J = 8.1 Hz), 4.94 (t, 1H,
J = 10 Hz), 6.17 (d, 1H, J = 8.3 Hz), 7.31 (t, 1H, J = 7.2 Hz), 7.41 (t, 2H, J = 7.4 Hz), 7.49
(d, 2H, J = 7.4 Hz), 7.88 (bs, 1H), 8.69 (d, 1H, J = 8.1 Hz), 8.77 (bs, 1H), 10.7 (bs, 1H).

N,β,β-trimethyl-L-phenylalanyl-N$^1$-[(1S,2E)-1-isopropyl-3-methyl-4-
(octyloxy)-4-oxobut-2-enyl]-N$^1$-3-dimethyl-L-valinamide (94). $^1$H NMR (CDCl$_3$) $\delta$ 0.79
(d, 3H, J = 6.8 Hz), 0.85 (d, 3H, J = 6.4 Hz), 0.85 - 0.90 (m, 6H), 0.88 (t, 3H, J = 6.8 Hz),
1.00 (s, 9H), 1.40 (s, 3H), 1.41 (s, 3H), 1.55 - 1.57 (m, 4H), 1.67 (m, 4H), 1.91 (d, 3H, J = 1.2 Hz), 2.04 (s, 3H), 3.04 (s, 3H), 3.12 (s, 1H), 4.85 (d, 1H, J = 10 Hz), 5.11 (t, 1H, J = 9.6 Hz), 6.65 (dd, 1H, J = 1.6 Hz, J = 9.6 Hz), 7.21 - 7.26 (m, 1H), 7.35 (t, 2H, J = 7.2 Hz), 7.41 (dd, 2H, J = 1.6 Hz, J = 8.8 Hz), 7.88 (d, 1H, J = 9.6 Hz).

Nβββ-trimethyl-L-phenylalanyl-N1-\{(\text{1R,2E})\}-4-\{(4-(benzyloxy)benzyl)\}-1-isopropyl-3-methyl-4-oxobut-2-enyl)-N1,3-dimethyl-L-valinamide (95). $^1$H NMR (CDCl$_3$) δ 0.78 (d, 3H, J = 6.8 Hz), 0.84 (d, 3H, J = 6.4 Hz), 1.00 (s, 9H), 1.40 (s, 3H), 1.41 (s, 3H), 1.86 - 1.88 (m, 1H), 1.91(d, 3H, J = 1.2 Hz), 2.03 (s, 3H), 3.02 (s, 3H), 3.11 (s, 1H), 4.84 (d, 1H, J = 1.0 Hz), 5.07 (s, 2H), 5.10 (s, 2H), 5.12 (t, 1H, J = 4.4 Hz), 6.68 (d, 1H, J = 9.6 Hz), 6.97 (d, 2H, J = 8.8 Hz), 7.23 - 7.44 (m, 12H), 7.87 (d, 1H, J = 10 Hz).

Nβββ-trimethyl-L-phenylalanyl-N1-\{(\text{1S,2E})\}-1-isopropyl-3-methyl-4-oxo-4-(thien-2-ylmethoxy)but-2-enyl]-N1,3-dimethyl-L-valinamide (96). $^1$H NMR (CDCl$_3$) δ 0.78 (d, 3H, J = 6.5 Hz), 0.84 (d, 3H, J = 6.5 Hz), 1.00 (s, 9H), 1.40 (s, 3H), 1.41 (s, 3H), 1.84 - 1.86 (m, 1H), 1.92 (d, 3H, J = 1.2 Hz), 2.04 (d, 3H, J = 2.7 Hz), 3.03 (s, 1H), 3.12 (s, 1H), 4.84 (d, 1H, J = 9.8 Hz), 5.11 (t, 1H, J = 9.9 Hz), 5.34 (s, 2H), 6.69 (d, 1H, J = 9.4 Hz), 7.00 (q, 1H, J = 3.5 Hz), 7.10 (d,1H, J = 3.1 Hz), 7.22 (d,1H, J = 7.0 Hz), 7.32 - 7.41 (m, 5H), 7.88 (d, 1H, J = 9.9 Hz).

$^1$H NMR Assignment of stereochemistry of 36 and 37.

The stereochemistry of the newly formed C-4 stereogenic center in 37 was determined using the J-based configuration analysis method. The $^3$J$_{\text{H-H}}$ coupling constants between the C3 protons and the adjacent methine protons (H2 and H4) were determined using e.COSY experiments.

The coupling constant between H4 and H$_u$ was 11 Hz and the scalar coupling between H4 and H$_d$ was 3 Hz. These values represent "large" and "small" coupling constants respectively. Thus, there were only two possibilities for the rotameric relationship between H4 and the methylene protons on C3 (A and B, Figure 1).
In order to stereospecifically differentiate between these two relationships, the use of two bond and three bond ($^2J_{CH}$ and $^3J_{CH}$) long-range heteronuclear coupling constants was required. These coupling constants were measured using the phase-sensitive G-BIRD$_{hs}$-HSQMB experiment.$^3$

Together with the $^3J_{HH}$ couplings, the heteronuclear coupling constants (H$_u$-C6 = 0 Hz, H$_u$-C4 = 1 Hz, H$_u$-C6 = 1 Hz, H$_u$-C4 = 4 Hz) indicates that only the stereochemical and rotameric relationship shown in Figure 1 is consistent with the NMR data.

Once the prochiral relationship between C3 and C4 was set, the next stage of the analysis was to relate this defined stereochemical relationship to C2. This relative stereochemistry was assigned using the same approach as was used for C4 and C3. The coupling constant between H4 and H$_u$ was 3 Hz and the scalar coupling between H4 and H$_d$ was 11 Hz. Since these values represent “small” and “large” coupling constants respectively, and the relative stereochemistry between C4 and C3 is known, there were two possibilities for the rotameric relationship between H2 and the methylene protons on C3 (C and D, Figure 2).
Once again, the relevant long-range heteronuclear coupling constants (H$_d$-C5 = 1 Hz, H$_d$-C1 = 2 Hz, H$_r$-C5 = 1 Hz, H$_r$-C1 = 5 Hz) could differentiate between the two potential rotamers. Using this information, it was possible to implement the information derived from $^{3}J_{CH}$ heteronuclear coupling constants to assign the relative stereochemistry between the final 2 stereocenters. Because the absolute stereochemistry of the C4 stereocenter was defined in the starting product for the hydrogenation, the configuration of this portion of 37 can be assigned as 2S, 4R.

This result is consistent with the 3 dimensional conformation of 37 predicted from unrestrained molecular dynamics calculations. These calculations were carried out using the Tripos$^\circledR$ force field within the SYBYL$^\circledR$ molecular modeling package. One million iterations in 5 fs steps were performed on a variety of randomized conformations. In all cases, the conformation shown in Figure 2 was returned. As can be seen, the rotameric relationship between C4 and C3 as well as between C3 and C2 match that expected from the J-configuration analysis method.

In addition, the other compound formed from the hydrogenation reaction (36) was modeled in the same manner as for 37. It was assumed that 36 would have the opposite
stereochemistry at C2 (2R, 4R) from 37 (2S, 4R). In all cases a structure was returned which fit with the homonuclear coupling constants determined for H2 and H4 to the diastereotopic methylene protons on C3. This conformation would have required long-range heteronuclear coupling constants that were opposite in magnitude from those determined for 37 for the stereochemical and rotameric relationship between C2, C3, and C4.


Assignment of Stereochemistry of SSS and RSS Diastereomers.

The double-pulsed field gradient spin echo 1D NOE experiment was used for all NOE experiments. NOE data were acquired using THF-$d_6$ as the solvent. This solvent provided a very well dispersed 1D $^1$H NMR spectrum and appeared to encourage the occurrence of one significant solution conformation. This observation was evidenced by the extreme magnitudes of the homonuclear coupling constants (both small and large) for 2. Some of the most important NOE correlations for the analysis of 2 are shown in Figure 3. As can be seen, the strong NOE correlations between the proR-methyl (CH$_3$-20), the N-3 Me, and the tert-butyl group (CH$_3$-12, a-c) require that all of these atoms be on the same face of the molecule. When this information is coupled with the fact that the proS-methyl (CH$_3$-19) shows correlations only to CH$_3$-20 and the H-14 proton, it becomes clear that this methyl must be on the opposite face of the molecule from CH$_3$-20 and the stereochemistry at C-14 must be S. In order to confirm this observation a complementary molecular modeling approach to add confidence to the analysis was employed.
The molecular modeling approach made use of the CONGEN® program and procedure developed by Falk and coworkers\textsuperscript{1} and designed to run with the SYBYL® molecular modeling package. This procedure uses constrained molecular mechanics where the constraints are based on the experimentally derived NOE enhancements. The main feature of this program is a period of high temperature dynamics in which frequent inversions occur at all chiral centers. This allows the distance constraints to guide the molecule into configurations consistent with the NOE data. After generating approximately 500 structures, the correct stereochemistry should be associated with the most prevalent structure returned, and all of these should have very few NOE violations and a very low σ value (rms violation index in angstroms). Any structures with the incorrect stereochemistry will generally be characterized by multiple NOE violations and a high σ value. Structures with the correct stereochemistry, no NOE violations, and a low relative total energy (in Kcal/mol) can be expected to be a good representation of the predominant solution conformation of the molecule of interest.

In the case of 2, the S,S,S stereochemistry was returned each time when the structure was associated with 0 or only 1 NOE violation. In addition, only the S,S,S stereochemistry was associated with structures having a σ value less that 0.5 angstroms. This confidently confirms the stereochemistry of 2 as S,S,S with an rms deviation (σ) of only 0.14 angstrom.

When the same procedure was applied to 41, the R,S,S stereochemistry was the only stereochemical conclusion drawn from the analogous data and results.

### Elemental Analyses

<table>
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<th>Compound</th>
<th>Formula</th>
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<th>found</th>
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</thead>
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<tr>
<td>7 R = CH₃ R₁ = 4-BrPh</td>
<td>C₁₁H₁₁BrO₃</td>
<td>C, 48.73; H, 4.09; N, 0.00.</td>
<td>C, 48.92; H, 4.26; N, 0.00.</td>
</tr>
<tr>
<td>8 R = CH₃ R₁ = 4-BrPh</td>
<td>C₁₂H₁₆BrNO₂</td>
<td>C, 50.37; H, 5.64; N, 4.89.</td>
<td>C, 50.57; H, 5.29; N, 4.91.</td>
</tr>
<tr>
<td>49</td>
<td>C₃₃H₴₂N₃O₄ · 3TFA · 2H₂O</td>
<td>C, 50.48; H, 5.86; N, 4.53.</td>
<td>C, 50.59; H, 5.60; N, 4.79.</td>
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<tr>
<td>15</td>
<td>C₁₇H₃₁NO₄</td>
<td>C, 65.14; H, 9.97; N, 4.47.</td>
<td>C, 65.29; H, 10.29; N, 4.43.</td>
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<tr>
<td>36</td>
<td>C₂₂H₄₃N₃O₄ · 1.5TFA · .15 H₂O</td>
<td>C, 53.46; H, 7.40; N, 2.3.</td>
<td>C, 53.51; H, 7.11; N, 6.15.</td>
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<td>42</td>
<td>C₂₇H₄₅N₃O₄ · 1.4TFA · H₂O</td>
<td>C, 54.93; H, 7.18; N, 6.45.</td>
<td>C, 54.81; H, 7.01; N, 6.57.</td>
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<tr>
<td>47</td>
<td>C₂₇H₄₆N₃O₄ · 1.5TFA</td>
<td>C, 55.35; H, 7.82; N, 6.46.</td>
<td>C, 53.80; H, 8.12; N, 6.14.</td>
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<td>C₂₈H₄₆N₃O₄ · 1.5TFA</td>
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<td>50</td>
<td>C₂₈H₄₅N₃O₄ · 1TFA</td>
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<td>C, 59.90; H, 7.52; N, 6.88.</td>
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<td>51</td>
<td>C₂₈H₄₅N₃O₄ · 0.6TFA · H₂O</td>
<td>C, 59.81; H, 8.05; N, 7.69.</td>
<td>C, 59.49; H, 8.20; N, 7.40.</td>
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<td>C₂₇H₄₁N₃O₄ · 1.25 TFA · 1.5 H₂O</td>
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<td>C₃₃H₄₇N₃O₄ · 1.6 TFA</td>
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<td>C₃₀H₄₇N₃O₄ · 2TFA</td>
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<td>C, 55.38; H, 6.70; N, 5.76.</td>
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<td>C, 55.06; H, 7.09; N, 6.34.</td>
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| 62 | C₂₃H₄₆N₅O₅ · TFA · H₂O | C, 56.16; H, 7.45; C, 55.86; H, 7.23;
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### Analytical HPLC Purity Determinations

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<th>Method C</th>
<th>Method D</th>
<th>Method E</th>
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**Gradient**

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**Injection volume:** 10uL of a 1mM DMSO solutions

**Detection:** DAD, 215nm

**Flow rate:** 1ml/min

**HPLC Method A** - pH1.8

Column: Prodigy ODS3, 150*4.6mm, 5um.

Mobile Phase: A=0.02% TFA water B=0.02%TFA Acetonitrile

**HPLC Method B** - pH6.5

Column: Aqua C18, 150*4.6mm, 5um.

Mobile Phase: A=10mM Ammonium acetate B= Acetonitrile

**HPLC Method C** - pH9.5

S31
Column: Xterra RP18, 150*4.6mm,5μm.
Mobile Phase: A=0.02% Ammonium hydroxide B= Acetonitrile

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<th>Time (min)</th>
<th>%A</th>
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Injection volume: 5 μL of a 2 mM DMSO solution
Detection: DAD, 220nm
Flow rate: 1ml/min

HPLC Method D
Column: Waters Xterra MS C18, 2 mm (i.d.) x 50 mm (length) 3.5 um column, set at 50 °C.
Mobile Phase: A=0.02% formic acid in water B=0.02% formic acid in ACN

HPLC Method E
Column: Polaris C8 - Ether, 2 mm (i.d.) x 30 mm (length), 3 um column, set at 50°C.
Mobile Phase: A=0.05% ammonium hydroxide in water B=0.05% ammonium hydroxide in ACN