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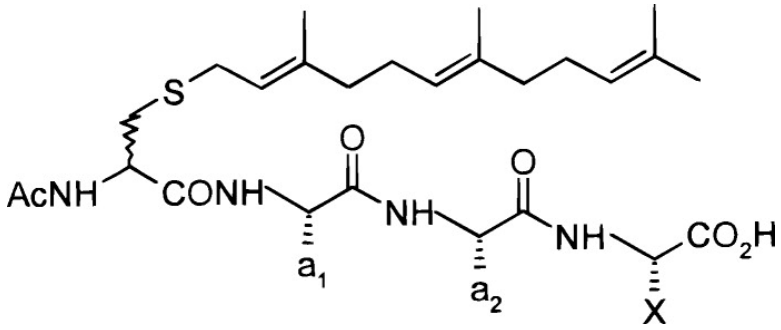

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Solid-Phase Synthesis of a Farnesylated CaaX Peptide Library: Inhibitors of the Ras CaaX Endoprotease†

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A solid-phase method, based on Kaiser's *p*-benzophenone oxime resin, was developed for the synthesis of a series of *N*-acetyl-*S*-(*E*,*E*-farnesylated) Ca_1a_2X tetrapeptides as potential inhibitors of recombinant Ras and **a**-factor converting enzyme (RCE). *N*-Acetyl-*S*-(*E*,*E*-farnesyl)-L-cysteine was coupled to resin-bound a_1a_2 dipeptide using HOBt/DCC activation in conjunction with *N*-BOC chemistry. The protected farnesylated tripeptide was cleaved from the resin with simultaneous addition of the X residue by treating the resin-bound farnesylated Ca_1a_2 tripeptide with L-amino acid benzyl ester tosylates under mildly acidic conditions. The benzyl ester was saponified, and the resulting carboxylate precipitated by ether to afford a library of tetrapeptides as a mixture of diastereomers at the cysteine center. The peptides were evaluated as inhibitors of recombinant yeast RCE endoprotease (yRCE) to obtain information about the affinity of the enzyme for the a_1a_2X portion of the Ca_1a_2X moiety.

Introduction

The posttranslational modification of a variety of eukaryotic proteins with isoprenoid groups is essential for the biological activity of these molecules.[1−3] Proteins with a C-terminal Ca_1a_2X motif, in which C is cysteine, a_1 and a_2 are typically small aliphatic amino acids, are prenylated by farnesyl diphosphate (FPP) when X = A, S, M, N or by geranylgeranyl diphosphate (GGPP) when X = L, F. Two additional processing steps occur in vivo after prenylation of the Ca_1a_2X motif. The first is an endoproteolytic cleavage to release the -a_1a_2X tripeptide, followed by carboxymethylation of the C-terminal isoprenylated cysteine. The Ras and Rho subfamilies of the Ras superfamily of small GTPases, fungal pheromones, nuclear lamins, and GTP-binding proteins are examples of prenylated Ca_1a_2X proteins.

The Ras proteins must be farnesylated in order to localize to the inner surface of the plasma membrane where they participate in the signal transduction network that stimulates cell division.[4−6] Ras oncogenes, which produce defective forms of the proteins, are involved in several forms of cancer, including those of the pancreas, colon, and lung, and inhibition of farnesylation can reverse oncogenic phenotypes. This observation has led to a major effort to find protein farnesyltransferase (PFTase) inhibitors that are effective against Ras-related cancers.[7] Somewhat unexpectedly, animal studies indicate that inhibitors of protein farnesylation have low toxicity and minimal side effects.[8] However, inhibition of Ras farnesylation may not be the source of antitumorgenesis activity, despite the fact that the molecules clearly inhibit PFTase. A recent study demonstrated that an alteration in the ratio of farnesylated and geranylgeranylated RhoB proteins occurs when cells are exposed to PFTase inhibitors. In the absence of farnesylation, RhoB is geranylgeranylated and an increase in the level of geranylgeranylated RhoB protein is associated with a loss of growth-transforming activity, suggesting a Ras-independent mechanism for PFTase inhibitors.[9]

A considerable amount of attention has been recently directed to the protein prenyltransferases and their inhibitors. In contrast, only a few studies of the Ca_1a_2X endoproteases have been reported. Ca_1a_2X prenylprotease[5] activity has been reported in yeast,[10] rat,[11] and bovine[12,13] membrane homogenates, and the rat and bovine enzymes have been partially purified.[12,14,15] These proteases selectively cleave a_1a_2 dipeptides and a_1a_2X tripeptides from substrates with prenylated carboxy-terminal C(prenyl)a_1a_2 and C(prenyl)a_1a_2X motifs.

Two different genes, *AFC1* and *RCE1*, encoding proteins with Ca_1a_2X prenyl protease activity have been identified in yeast.[16] **a**-Factor converting enzyme (AFC) has Ca_1a_2X prenyl protease activity but also cleaves pre-**a**-mating factor toward the N-terminus. Ras and **a**-factor converting enzyme (RCE) has Ca_1a_2X prenyl protease activity and shows selectivity for processing Ras proteins. Both enzymes appear to be polytopic integral membrane proteins that are localized in the endoplasmic reticulum.[17] We recently reported construction of a yeast expression system for overproduction of

† Abbreviations: AFC, **a**-factor converting enzyme; A, L-alanine; D, L-aspartic acid; (*O*-Bz)S, (*O*-benzyl)-L-serine; (*O*-Bz)T, (*O*-benzyl)-L-threonine; *N*-BOC, *N*-*tert*-butoxycarbonyl; (N^{ϵ}-Cbz)K, (N^{ϵ}-carbobenzyloxy)-L-lysine; DCC, *N*-*N*′-dicyclohexylcarbodiimide; DMF, dimethylformamide; EDTA, ethylenediaminetetraacetic acid; F, L-phenylalanine; FABMS, fast atom bombardment mass spectroscopy; G, glycine; Q, L-glutamine; E, L-glutamic acid; t_r, HPLC retention time; HOBt, *N*-hydroxybenzotriazole; I, L-isoleucine; L, L-leucine; M, L-methionine; monoBz, monobenyl ester; PhG, D-phenylglycine; PMSF, phenylmethylsulfonyl fluoride; P, L-proline; PFTase, protein farnesyltransferase; RCE, Ras and **a**-factor converting enzyme; S, L-serine; T, L-threonine; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TLC, thin-layer chromatography; R_f, TLC retention time; V, L-valine; yRCE, yeast RCE.

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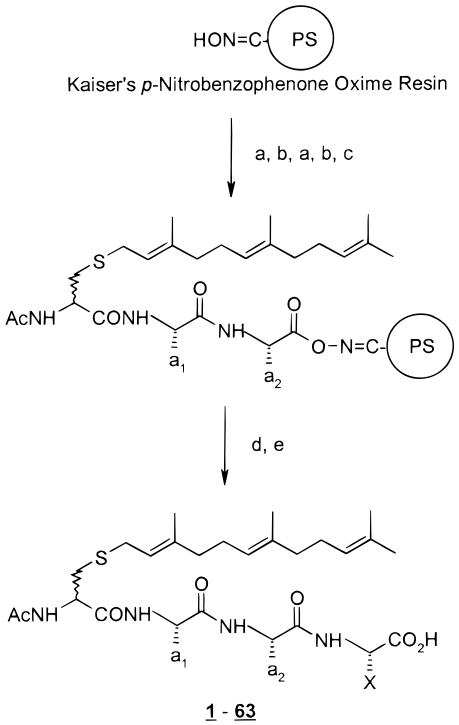
Scheme 1. Synthesis of Farnesylated CaaX Tetrapeptides[a] Using Kaiser's Resin Methodology



1 - **63**

[a] Reagents: (a) *N*-BOC-L-amino acid, DCC, HOBt, THF then Et_3N, CH_2Cl_2; (b)TFA, CH_2Cl_2; (c) *N*-acetyl-(*S*-*E*,*E*-farnesyl)-L-cysteine, DCC, HOBt, THF then Et_3N, CH_2Cl_2; (d) "X" L-amino acid benzyl ester tosylate, Et_3N, HOAc, CH_2Cl_2; (e) aq KOH, THF followed by acidification.

yeast RCE (yRCE).[18] The corresponding human gene (*hRCE1*) has been identified. The yeast and human *RCE1* genes have also been expressed in insect cells.[19] Studies with *RCE1* deficient mice indicate that Ras proteins are mislocalized to the cytosol when endoproteolytic processing is blocked.[20] These results suggest that selective potent inhibitors of RCE endoproteolytic activity are attractive targets for developing anticancer agents.

The pioneering solid-phase methods developed by Merrifield[21] have greatly simplified the multistep synthesis of peptides. We incorporated solid-phase techniques into a strategy for construction of a prenylated tetrapeptide Ca_1a_2X library. Various combinations of the Ca_1a_2X tetrapeptides were generated in good yield utilizing the *p*-benzophenone oxime ester methodology developed by DeGrado and Kaiser.[22] The mildly acidic conditions used for cleaving the peptide from the resin were ideal for preserving the acid-sensitive farnesyl group in the prenylated Ca_1a_2X library. In this paper, we report the synthesis of a family of *N*-acetyl-(*S*-*E*,*E*-farnesylated) Ca_1a_2X tetrapeptides and evaluate the compounds as inhibitors of recombinant Rce1p endoprotease using an avidin−biotin radioassay.[23]

Results and Discussion

The *p*-nitrobenzophenone oxime ester resin was prepared on a 100 g scale using the method of DeGrado and Kaiser (Scheme 1).[22] Briefly, *p*-nitrobenzophenone moieties were appended to polystyrene resin by a Friedel−Crafts acylation, and the ketone moiety was converted to the corresponding oxime by refluxing in hydroxylamine hydrochloride in ethanol and pyridine. Extended reflux (72 h) with vigorous mechanical stirring was required for the reaction to proceed to completion. The loading capacity of the resin, based on nitrogen present in the oxime moiety, was 0.7−0.8 mmol per gram.

N-BOC amino acids were activated with DCC/HOBt in THF at 0 °C. Coupling was conducted in CH_2Cl_2/triethylamine with rotation of the suspension overnight. All of the amino acids we studied loaded smoothly except for *N*-BOC-(*S*-benzyl)-L-cysteine, which consistently gave truncated mixtures despite longer reaction times and use of DMF as a cosolvent in the coupling reaction. It should be noted that the "a_2" amino acid is first attached to the resin followed by elongation of the peptide chain. This elongation order was exploited using various "X" amino acids to produce an array of compounds from a single lot of loaded resin.

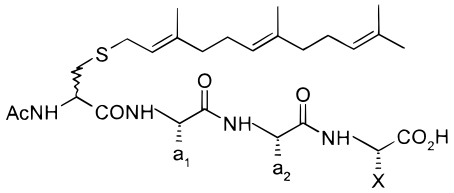
The *N*-BOC protecting group was removed with TFA in CH_2Cl_2 by rotation for a minimum of 1 h in order to avoid incomplete deprotection. Ethylmethyl sulfide was used as a cation scavenger for reactions with resins containing cysteine or methionine residues. Peptide bonds between a_1 and a_2 were formed by neutralization of the resin TFA salt with triethylamine in the presence of the "a_1" L-amino acid HOBt active ester in CH_2Cl_2.

N-Acetyl-L-cysteine was alkylated using either farnesyl chloride or bromide in NH_3/methanol to give the optically active thioether according to the method of Brown.[24] Activation of the *N*-acetyl thioether using DCC/HOBt in THF was accompanied by racemization of the chiral center to give a mixture of diastereomers upon coupling. The diastereomers were used to expand the number of compounds in the library and to probe the effect of stereochemistry at the cysteine center in the enzymatic inhibition assays. Control reactions using the cysteine amino protecting group, 2-(trimethylsilyl)-ethoxycarbonyl carbamate,[25] gave no racemization during activation by DCC/HOBt as determined by ^{13}C NMR and C_{18} HPLC. Racemization was also not detected during synthesis of tripeptides using *N*-BOC protection and DCC/HOBt activation. The synthesis of a representative farnesylated oxime resin, *N*-acetyl-(*S*-(*E*,*E*-farnesyl)-(D,L)-cysteinyl)-L-valinyl-L-isoleucinyl *p*-nitrobenzophenone oxime ester resin, is described in detail in the Experimental Section.

Peptides were cleaved from the resin under mildly acidic conditions using L-amino acid benzyl ester tosylates in CH_2Cl_2 in the presence of equal molar amounts of glacial acetic acid and triethylamine. In early experiments we found that acetate salts of L-amino acid benzyl esters in CH_2Cl_2 failed to remove the peptide. However, the rate of cleavage was substantially greater for tosylate salts of the amino acid benzyl esters,[26] and the tosylate salts were compatible with the acid sensitive farnesyl thioether.

The newly cleaved peptide benzyl esters were subjected to an aqueous workup to remove the slight excess of amino acid benzyl ester used in the cleavage reactions. However, some amino acids, including L-aspartate dibenzyl ester, L-phenylalanine benzyl ester, and L-glutamic acid dibenzyl ester, were not sufficiently soluble in water and were removed by preparative TLC. The diastereomeric benzyl

Table 1. Percent Inhibition[a] of Recombinant yRCE by Tetrapeptides[b]



compd	amino acid a_1	amino acid a_2	amino acid X	%	compd	amino acid a_1	amino acid a_2	amino acid X	%
64	V	I	M	95	**59**[c]	A	D	D	12
61[c]	A	(*S*-Bz)C	D monoBz	97	**22**	A	(*O*-Bz)T	D	7
63[c]	(*S*-Bz)C	F	D monoBz	95	**32**	A	M	A	7
57	A	I	D monoBz	94	**9**, **10**	A	D	A	7
45	V	I	A	93	**13**	A	G	A	3
46	(*O*-Bz)T	F	D	92	**51**	S	F	D	2
60[c]	A	F	D monoBz	89	**53**	D	F	D	2
40	A	V	(N$^{\epsilon}$-Cbz)K	88	negative control				0
49	(N$^{\epsilon}$-Cbz)K	F	D	83	**50**	A	F	D	0
41	A	V	(*S*-Bz)C	80	**47**	E	F	D	0
12	A	L	A	77	**35**	A	I	D	0
30	A	(*S*-Bz)C	A	72	**33**	A	M	D	0
16	A	I	A	70	**25**	A	S	D	0
38	A	V	M	68	**34**	A	A	D	0
43	A	V	I	68	**24**	A	(*O*-Bz)S	D	0
39	A	V	PhG	57	**58**	A	Q	D monoBz	0
55	A	M	D monoBz	54	**36**	A	Q	D	0
27	A	(*O*-Bz)T	A	54	**21**	A	PhG	D	0
48	(*O*-Bz)S	F	D	42	**19**	A	E	D	0
42	A	V	V	41	**20**	A	G	D	0
52	P	F	D	32	**26**	A	T	D	0
31	A	PhG	A	29	**37**	A	P	A	0
17	A	F	A	25	**14**	A	Q	A	0
29	A	(N$^{\epsilon}$-Cbz)K	A	23	**11**	A	E	A	0
56	A	A	D monoBz	19	**15**	A	A	A	0
28	A	(*O*-Bz)S	A	18	**44**	A	V	P	0
7, **8**	A	V	A	15	**62**[c]	A	V	E	0
23	A	(N$^{\epsilon}$-Cbz)K	D	13	**54**	PhG	F	D	0
18	A	L	D	12	**1**, **2**	V	A	D	0

[a] Tested in duplicate at 25 μM. [b] A mixture of diasteromers at the cysteine center. [c] A mixture of diacid and monobenzyl ester.

esters **1**−**10** were purified to homogeneity, and their structures were confirmed by NMR and mass spectroscopy.

The benzyl esters were saponified with KOH, and the progress of the reactions were monitored by TLC. Several of the di- and tribenzyl esters were resistant to complete hydrolysis despite addition of a slight excess of KOH. The hydrolysis mixtures were acidified, and the peptide products were extracted into *n*-butanol. Solvent was removed at reduced pressure, and the residues were triturated with diethyl ether to give the peptides as off-white solids.

Mixtures of acids and monobenzyl esters or cysteine diastereomers were easily resolved by either analytical TLC on silica or by reversed-phase HPLC. The structures of the acids and monobenzyl esters were confirmed by NMR and mass spectroscopy, and their overall purity was determined by HPLC. Representative procedures for the cleavage and saponification steps are described for *N*-acetyl-(*S*-(*E*,*E*-farnesyl)-(D,L)-cysteinyl)-L-valinyl-L-isoleucinyl-L-alanine **45** in the Experimental Section.

Mixtures of tetrapeptides diastereomeric at the cysteine center, mixtures of free acids and monobenzyl esters, and the purified diastereomers, were evaluated as inhibitors of recombinant yRCE[18] using the avidin-mediated assay we developed based on the biotinylated radiolabeled substrate 1-*N*-biotinyl-(13-*N*-succinimidyl-(*S*-(*E*,*E*-farnesyl)-L-cysteinyl)-L-valinyl-L-isoleucinyl-L-[^{14}C]-alanine))-4,7,10-trioxatridecanediamine.[23] A nonhydrolyzable Ca_1a_2X protease inhibitor, **64**, reported by Ma et al.[27] was used as a positive inhibitor control in the assays.

The farnesylated tetrapeptides in our library were obtained in sufficient quantities to use in inhibitor assays. Since synthesis of all possible combinations of the naturally occurring amino acids at the three a_1a_2X positions (20^3 possible combinations) was beyond the scope of the study, we decided initially to vary the side chain at the "a_2" position while fixing the "a_1" amino acid as L-alanine. The "X" amino acid was either L-alanine (nonpolar aliphatic side chain) or L-aspartate (polar side chain) in the first series of peptides. The selection of targets was also guided by the Ca_1a_2X sequences present in nature for vertebrate GTP-binding proteins and fungal mating factors[1,2] and, more generally, by naturally occurring Ca_1a_2X sequences that are prenylated.[28]

The results of the inhibition studies (Table 1) are presented in descending order of potency for inhibition of endoproteolysis catalyzed by recombinant yRCE. A tetrapeptide with

Table 2. Purified Cysteine Center Diastereomer Tetrapeptides and Percentage Inhibition[a] of the Recombinant yRCE

	amino acid			
compd:R_f[b]	a_1	a_2	X	%
5[c]	A	V	F	70
6[c]	A	V	F	33
16:0.45	A	I	A	66
16:0.61	A	I	A	71
38:0.59	A	V	M	57
38:0.49	A	V	M	60
39:0.36	A	V	PhG	48
39:0.46	A	V	PhG	65
12:0.38	A	L	A	39
12:0.58	A	L	A	54
29:0.39	A	(N^{ϵ}-Cbz)K	A	23
29:0.32	A	(N^{ϵ}-Cbz)K	A	16
7[c]	A	V	A	21
8[c]	A	V	A	11
9[c]	A	D	A	9
10[c]	A	D	A	4
27:0.45	A	(*O*-Bz)T	A	7
27:0.33	A	(*O*-Bz)T	A	11
3[c]	A	V	G	4
4[c]	A	V	G	1
1[c]	A	V	D	0
2[c]	A	V	D	0

[a] Tested in duplicate at 25 μM. [b] Silica TLC; 1:10 MeOH:$CHCl_3$ containing 2.5% acetic acid. [c] Diastereomers were separated as benzyl esters and then subjected to saponification.

the natural Ca_1a_2X sequence for yeast **a**-mating factor (CVIA), **45**, gave 93% inhibition under our standard screening conditions. Several trends were seen for the first series of compounds. The three most potent peptides, **57**, **61,** and **63,** all contained an intact aspartate monobenzyl ester in the "X" position. When the benzyl ester in **57** was saponified, the corresponding diacid, **35**, was inactive. In general, little or no inhibitory activity was seen when X = L-aspartate. The most potent inhibitors (80% or greater inhibitory activity) had isoleucine, valine, phenylalanine, or (*S*-benzyl)-cysteine at the "a_2" position. The results for valine or isoleucine were anticipated based on their common occurrence at a_2 in Ca_1a_2X proteins found in nature. However, L-phenylalanine is not found at a_2 for Ca_1a_2X proteins, and (*S*-benzyl)-L-cysteine is not, of course, a natural amino acid. Finally, tetrapeptides **9**, **10**, **11**, and **14** with polar amino acids at a_2 were poor inhibitors. Our results are reminiscent of those made by Jang and Gelb[14] with *N*-acetyl(farnesylated)Ca_1a_2 tripeptides, where they found that peptides with hydrophobic "a_1a_2" dipeptides were the best inhibitors.

On the basis of the potent inhibition seen for **61** and **63**, L-phenylalanine was selected as the "a_2" fixed amino acid, and the "a_1" amino acid was varied with the "X" amino acid fixed as L-aspartate. A slight excess of KOH was sufficient to hydrolyze the benzyl esters, except for those of **60** and **63**. When both of the L-aspartate carboxylates were free acids, the most active compounds (>80% inhibition) in the a_1 series, **46** (a_1 = (*O*-benzyl)-L-threonine) and **49** (a_1 = (N^{ϵ}-Cbz)-L-lysine), both contained large aromatic hydrophobic groups at the "a_1" position. It is interesting to note that tetrapeptide **48** (a_1 = (*O*-benzyl)-L-serine), which differed from **46** by only a single methyl group, was only 50% as potent. The L-serine analogue, **51**, gave barely detectable inhibition. Interestingly, no inhibition was seen for the hydrophobic D-phenylglycine analogue.

Table 3. Inhibition Concentrations (IC_{50}) of Selected Tetrapeptides

compd	IC_{50} (μM)
64	0.103 ± 0.01
45	3.3 ± 0.1
57	17.6 ± 0.5
61	7.3 ± 1.5
63	7.2 ± 0.9
46	15.8 ± 1.7

The effect of the "X" amino acid on inhibitory activity was evaluated by fixing the "a_1a_2" sequence as L-alanine-L-valine. As seen for the other tetrapeptides, large aromatic hydrophobic groups at the "X" position produced the most potent inhibitors. The (N^{ϵ}-Cbz)-L-lysine (**40**) or (*S*-benzyl)-L-threonine (**41**) analogues gave 88% and 80% inhibition, respectively. The methionine (**38**), isoleucine (**43**), phenylglycine (**39**), valine (**41**), and phenylalanine (**5**, **6**) tetrapeptides were moderate inhibitors. Compounds with L-glutamate and L-aspartate at the "X" position and a glycine analogue were not inhibitory.

The effect of stereochemistry for cysteine in the Ca_1a_2X sequence for purified diastereomers is shown in Table 2. None of the stereoisomers was substantially more active than its diastereomeric counterpart (see Table 2).

IC_{50}'s were measured for a group of selected peptides (see Table 3). The natural Ca_1a_2X sequence analogue **45** (fungal mating factor) and **64**, the nonhydrolyzable analogue reported by Ma et al.,[27] were included for comparison. Although **64** was a slightly more potent inhibitor; peptides **46**, **57**, **61**, and **63** are all comparable to **45** with the **a**-mating factor CVIA sequence.

Conclusion

A strategy was developed for the solid-phase synthesis of a library of farnesylated Ca_1a_2X tetrapeptides based on Kaiser's oxime methodology. The penultimate peptides were cleaved from the resin with concomitant introduction of the carboxy-terminal amino acid under mild acidic conditions compatible with the sensitive *S*-farnesyl cysteinyl group. Analysis of a small group of tetrapeptides established that hydrophobic amino acid side chains were preferred at the a_1, a_2, and X positions of the Ca_1a_2X moiety. These results are being extended in a search for more potent inhibitors for the Ras-selective endoproteases.

Experimental Section

General. Amino acids, *N*-BOC protected amino acids, farnesyl bromide, farnesyl chloride, di-*tert*-butyl dicarbonate, *N*,*N*′-dicyclohexylcarbodiimide, and *N*-hydroxybenzotriazole and other chemicals were purchased from Aldrich Chemical Co. Polystyrene resin was purchased from BioRad. L-Amino acid benzyl ester tosylates of glycine, L-alanine, L-aspartic acid, and L-phenylalanine were synthesized by Fischer esterification using benzene, benzyl alcohol, and *p*-toluenesulfonic acid, followed by recrystallization from MeOH and diethyl ether. *N*-BOC protected derivatives of the other amino acids were esterified using (*O*-benzyl)-diisopropylisourea[30] followed by *N*-BOC deprotection with TFA/CH_2Cl_2 in the

presence of 1.0 equiv of *p*-toluenesulfonic acid. The nonhydrolyzable inhibitor **64**, was synthesized as described by Ma et al.[27] Yields are reported for solid peptides after chromatography, saponification, and ether precipitation.

THF was dried and distilled from Na/benzophenone. CH_2Cl_2 was distilled from CaH_2. DMF was vacuum distilled from CaH_2. Analytical TLC was carried out on either E. Merck or Whatman precoated silica gel 60 plates (0.2 mm, aluminum support). Preparative TLC was carried out using E. Merck silica gel 60 glass backed plates. C_{18} reverse-phase HPLC was carried out using Vydac Protein and Peptide column with monitoring at 214 nm. Solvents for C_{18} HPLC were a gradient of 20% acetonitrile and 80% water to 80% acetonitrile and 20% water, each containing 0.1% v/v TFA.

^1H, ^{13}C, and DEPT NMR spectra were obtained on a UNITY Varian 300 MHz spectrometer and are referenced to internal TMS or the residual signal for DMSO-d_6 at 2.50 ppm for ^1H or 39.5 ppm for ^{13}C NMR. Optical rotations were obtained in spectral grade solvents. Infrared spectra were obtained as thin films on NaCl plates. Mass spectra were obtained from the University of Utah Department of Chemistry using either positive or negative ion FAB or electrospray mass spectrometry.

Syntheses. General Peptide Coupling Protocol: Synthesis of *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-valinyl-L-isoleucinyl *p*-Nitrobenzophenone Oxime Ester Resin. A solution of 1.47 g of DCC (7.11 mmol) in 10 mL of THF was added dropwise to a solution of *N*-BOC-L-isoleucine (1.64 g, 7.11 mmol) and HOBt (0.96 g, 7.11 mmol) in 20 mL of anhydrous THF at 0 °C under nitrogen. The reaction mixture was stirred for 3 h while warming to ambient temperature. Solid dicyclohexylurea was removed by filtration through a plug of Celite, and the plug was washed with ice cold THF. THF was removed in vacuo to afford the L-isoleucine active ester.

The isoleucine active ester was dissolved in 100 mL of anhydrous CH_2Cl_2 and transferred to 10.0 g of Kaiser's *p*-nitrobenzophenone oxime resin. Anhydrous triethylamine (0.91 mL, 6.52 mmol) was added, and the mixture was rotated under N_2 overnight. The resin was collected by suction filtration on a medium porosity sintered glass funnel and washed with the following standard solvent wash protocol: (1) four 100 mL portions of CH_2Cl_2; (2) four 100 mL portions of DMF; (3) four 100 mL portions of 2-propanol; and (4) four 100 mL portions of CH_2Cl_2. The resin was dried under high vacuum overnight.

N-BOC-L-valine (1.54 g, 7.11 mmol) was converted to the HOBt active ester as described previously for *N*-BOC-L-isoleucine. The active ester was isolated in a manner similar to the process described above.

The *N*-BOC-L-isoleucinyl resin was suspended in 160 mL of anhydrous CH_2Cl_2, 40 mL of TFA was added, and the suspension was rotated for 1 h under nitrogen. The resin was collection by suction filtration on a medium porosity sintered glass funnel, washed with four 100 mL portions of CH_2Cl_2, and added to a solution of L-valine active ester in 100 mL of anhydrous CH_2Cl_2. Following addition of 2.0 mL of anhydrous triethylamine (14.21 mmol), the flask was rotated under nitrogen overnight. The resin was collected by suction filtration and washed with the four solvent wash protocol described above. The resin was dried under high vacuum overnight to afford 11.32 g of a tan solid.

The *N*-BOC protecting group was removed from 0.51 g of the L-valinyl-L-isoleucinyl resin by rotation for 1 h using 2.5 mL of TFA in 10 mL of CH_2Cl_2. The resin was collected by filtration, washed with CH_2Cl_2, and dried in vacuo.

N-Acetyl-*S*-(*E,E*-farnesyl)-L-cysteine (0.14 g, 0.39 mmol) was converted to the HOBt active ester as described previously for *N*-BOC-L-isoleucine. The racemic active ester was isolated as described above. The active ester was added to 0.51 g of the TFA salt of L-valinyl-L-isoleucinyl resin in CH_2Cl_2 followed by addition of 0.11 mL of anhydrous triethylamine (0.78 mmol). The suspension was rotated overnight, collected by filtration on a sintered glass funnel, and washed with the four solvent protocol. The resin was dried under high vacuum overnight to afford 0.51 g of *N*-acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-valinyl-L-isoleucinyl resin as a tan solid.

General Peptide Cleavage and Saponification Protocol: *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-valinyl-L-isoleucinyl-L-alanine 45. Glacial acetic acid (61 μL, 1.06 mmol) and 148 μL of anhydrous triethylamine (1.06 mmol) were added to a slurry of 0.51 g of *N*-acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-valinyl-L-isoleucinyl resin and 0.36 g L-alanine benzyl ester tosylate (1.06 mmol) in 10 mL of anhydrous CH_2Cl_2. The slurry was rotated for 44 h. The resin was collected by filtration and washed with three 20 mL portions of CH_2Cl_2. The combined filtrates were washed with 50 mL of 1 M aqueous acetic acid, 50 mL of saturated $NaHCO_3$ and 50 mL of brine. The organic phase was dried over anhydrous $MgSO_4$ and filtered. Solvent was removed at reduced pressure to afford 0.15 g of a crude oil that was purified by preparative silica TLC (1:20 MeOH:$CHCl_3$) to afford 0.13 g of the benzyl ester as an oil.

KOH (1.34 mL, 0.25 M, 0.33 mmol) was added dropwise to a solution of the benzyl ester (0.13 g, 0.17 mmol) in 1.7 mL of freshly distilled THF. The mixture was stirred for 24 h, at which time TLC analysis indicated no benzyl ester was present. The THF was evaporated in vacuo, and the residue was dissolved in 20 mL of distilled water. The aqueous phase was extracted with 30 mL of diethyl ether, and the ether was discarded. The aqueous phase was acidified with 15 mL of 1 M acetic acid, and the resulting milky white suspension was extracted with three 25 mL portions of water-saturated *n*-butanol. The solvent was removed in vacuo, and the residue was triturated with 10 mL of diethyl ether to afford a white solid. This material was collected by filtration, washed with diethyl ether, and dried in vacuo to afford 75 mg of **45** (68%): ^1H NMR (DMSO-d_6) δ 7.70−8.24 (m, 4, NH), 5.16 (t, 1, J = 7.8 Hz, olefinic H), 5.00−5.10 (m, 2, olefinic H), 4.42−4.64 (m, 1, α CH), 4.08−4.26 (m, 3, α CH), 3.10−3.25 (m, 2, allylic CH_2S), 2.46−2.60 (m, 2, CH_2S), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.66−1.80 (m, 1, β CH), 1.60−1.66 (s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.32−1.50 (m, 1, diastereotopic CH_2), 1.24 (d, 3, CH_3), 0.98−1.16 (m, 1, diastereotopic CH_2), 0.74−0.88 (m, 12, CH_3); ^{13}C NMR (DMSO-d_6) δ 173.94, 170.54, 170.45, 170.35, 169.20, 169.09, 138.28,

134.56, 130.66, 124.14, 123.68, 120.36, 120.28, 57.63 (m), 56.44 (m), 52.39, 52.20, 47.52, 39.11, 36.72 (m), 32.84 (m), 30.53 (m), 28.94, 28.68, 26.20, 25.92, 25.53, 24.18, 22.46, 19.29, 19.17, 17.98, 17.58, 17.14, 15.82, 15.20, 11.00 ppm; HPLC t_R = 16.01 (67%) and 17.18 (29%) min; Positive ion Electrospray MS: Calculated: $C_{34}H_{59}N_4O_6S_1$ *m/z* 651.4 (M + H), $C_{34}H_{58}N_4O_6S_1Na_1$ *m/z* 673.4 (M + Na); Found: *m/z* 651.8 (M + H), 673.7 (M + Na).

Biotin/Avidin-Binding Protease Assays. Assays (50 μL total volume) contained AC-P139 membranes (0.26 μg of protein), 25 μM of the tetrapeptide being evaluated and the radiolabeled (1-*N*-Biotinyl-(13-*N*-succinimidyl-(*S*-(*E*,*E*-farnesyl)-L-cysteinyl)-L-valinyl-L-isoleucinyl-L-[^{14}C]-alanine))-4,7,10-trioxatridecanediamine)[23] in 100 mM Tris buffer, pH 7.4, containing 0.5 mM 1,10-phenanthroline, and 1 mM PMSF. Reactions were initiated by the addition of the biotinylated substrate in 2.5 μL of DMF (final concentration of 2 μM). After incubation for 15 min at 37 °C, yRCE was inactivated by heating at 80 °C for 5 min. The incubation mixtures were briefly cooled on ice, avidin resin (150 μL, Pierce) was added, and the material was allowed to stand at room temperature for 15 min with frequent mixing. Assay buffer (150 μL) was added, the tubes were centrifuged for 1 min, and radioactivity in a 200 μL sample of the supernatant was measured by liquid scintillation spectrometry.

Library Compounds Obtained after Complete Saponification. 1. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-cysteinyl)-L-alaninyl-L-valinyl-L-aspartic acid (1 diastereomer): 14.6 mg; ^{1}H NMR (DMSO-d_6) δ 8.05−8.15 (m, 3, NH), 7.68 (d, 1, *J* = 9.6 Hz, NH), 5.12−5.22 (m, 1, olefinic H), 5.00−5.10 (m, 2, olefinic H), 4.42−4.56 (m, 2, α CH), 4.10−4.18 (m, 1, α CH), 4.14−4.24 (m, 1, α CH), 3.16 (d, 2, *J* = 7.5 Hz, allylic CH_2S), 2.54−2.80 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 9, allylic CH_2 and β CH), 1.84 (s, 3, $COCH_3$), 1.63 (s, 3, vinylic CH_3), 1.61 (s, 3, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.20 (d, 3, *J* = 7.2 Hz, CH_3), 0.83 (q, 6, *J* = 6.9 Hz and 7.2, CH_3); HPLC t_R = 10.13 min; Positive ion FABMS using the matrix glycerol/MeOH: Calculated: $C_{32}H_{53}N_4O_8S_1$ *m/z* 653 (M + H), $C_{32}H_{52}N_4O_8S_1Na_1$ *m/z* 675 (M + Na); Found: *m/z* 653 (M + H), 675 (M + Na).

2. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-cysteinyl)-L-alaninyl-L-valinyl-L-aspartic acid (1 diastereomer): 13.1 mg; ^{1}H NMR (DMSO-d_6) δ 8.34 (d, 1, *J* = 6.9 Hz, NH), 8.05−8.20 (m, 2, NH), 7.75 (d, 1, *J* = 8.1 Hz, NH), 5.12−5.20 (m, 1, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.10−4.54 (m, 3, α CH), 4.10−4.20 (m, 1, α CH), 3.14−3.20 (m, 2, allylic CH_2S), 2.52−2.72 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 9, allylic CH_2 and β CH), 1.83 (s, 3, $COCH_3$), 1.60−1.64 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.20 (d, 3, *J* = 6.9 Hz, CH_3), 0.82 (t, 6, *J* = 6.6 and 6.9 Hz, CH_3); HPLC t_R = 10.99 min; High-resolution positive ion FABMS using the matrix 3-nitrobenzyl alcohol/1:1 $CHCl_3$:MeOH: Calculated: $C_{32}H_{53}N_4O_8S_1$ *m/z* 653.3584 (M + H), $C_{32}H_{52}N_4O_8S_1Na_1$ 675.3404 (M + Na). Found: *m/z* 653.3511 (M + H), 675.3360 (M + Na).

3. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-cysteinyl)-L-alaninyl-L-valinyl-glycine (1 diastereomer): 18.7 mg; ^{1}H NMR (DMSO-d_6) δ 8.24 (d, 2, *J* = 6.6 Hz, NH), 8.16 (d, 1, *J* = 7.8 Hz, NH), 7.64 (d, 1, *J* = 9.0 Hz, NH), 5.12−5.20 (m, 1, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.40−4.50 (m, 1, α CH), 4.28−4.36 (m, 1, α CH), 4.10−4.22 (m, 1, α CH), 3.74−3.82 (m, 1, glycine CH_2), 3.16 (d, 2, *J* = 6.9 Hz, allylic CH_2S), 2.70−2.78 (m, 1, CH_2S), 2.50−2.88 (m, 1, CH_2S), 1.88−2.08 (m, 9, allylic CH_2 and β CH), 1.84 (s, 3, $COCH_3$), 1.63 (s, 3, vinylic CH_3), 1.62 (s, 3, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.20 (d, 3, *J* = 6.9 Hz, CH_3), 0.84 (q, 6, *J* = 6.6 and 6.9 Hz, CH_3); HPLC t_R = 12.16 min; Positive ion FABMS using MeOH: Calculated: $C_{30}H_{51}N_4O_6S_1$ *m/z* 595 (M + H), Found: *m/z* 595 (M + H); Negative ion FABMS using MeOH: Calculated: $C_{30}H_{49}N_4O_6S_1$ *m/z* 593 (M − H), Found: *m/z* 593 (M − H).

4. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-cysteinyl)-L-alaninyl-L-valinyl-glycine (1 diastereomer): 11.5 mg; ^{1}H NMR (DMSO-d_6) δ 8.39 (d, 2, *J* = 7.2 Hz, NH), 8.18 (d, 1, *J* = 7.5 Hz, NH), 7.68 (d, 1, *J* = 9.9 Hz, NH), 5.12−5.20 (m, 1, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.40−4.50 (m, 1, α CH), 4.30−4.38 (m, 1, α CH), 4.12−4.20 (m, 1, α CH), 3.62−3.82 (m, 1, glycine CH_2), 3.14−3.18 (m, 2, allylic CH_2S), 2.62−2.72 (m, 1, CH_2S), 2.52−2.60 (m, 1, CH_2S), 1.88−2.10 (m, 9, allylic CH_2 and β CH), 1.83 (s, 3, $COCH_3$), 1.62 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.19 (d, 3, *J* = 6.9 Hz, CH_3), 0.84 (t, 6, *J* = 5.7 and 6.0 Hz, CH_3); HPLC t_R = 12.64 min; Positive ion FABMS using MeOH: Calculated: $C_{30}H_{51}N_4O_6S_1$ *m/z* 595 (M + H), Found: *m/z* 595 (M + H); Negative ion FABMS using MeOH: Calculated: $C_{30}H_{49}N_4O_6S_1$ *m/z* 593 (M − H), Found: *m/z* 593 (M − H).

5. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-cysteinyl)-L-alaninyl-L-valinyl-L-phenylalanine (1 diastereomer): 3.8 mg; ^{1}H NMR (DMSO-d_6) δ 8.30−8.38 (m, 1, NH), 8.10−8.22 (m, 2, NH), 7.64−7.74 (m, 1, NH), 7.14−7.26 (m, 5, aromatic H), 5.16 (t, 1, *J* = 6.9 and 8.1 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.24−4.56 (m, 3, α CH), 4.10−4.20 (m, 1, α CH), 3.00−3.25 (m, 3, allylic CH_2S and benzylic CH_2), 2.98−3.10 (m, 1, allylic CH_2S), 2.82−2.96 (m, 1, CH_2S), 2.62−2.76 (m, 1, CH_2S), 1.88−2.10 (m, 9, allylic CH_2 and β CH), 1.83 (s, 3, $COCH_3$), 1.62 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.10−1.26 (m, 3, CH_3), 0.70−0.90 (m, 6, CH_3); HPLC t_R = 14.85 min; Positive ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{37}H_{57}N_4O_6S_1$ *m/z* 685 (M + H), Found: *m/z* 685 (M + H).

6. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-cysteinyl)-L-alaninyl-L-valinyl-L-phenylalanine (1 diastereomer): 9.1 mg; ^{1}H NMR (DMSO-d_6) δ 8.12−8.24 (m, 3, NH), 7.58−7.72 (m, 1, NH), 7.14−7.28 (m, 5, aromatic H), 5.16 (t, 1, *J* = 6.9 and 8.1 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.24−4.54 (m, 3, α CH), 4.10−4.20 (m, 1, α CH), 3.00−3.25 (m, 3, allylic CH_2S and benzylic CH_2), 2.98−3.10 (m, 1, allylic CH_2S), 2.83−2.94 (m, 1, CH_2S), 2.68−2.78 (m, 1, CH_2S), 1.88−2.10 (m, 9, allylic CH_2 and β CH), 1.84 (s, 3, $COCH_3$), 1.63 (s, 3, vinylic CH_3), 1.61 (s, 3, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.12−1.26 (m, 3, CH_3), 0.74−0.86 (m, 6, CH_3); HPLC t_R = 14.61 min; Positive ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{37}H_{57}N_4O_6S_1$ *m/z* 685 (M + H), Found: *m/z* 685 (M + H).

7. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-cysteinyl)-L-alaninyl-L-valinyl-L-alanine (1 diastereomer): 1.7 mg; ^{1}H NMR (DMSO-d_6) δ 8.36 (d, 1, *J* = 7.5 Hz, NH), 8.10−8.22 (m,

2, NH), 7.64−7.74 (m, 1, NH), 5.16 (t, 1, J = 6.9 and 7.5 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.26−4.56 (m, 2, α CH), 4.06−4.22 (m, 2, α CH), 3.10−3.24 (m, 2, allylic CH_2S), 2.62−2.76 (m, 2, CH_2S), 1.88−2.10 (m, 9, allylic CH_2 and β CH), 1.83 (s, 3, $COCH_3$), 1.63 (br d, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.14−1.32 (m, 6, CH_3), 0.78−0.92 (m, 6, CH_3); HPLC t_R = 12.52 min; Positive ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{31}H_{53}N_4O_6S_1$ *m/z* 609 (M + H), Found: *m/z* 609 (M + H).

8. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-cysteinyl)-L-alaninyl-L-valinyl-L-alanine (1 diastereomer): 1.0 mg; ^{1}H NMR (DMSO-d_6) δ 8.10−8.45 (m, 3, NH), 7.60−7.78 (m, 1, NH), 5.12−5.22 (m, 1, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.26−4.56 (m, 2, α CH), 4.04−4.22 (m, 2, α CH), 3.10−3.24 (m, 2, allylic CH_2S), 2.68−2.80 (m, 2, CH_2S), 1.88−2.10 (m, 9, allylic CH_2 and β CH), 1.84 (s, 3, $COCH_3$), 1.63 (br d, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.18−1.34 (m, 6, CH_3), 0.78−0.92 (m, 6, CH_3); HPLC t_R = 12.04 min; Positive ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{31}H_{53}N_4O_6S_1$ *m/z* 609 (M + H), Found: *m/z* 609 (M + H).

9. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-cysteinyl)-L-alaninyl-L-aspartate-L-alanine (1 diastereomer): 4.0 mg; ^{1}H NMR (DMSO-d_6) δ 7.78−8.60 (m, 4, NH), 5.20−5.38 (m, 1, olefinic H), 5.00−5.18 (m, 2, olefinic H), 4.04−4.80 (m, 4, α CH), 3.10−3.20 (m, 2, allylic CH_2S), 2.50−2.80 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.63 (s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.08−1.30 (m, 6, CH_3); HPLC t_R = 9.73 min; Positive ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{30}H_{48}N_4O_8S_1$ *m/z* 625 (M + H), Found: *m/z* 625 (M + H).

10. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-cysteinyl)-L-alaninyl-L-aspartate-L-alanine (1 diastereomer): 4.0 mg; ^{1}H NMR (DMSO-d_6) δ 7.90−8.50 (m, 4, NH), 5.20−5.32 (m, 1, olefinic H), 5.00−5.12 (m, 2, olefinic H), 4.04−4.80 (m, 4, α CH), 3.10−3.20 (m, 2, allylic CH_2S), 2.40−2.75 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.63 (s, 6, vinylic CH_3), 1.56 (s, 6, vinylic CH_3), 1.08−1.30 (m, 6, CH_3); HPLC t_R = 9.23 min; Negative ion FABMS using the matrix triethanolamine/*n*-butanol: Calculated: $C_{30}H_{48}N_4O_8S_1$ *m/z* 623 (M − H), Found: *m/z* 623 (M − H).

11. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-glutamyl-L-alanine (2 diastereomers): 10.7 mg; ^{1}H NMR (DMSO-d_6) δ 7.84−8.46 (m, 4, NH), 5.16 (t, 1, J = 7.8 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.38−4.50 (m, 1, α CH), 4.20−4.36 (m, 2, α CH), 4.10−4.16 (m, 1, α CH), 3.10−3.20 (m, 2, allylic CH_2S), 2.62−2.80 (m, 1, CH_2S), 2.50−2.60 (m, 1, CH_2S), 2.25 (t, 2, J = 6.9 and 7.8 Hz, CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.66−1.80 (m, 2, CH_2), 1.63 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.22 (t, 6, J = 7.2 and 7.8 Hz, CH_3); HPLC t_R = 9.41 (39%) and 10.27 (54%) min; Positive ion FABMS using the matrix 3-nitrobenzyl alcohol/*n*-butanol: Calculated: $C_{31}H_{51}N_4O_8S_1$ *m/z* 639 (M + H), Found: *m/z* 639 (M + H).

12. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-leucinyl-L-alanine (2 diastereomers): 26.3 mg; ^{1}H NMR (DMSO-d_6) δ 7.76−8.50 (m, 4, NH), 5.16 (t, 1, J = 7.2 and 7.8 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.36−4.50 (m, 1, α CH), 4.18−4.36 (m, 2, α CH), 4.00−4.16 (m, 1, α CH), 3.17 (d, 2, J = 7.8 Hz, allylic CH_2S), 2.62−2.80 (m, 1, CH_2S), 2.50−2.60 (m, 1, CH_2S), 1.88−2.10 (m, 9, allylic CH_2 and δ CH), 1.84 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.63 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.38−1.52 (m, 2, β CH_2), 1.16−1.30 (m, 6, CH_3), 0.78−0.92 (m, 6, CH_3); HPLC t_R = 12.96 (48%) and 13.49 (47%) min; Positive ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{32}H_{54}N_4O_6S_1$ *m/z* 623 (M + H), Found: *m/z* 623 (M + H).

Purified Diastereomers: R_f 0.38 (silica TLC using 1:10 MeOH:$CHCl_3$ plus 2.5% v/v acetic acid, 2 elutions): 3.9 mg; ^{1}H NMR (DMSO-d_6) δ 8.19 (d, 2, J = 8.1 Hz, NH), 8.03 (d, 1, J = 8.1 Hz, NH), 7.69 (br d, 1, NH), 5.16 (t, 1, J = 7.2 and 7.8 Hz, olefinic H), 5.06 (t, 2, J = 5.7 and 6.6 Hz, olefinic H), 4.44 (q, 1, J = 13.8 Hz, α CH), 4.12−4.32 (m, 2, α CH), 3.77 (br s, 1, α CH), 3.17 (d, 2, J = 8.1 Hz, allylic CH_2S), 2.74 (dd, 1, J = 5.4 Hz, CH_2S), 2.50−2.60 (m, 1, CH_2S obscured by DMSO-d_6 signal), 1.88−2.10 (m, 9, allylic CH_2 and δ CH), 1.84 (s, 3, $COCH_3$), 1.63 (s, 3, vinylic CH_3), 1.62 (s, 3, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.38−1.52 (m, 2, β CH_2), 1.24 (d, 3, J = 7.2 Hz, CH_3), 1.16 (d, 3, J = 6.9 Hz, CH_3), 0.86 (d, 3, J = 6.3 Hz, CH_3), 0.80 (d, 3, J = 6.3 Hz, CH_3); HPLC t_R = 14.60 min; Positive ion electrospray MS: Calculated: $C_{32}H_{55}N_4O_6S_1$ *m/z* 623.4 (M + H), $C_{32}H_{54}N_4O_6S_1Na_1$ *m/z* 645.3 (M + Na); Found: *m/z* 623.3 (M + H), *m/z* 645.3 (M + Na).

R_f 0.58 (silica TLC using 1:10 MeOH:$CHCl_3$ plus 2.5% v/v acetic acid, 2 elutions): 3.3 mg; ^{1}H NMR (DMSO-d_6) δ 8.37 (d, 1, J = 7.2 Hz, NH), 8.28 (d, 1, J = 7.5 Hz, NH), 7.97 (d, 1, J = 7.8 Hz, NH), 7.72 (d, 1, J = 5.4 Hz, NH), 5.16 (t, 1, J = 7.2 and 8.4 Hz, olefinic H), 5.06 (t, 2, J = 5.7 and 6.6 Hz, olefinic H), 4.43 (q, 1, J = 14.4 and 14.7 Hz, α CH), 4.14−4.32 (m, 2, α CH), 3.87 (br s, 1, α CH), 3.17 (d, 2, J = 7.5 Hz, allylic CH_2S), 2.67 (dd, 1, J = 6.6 and 6.3 Hz, CH_2S), 2.50−2.60 (m, 1, CH_2S obscured by DMSO-d_6 signal), 1.88−2.10 (m, 9, allylic CH_2 and δ CH), 1.83 (s, 3, $COCH_3$), 1.63 (s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.38−1.52 (m, 2, β CH_2), 1.16−1.26 (m, 6, CH_3), 0.87 (d, 3, J = 6.3 Hz, CH_3), 0.81 (d, 3, J = 6.3 Hz, CH_3); HPLC t_R = 15.14 min; Positive ion electrospray MS: Calculated: $C_{32}H_{55}N_4O_6S_1$ *m/z* 623.4 (M + H), $C_{32}H_{54}N_4O_6S_1Na_1$ *m/z* 645.3 (M + Na); Found: *m/z* 623.2 (M + H), *m/z* 645.3 (M + Na).

13. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-glycinyl-L-alanine (2 diastereomers): 9.3 mg; ^{1}H NMR (DMSO-d_6) δ 7.90−8.50 (m, 4, NH), 5.12−5.25 (m, 1, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.38−4.50 (m, 1, α CH), 4.10−4.36 (m, 2, α CH), 3.70 (d, 2, J = 5.7 Hz, glycine CH_2), 3.14−3.24 (m, 2, allylic CH_2S), 2.72−2.80 (m, 1, CH_2S), 2.50−2.60 (m, 1, CH_2S), 1.88−2.10 (m, 8, allylic CH_2), 1.85 (br s, 3, $COCH_3$), 1.63 (br s, 6, vinylic CH_3), 1.56 (s, 6, vinylic CH_3), 1.20−1.34 (m, 6, CH_3); HPLC t_R = 10.60 min; Mass Spectra: Positive ion FABMS using the matrix 3-nitrobenzyl alcohol/*n*-butanol: Calculated: $C_{28}H_{47}N_4O_6S_1$ *m/z* 567 (M + H), Found: *m/z* 567 (M + H).

14. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-glutaminyl-L-alanine (2 diastereomers): 10.3 mg; ^{1}H

NMR (DMSO-d_6) δ 7.80−8.46 (m, 4, NH), 7.24 (d, 1, J = 5.4 Hz, $CONH_2$), 6.76 (s, 1, $CONH_2$), 5.17 (t, 1, J = 7.2 and 8.7 Hz, olefinic H), 5.02−5.12 (m, 2, olefinic H), 4.38−4.50 (m, 1, α CH), 4.16−4.34 (m, 2, α CH), 4.06−4.16 (m, 1, α CH), 3.10−3.22 (m, 2, allylic CH_2S), 2.62−2.80 (m, 1, CH_2S), 2.50−2.60 (m, 4, CH_2S and CH_2CO), 1.88−2.16 (m, 10, allylic CH_2 and CH_2), 1.85 (s, 3, $COCH_3$), 1.84 (s, 3, $COCH_3$), 1.66−1.78 (m, 2, CH_2), 1.63 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.18−1.30 (m, 6, CH_3); HPLC t_R = 8.51 (57%) and 9.23 (43%) min; Positive ion FABMS using the matrix 3-nitrobenzyl alcohol/*n*-butanol: Calculated: $C_{31}H_{52}N_5O_7S_1$ *m*/*z* 638 (M + H), Found: *m*/*z* 638 (M + H).

15. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-alaninyl-L-alanine (2 diastereomers): 14.1 mg; ^{1}H NMR (DMSO-d_6) δ 7.80−8.50 (m, 4, NH), 5.12−5.25 (m, 1, olefinic H), 5.02−5.12 (m, 2, olefinic H), 4.00−4.50 (m, 4, α CH), 3.15−3.20 (m, 2, allylic CH_2S), 2.68−2.76 (m, 1, CH_2S), 2.50−2.60 (m, 1, CH_2S), 1.88−2.10 (m, 8, allylic CH_2), 1.85 (br s, 3, $COCH_3$), 1.63 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.00−1.30 (m, 9, CH_3); HPLC t_R = 10.34 min; Positive ion FABMS using the matrix 3-nitrobenzyl alcohol/*n*-butanol: Calculated: $C_{29}H_{49}N_4O_6S_1$ *m*/*z* 581 (M + H), Found: *m*/*z* 581 (M + H).

16. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-isoleucinyl-L-alanine (2 diastereomers): 34.4 mg; ^{1}H NMR (DMSO-d_6) δ 8.10−8.40 (m, 3, NH), 7.60−7.76 (m, 1, NH), 5.12−5.25 (m, 1, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.40−4.55 (m, 1, α CH), 4.25−4.38 (m, 1, α CH), 4.06−4.22 (m, 2, α CH), 3.10−3.24 (m, 2, allylic CH_2S), 2.62−2.80 (m, 1, CH_2S), 2.50−2.60 (m, 1, CH_2S), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (br s, 3, $COCH_3$), 1.66−1.80 (m, 1, β CH), 1.63 (s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.38−1.50 (m, 1, diastereotopic CH_2), 1.15−1.30 (m, 6, CH_3), 0.98−1.10 (m, 1, diastereotopic CH_2), 0.74−0.90 (m, 6, CH_3); HPLC t_R = 12.89 (54%) and 13.33 (46%) min; Positive ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{32}H_{55}N_4O_6S_1$ *m*/*z* 623 (M + H), Found: *m*/*z* 623 (M + H).

Purified Diastereomers: R_f 0.45 (silica TLC using 1:10 MeOH:$CHCl_3$ plus 2.5% v/v acetic acid, 2 elutions): 3.0 mg; ^{1}H NMR (DMSO-d_6) δ 8.16 (t, 2, J = 7.5 and 8.1 Hz, NH), 7.74−7.90 (m, 2, NH), 5.17 (t, 1, J = 6.9 and 7.8 Hz, olefinic H), 5.00−5.10 (m, 2, olefinic H), 4.38−4.50 (m, 1, α CH), 4.26−4.37 (m, 1, α CH), 4.06−4.16 (m, 1, α CH), 3.80−3.94 (m, 1, α CH), 3.16 (d, 2, J = 7.8 Hz, allylic CH_2S), 2.74 (dd, 1, J = 5.4 and 5.7 Hz, CH_2S), 2.50−2.60 (m, 1, CH_2S obscured by the DMSO-d_6 signal), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.70−1.80 (m, 1, β CH), 1.63 (s, 3, vinylic CH_3), 1.62 (s, 3, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.32−1.46 (m, 1, diastereotopic CH_2), 1.15−1.26 (m, 6, CH_3), 1.00−1.14 (m, 1, diastereotopic CH_2), 0.74−0.84 (m, 6, CH_3); HPLC t_R = 13.85 min; Positive ion electrospray MS: Calculated: $C_{32}H_{55}N_4O_6S_1$ *m*/*z* 623.4 (M + H), $C_{32}H_{54}N_4O_6S_1Na_1$ *m*/*z* 645.4 (M + Na); Found: *m*/*z* 623.3 (M + H), *m*/*z* 645.2 (M + Na).

R_f 0.61 (silica TLC using 1:10 MeOH:$CHCl_3$ plus 2.5% v/v acetic acid, 2 elutions): 2.2 mg; ^{1}H NMR (DMSO-d_6) δ 8.24−8.36 (m, 2, NH), 8.00 (d, 1, J = 8.7 Hz, NH), 7.48 (d, 1, J = 5.1 Hz, NH), 5.16 (t, 1, J = 6.9 and 8.1 Hz, olefinic H), 5.00−5.10 (m, 2, olefinic H), 4.44−4.54 (m, 1, α CH), 4.30−4.42 (m, 1, α CH), 4.00−4.08 (m, 1, α CH), 3.50−3.62 (m, 1, α CH), 3.16 (d, 2, J = 7.8 Hz, allylic CH_2S), 2.69 (dd, 1, J = 6.3 and 6.0 Hz, CH_2S), 2.50−2.60 (m, 1, CH_2S obscured by the DMSO-d_6 signal), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.74−1.82 (m, 1, β CH), 1.63 (s, 3, vinylic CH_3), 1.62 (s, 3, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.32−1.42 (m, 1, diastereotopic CH_2), 1.24 (d, 3, J = 7.2 Hz, CH_3), 1.12 (d, 3, J = 6.6 Hz, CH_3), 1.00−1.10 (m, 1, diastereotopic CH_2), 0.76−0.86 (m, 6, CH_3); HPLC t_R = 14.34 min; Positive ion electrospray MS: Calculated: $C_{32}H_{55}N_4O_6S_1$ *m*/*z* 623.4 (M + H), $C_{32}H_{54}N_4O_6S_1Na_1$ *m*/*z* 645.4 (M + Na); Found: *m*/*z* 623.2 (M + H), *m*/*z* 645.2 (M + Na).

17. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-phenylalaninyl-L-alanine (2 diastereomers): 16.8 mg; ^{1}H NMR (DMSO-d_6) δ 7.80−8.50 (m, 4, NH), 7.10−7.30 (m, 5, aromatic H), 5.16 (t, 1, J = 6.9 and 7.8 Hz, olefinic H), 5.00−5.10 (m, 2, olefinic H), 4.32−4.54 (m, 2, α CH), 4.06−4.26 (m, 2, α CH), 3.00−3.25 (m, 4, allylic CH_2S and benzylic CH_2), 2.50−2.85 (m, 2, CH_2S), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.63 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.25−1.34 (m, 6, CH_3); HPLC t_R = 13.43 (49%) and 14.29 (51%) min; Positive ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{35}H_{53}N_4O_6S_1$ *m*/*z* 657 (M + H), Found: *m*/*z* 657 (M + H).

***18*. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-leucinyl-L-aspartic acid** (2 diastereomers): 25.3 mg; ^{1}H NMR (DMSO-d_6) δ 7.80−8.40 (m, 4, NH), 5.16 (t, 1, J = 7.5 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.38−4.50 (m, 2, α CH), 4.20−4.34 (m, 2, α CH), 3.10−3.24 (m, 2, allylic CH_2S), 2.50−2.90 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 9, allylic CH_2 and δ CH), 1.84 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.63 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.38−1.50 (m, 2, β CH_2), 1.21 (d, 3, J = 6.9 Hz, CH_3), 0.78−0.90 (m, 6, CH_3); HPLC t_R = 11.42 (52%) and 12.07 (48%) min; Negative ion FABMS using the matrix 3-nitrobenzyl alcohol/*n*-butanol: Calculated: $C_{33}H_{53}N_4O_8S_1$ *m*/*z* 665 (M − H), Found: *m*/*z* 665 (M − H).

19. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-glutamyl-L-aspartic acid (2 diastereomers): 16.0 mg; ^{1}H NMR (DMSO-d_6) δ 7.86−8.40 (m, 4, NH), 5.16 (t, 1, J = 7.5 and 7.8 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.38−4.52 (m, 2, α CH), 4.20−4.36 (m, 2, α CH), 3.08−3.24 (m, 2, allylic CH_2S), 2.50−2.80 (m, 4, CH_2S and CH_2-CO), 2.15−2.30 (m, 2, CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.66−1.80 (m, 2, CH_2), 1.63 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.20 (d, 3, J = 7.2 Hz, CH_3); HPLC t_R = 8.98 (39%) and 9.83 (54%) min; Negative ion FABMS using the matrix 3-nitrobenzyl alcohol/*n*-butanol: Calculated: $C_{32}H_{50}N_5O_9S_1$ *m*/*z* 680 (M − H), Found: *m*/*z* 680 (M − H).

20. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-glycinyl-L-aspartic acid (2 diastereomers): 26.5 mg; ^{1}H NMR (DMSO-d_6) δ 8.02−8.42 (m, 4, NH), 5.16 (t, 1, J = 7.2 and 7.8 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.40−4.54 (m, 2, α CH), 4.20−4.34 (m, 1, α CH), 3.71 (d, 2, J = 5.7 Hz, glycine CH_2), 3.10−3.24 (m, 2, allylic CH_2S),

2.50−2.82 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.84 (s, 3, $COCH_3$), 1.63 (br s, 6, vinylic CH_3), 1.56 (s, 6, vinylic CH_3), 1.20−1.26 (m, 3, CH_3); HPLC t_R = 9.25 (57%) and 9.86 (43%) min; Negative ion FABMS using the matrix 3-nitrobenzyl alcohol/*n*-butanol: Calculated: $C_{29}H_{45}N_4O_8S_1$ *m/z* 609 (M − H), Found: *m/z* 609 (M − H).

21. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-phenylglycinyl-L-aspartic acid (2 diastereomers): 30.6 mg; ^{1}H NMR (DMSO-d_6) δ 8.08−8.80 (m, 4, NH), 7.20−7.46 (m, 5, aromatic H), 5.44−5.64 (m, 1, benzylic α CH), 5.10−5.20 (m, 1, olefinic H), 5.02−5.09 (m, 2, olefinic H), 4.30−4.60 (m, 3, α CH), 3.02−3.24 (m, 2, allylic CH_2S), 2.50−2.80 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.63 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.18−1.26 (m, 3, CH_3); HPLC t_R = 11.59 (53%) and 12.44 (47%) min; Negative ion FABMS using glycerol: Calculated: $C_{35}H_{49}N_4O_8S_1$ *m/z* 685 (M − H), Found: *m/z* 685 (M − H).

22. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-(*O*-benzyl)-threoninyl-L-aspartic acid (2 diastereomers): 20.0 mg; ^{1}H NMR (DMSO-d_6) δ 7.76−8.36 (m, 4, NH), 7.20−7.36 (m, 5, aromatic H), 5.10−5.20 (m, 1, olefinic H), 5.02−5.09 (m, 2, olefinic H), 4.30−4.60 (m, 5, α CH and benzylic CH_2), 3.84−4.00 (m, 2, α CH and β CH), 3.04−3.24 (m, 2, allylic CH_2S), 2.50−2.90 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.82 (s, 3, $COCH_3$), 1.63 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.18−1.26 (m, 3, CH_3), 1.04−1.10 (m, 3, CH_3); HPLC t_R = 12.24 (66%) and 12.74 (34%) min; Negative ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{38}H_{55}N_4O_9S_1$ *m/z* 743 (M − H), Found: *m/z* 743 (M − H).

23. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-(N^{ϵ}-carbobenzyloxy)-lysinyl-L-aspartic acid (2 diastereomers): 7.2 mg; ^{1}H NMR (DMSO-d_6) δ 7.80−8.40 (m, 4, NH), 7.18−7.40 (m, 5, aromatic H), 5.16 (t, 1, J = 7.5 and 8.1 Hz, olefinic H), 5.06 (t, 1, J = 6.0 Hz, olefinic H), 4.99 (s, 2, benzylic CH_2), 4.38−4.54 (m, 2, α CH), 4.15−4.35 (m, 2, α CH), 3.10−3.25 (m, 2, allylic CH_2S), 2.90−3.00 (m, 2, CH_2N), 2.50−2.80 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.63 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.25−1.50 (m, 6, CH_2), 1.20 (d, 3, J = 6.9 Hz, CH_3); HPLC t_R = 11.93 (42%) and 12.74 (58%) min; Negative ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{41}H_{60}N_5O_{10}S_1$ *m/z* 814 (M − H), Found: *m/z* 814 (M − H).

24. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-(*O*-benzyl)-serinyl-L-aspartic acid (2 diastereomers): 14 mg; ^{1}H NMR (DMSO-d_6) δ 7.96−8.40 (m, 4, NH), 7.22−7.38 (m, 5, aromatic H), 5.16 (t, 1, J = 7.5 and 7.8 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.26−4.66 (m, 6, α CH and benzylic CH_2), 3.52−3.55 (m, 2, serine CH_2), 3.06−3.24 (m, 2, allylic CH_2S), 2.50−2.90 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.63 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.18−1.26 (m, 3, CH_3); HPLC t_R = 11.71 (61%) and 12.36 (39%) min; Negative ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{37}H_{53}N_4O_9S_1$ *m/z* 729 (M − H), Found: *m/z* 729 (M − H).

25. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-serinyl-L-aspartic acid (2 diastereomers): 11.0 mg; ^{1}H NMR (DMSO-d_6) δ 7.90−8.56 (m, 4, NH), 5.17 (m, 1, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.24−4.60 (m, 4, α CH), 3.50−3.62 (m, 2, serine CH_2), 3.08−3.24 (m, 2, allylic CH_2S), 2.50−2.95 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.84 (s, 3, $COCH_3$), 1.63 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.18−1.26 (m, 3, CH_3); HPLC t_R = 8.20 (61%) and 8.95 (39%) min; Negative ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{37}H_{47}N_4O_9S_1$ *m/z* 639 (M − H), Found: *m/z* 639 (M − H).

26. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-threoninyl-L-aspartic acid (2 diastereomers): 20.0 mg; ^{1}H NMR (DMSO-d_6) δ 7.76−8.44 (m, 4, NH), 5.16 (t, 1, J = 6.9 and 7.5 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.94 (br s, 1, OH), 4.30−4.56 (m, 3, α CH), 4.12−4.22 (m, 1, α CH), 3.90−4.02 (m, 1, β CH), 3.08−3.24 (m, 2, allylic CH_2S), 2.50−2.80 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.84 (s, 3, $COCH_3$), 1.63 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.20−1.24 (m, 3, CH_3), 0.98−1.08 (m, 3, CH_3); HPLC t_R = 8.82 (63%) and 9.60 (37%) min; Negative ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{31}H_{49}N_4O_9S_1$ *m/z* 653 (M−H), Found: *m/z* 653 (M − H).

27. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-(*O*-benzyl)-threoninyl-L-alanine (2 diastereomers): 39.0 mg; ^{1}H NMR (DMSO-d_6) δ 7.74−8.40 (m, 4, NH), 7.20−7.38 (m, 5, aromatic H), 5.10−5.20 (m, 1, olefinic H), 5.02−5.09 (m, 2, olefinic H), 4.32−4.56 (m, 5, α CH and benzylic CH_2), 4.12−4.24 (m, 1, α CH), 3.90−4.02 (m, 1, β CH), 3.10−3.20 (m, 2, allylic CH_2S), 3.00−3.08 (m, 1, CH_2S), 2.62−2.74 (m, 1, CH_2S), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.82 (s, 3, $COCH_3$), 1.63 (s, 3, vinylic CH_3), 1.60 (s, 3, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.20−1.32 (m, 6, CH_3), 1.08 (d, 3, J = 6.0, CH_3); HPLC t_R = 16.19 (64%) and 16.58 (36%) min; Negative ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{37}H_{55}N_4O_7S_1$ *m/z* 699 (M − H), Found: *m/z* 699 (M − H).

Purified Diastereomers: R_f 0.33 (silica TLC using 1:10 MeOH:$CHCl_3$ plus 2.5% v/v acetic acid): 4.6 mg; ^{1}H NMR (DMSO-d_6) δ 8.24−8.40 (m, 2, NH), 8.09 (d, 1, J = 8.4 Hz, NH), 7.64 (br s, 1, NH), 7.20−7.36 (m, 5, aromatic H), 5.00−5.20 (m, 3, olefinic H), 4.32−4.56 (m, 4, α CH and benzylic CH_2), 4.20−4.30 (m, 1, α CH), 4.04−4.14 (m, 1, α CH), 3.77 (br s, 1, β CH), 2.98−3.22 (m, 2, allylic CH_2S), 2.68−2.84 (m, 1, CH_2S), 2.40−2.60 (m, 1, CH_2S partially obscured by the DMSO-d_6 signal), 1.70−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.63 (s, 3, vinylic CH_3), 1.59 (s, 3, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.15−1.35 (m, 6, CH_3), 1.05 (d, 3, J = 5.7, CH_3); HPLC t_R = 16.71 min; Positive ion electrospray MS: Calculated: $C_{37}H_{57}N_4O_7S_1$ *m/z* 701.4 (M + H), $C_{37}H_{56}N_4O_7S_1Na_1$ *m/z* 723.4 (M + Na); Found: *m/z* 701.8 (M + H), *m/z* 723.7 (M + Na).

R_f 0.45 (silica TLC using 1:10 MeOH:$CHCl_3$ plus 2.5% v/v acetic acid): 3.3 mg; ^{1}H NMR (DMSO-d_6) δ 8.28−8.40

(m, 2, NH), 8.17 (d, 1, $J = 9.0$ Hz, NH), 7.65 (br s, 1, NH), 7.20−7.38 (m, 5, aromatic H), 5.16 (t, 1, $J = 6.6$ and 7.8 Hz, olefinic H), 5.06 (t, 1, $J = 6.6$ and 5.7 Hz, olefinic H), 4.38−4.56 (m, 4, α CH and benzylic CH_2), 4.20−4.28 (m, 1, α CH), 4.04−4.16 (m, 1, α CH), 3.75 (br s, 1, β CH), 3.08−3.22 (m, 2, allylic CH_2S), 2.64−2.76 (m, 1, CH_2S), 2.40−2.60 (m, 1, CH_2S partially obscured by the DMSO-d_6 signal), 1.70−2.10 (m, 8, allylic CH_2), 1.83 (s, 3, $COCH_3$), 1.63 (s, 3, vinylic CH_3), 1.62 (s, 3, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.15−1.32 (m, 6, CH_3), 1.06 (d, 3, $J = 6.0$, CH_3); HPLC $t_R = 16.77$ min; Positive ion electrospray MS: Calculated: $C_{37}H_{57}N_4O_7S_1$ *m/z* 701.4 (M + H), $C_{37}H_{56}N_4O_7S_1Na_1$ *m/z* 723.4 (M + Na); Found: *m/z* 701.8 (M + H), *m/z* 723.7 (M + Na).

28. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-(*O*-benzyl)-serinyl-L-alanine (2 diastereomers): 19.0 mg; ^{1}H NMR (DMSO-d_6) δ 7.94−8.48 (m, 4, NH), 7.22−7.38 (m, 5, aromatic H), 5.10−5.20 (m, 1, olefinic H), 5.02−5.09 (m, 2, olefinic H), 4.38−4.60 (m, 4, α CH and benzylic CH_2), 4.25−4.38 (m, 1, α CH), 4.10−4.24 (m, 1, α CH), 3.55−3.70 (m, 2, serine CH_2), 3.06−3.24 (m, 2, allylic CH_2S), 2.62−2.78 (m, 1, CH_2S), 2.50−2.62 (m, 1, CH_2S), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.82 (s, 3, $COCH_3$), 1.63 (s, 3, vinylic CH_3), 1.60 (s, 3, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.18−1.30 (m, 6, CH_3); HPLC $t_R = 14.42$ (55%) and 15.09 (45%) min; Negative ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{36}H_{53}N_4O_7S_1$ *m/z* 685 (M − H), Found: *m/z* 685 (M − H).

29. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-(N^{ϵ}-carbobenzyloxy)-lysinyl-L-alanine (2 diastereomers): 27.0 mg; ^{1}H NMR (DMSO-d_6) δ 7.74−8.46 (m, 4, NH), 7.20−7.40 (m, 5, aromatic H), 5.16 (t, 1, $J = 7.8$ Hz, olefinic H), 5.06 (t, 1, $J = 5.7$ and 6.6 Hz, olefinic H), 4.99 (s, 2, benzylic CH_2), 4.36−4.48 (m, 1, α CH), 4.06−4.32 (m, 3, α CH), 3.10−3.25 (m, 2, allylic CH_2S), 2.90−3.00 (m, 2, CH_2N), 2.50−2.80 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.63 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.25−1.55 (m, 6, CH_2), 1.25 (d, 3, $J = 7.2$ Hz, CH_3), 1.21 (d, 3, $J = 7.2$ Hz, CH_3); HPLC $t_R = 14.69$ (55%) and 15.93 (45%) min; Negative ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{40}H_{60}N_5O_8S_1$ *m/z* 770 (M − H), Found: *m/z* 770 (M − H).

Purified Diastereomers: R_f 0.32 (silica TLC using 1:10 MeOH:$CHCl_3$ plus 2.5% v/v acetic acid): 3.4 mg; ^{1}H NMR (DMSO-d_6) δ 8.06−8.36 (m, 4, NH), 7.20−7.40 (m, 5, aromatic H), 5.16 (t, 1, $J = 7.2$ and 7.8 Hz, olefinic H), 5.02−5.10 (m, 1, olefinic H), 4.99 (s, 2, benzylic CH_2), 4.40−4.50 (m, 1, α CH), 4.20−4.34 (m, 1, α CH), 4.02−4.14 (m, 1, α CH), 3.60−3.90 (br s, 1, α CH), 3.10−3.25 (m, 2, allylic CH_2S), 2.90−3.00 (m, 2, CH_2N), 2.70−2.84 (m, 1, CH_2S), 2.20−2.60 (m, 3, CH_2S and CH_2CO), 1.70−2.10 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.63 (s, 3, vinylic CH_3), 1.61 (s, 3, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.25−1.70 (m, 6, CH_2), 1.10−1.30 (m, 6, CH_3); HPLC $t_R = 15.45$ min; Positive ion electrospray MS: Calculated: $C_{40}H_{62}N_5O_8S_1$ *m/z* 772.4 (M + H), $C_{40}H_{61}N_5O_{78}S_1Na_1$ *m/z* 794.4 (M + Na); Found: *m/z* 772.7 (M + H), *m/z* 794.8 (M + Na).

R_f 0.39 (silica TLC using 1:10 MeOH:$CHCl_3$ plus 2.5% v/v acetic acid): 4.8 mg; ^{1}H NMR (DMSO-d_6) δ 8.34−8.48 (m, 3, NH), 8.14−8.22 (m, 1, NH), 7.24−7.40 (m, 5, aromatic H), 5.16 (t, 1, $J = 7.2$ and 8.4 Hz, olefinic H), 5.06 (t, 2, $J = 5.7$ and 6.2 Hz, olefinic H), 4.90 (s, 2, benzylic CH_2), 4.40−4.50 (m, 1, α CH), 4.24−4.36 (m, 1, α CH), 4.00−4.12 (m, 1, α CH), 3.60−3.80 (br s, 1, α CH), 3.10−3.25 (m, 2, allylic CH_2S), 2.86−3.04 (m, 2, CH_2N), 2.64−2.76 (m, 1, CH_2S), 2.20−2.60 (m, 3, CH_2S and CH_2CO), 1.70−2.10 (m, 8, allylic CH_2), 1.83 (s, 3, $COCH_3$), 1.63 (s, 3, vinylic CH_3), 1.62 (s, 3, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.30−1.70 (m, 6, CH_2), 1.10−1.30 (m, 6, CH_3); HPLC $t_R = 16.75$ min; Positive ion electrospray MS: Calculated: $C_{40}H_{62}N_5O_8S_1$ *m/z* 772.4 (M + H), Found: *m/z* 772.7 (M + H).

30. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-(*S*-benzyl)-cysteinyl-L-alanine (2 diastereomers): 12.0 mg by HPLC; ^{1}H NMR (DMSO-d_6) δ 7.94−8.56 (m, 4, NH), 7.18−7.36 (m, 5, aromatic H), 5.16 (t, 1, $J = 7.8$ and 7.2 Hz, olefinic H), 5.06 (t, 2, $J = 6.0$ and 6.3 Hz, olefinic H), 4.36−4.58 (m, 2, α CH), 4.08−4.34 (m, 2, α CH), 3.75 (s, 2, benzylic CH_2), 3.08−3.24 (m, 2, allylic CH_2S), 2.50−2.86 (m, 4, CH_2S), 1.88−2.10 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.82 (s, 3, $COCH_3$), 1.63 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.20−1.32 (m, 6, CH_3); HPLC $t_R = 17.06$ (48%) and 18.05 (52%) min; Negative ion FABMS using the matrix glycerol/25 mM NH_4HCO_3: Calculated: $C_{36}H_{53}N_4O_6S_2$ *m/z* 701 (M − H), Found: *m/z* 701 (M − H).

31. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-phenylglycinyl-L-alanine (2 diastereomers): 25.0 mg; ^{1}H NMR (DMSO-d_6) δ 8.10−8.68 (m, 4 NH), 7.20−7.44 (m, 5, aromatic H), 5.46−5.56 (m, 1, α CH), 5.16 (m, 1, olefinic H), 5.06 (m, 2, olefinic H), 4.30−4.54 (m, 2, α CH), 4.12−4.26 (m, 1, α CH), 3.02−3.24 (m, 2, allylic CH_2S), 2.62−2.76 (m, 1, CH_2S), 2.45−2.58 (m, 1, CH_2S obscured by the DMSO-d_6 signal), 1.87−2.10 (m, 8, allylic CH_2), 1.80−1.85 (m, 3, $COCH_3$), 1.58−1.64 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.28 (d, 3, $J = 7.5$ Hz, CH_3), 1.12−1.25 (m, 3, CH_3); HPLC $t_R = 13.08$ (31%), 13.38 (22%) and 13.85 (47%) min. These could not be resolved by preparative HPLC; Positive ion FABMS using the matrix glycerol/*n*-butanol: Calculated: $C_{34}H_{51}N_4O_6S_1$ *m/z* 643 (M + H), Found: *m/z* 643 (M + H).

32. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-methioninyl-L-alanine (2 diastereomers): 21.6 mg; ^{1}H NMR (DMSO-d_6) δ 7.82−8.46 (m, 4, NH), 5.17 (t, 1, $J = 8.1$ Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.10−4.48 (m, 4, α CH), 3.12−3.22 (m, 2, allylic CH_2S), 2.62−2.78 (m, 1, CH_2S), 2.45−2.58 (m, 3, CH_2S partially obscured by the DMSO-d_6 signal), 1.88−2.10 (m, 8, allylic CH_2), 2.03 (s, 3, SCH_3), 2.02 (s, 3, SCH_3), 1.85 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.70−1.80 (m, 2, CH_2), 1.60−1.65 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.27 (d, 3, $J = 7.2$ Hz, CH_3), 1.20 (d, 3, $J = 7.2$ Hz, CH_3); HPLC $t_R = 13.34$ (44%) and 14.30 (42%) min; Positive ion Electrospray MS: Calculated: $C_{31}H_{53}N_4O_6S_2$ *m/z* 641.3 (M + H), Found: *m/z* 641.7 (M + H).

33. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-methioninyl-L-aspartic acid (2 diastereomers): 20.5

mg; ^{1}H NMR (DMSO-d_6) δ 7.84−8.42 (m, 4, NH), 5.16 (t, 1, J = 7.8 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.20−4.56 (m, 4, α CH), 3.10−3.24 (m, 2, allylic CH_2S), 2.50−2.80 (m, 4, CH_2S and CH_2CO), 2.36−2.48 (m, 2, CH_2S), 1.88−2.10 (m, 8, allylic CH_2), 2.02 (s, 3, SCH_3), 2.01 (s, 3, SCH_3), 1.85 (s, 3, $COCH_3$), 1.84 (s, 3, $COCH_3$), 1.60−1.63 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.20 (d, 3, J = 6.9 Hz, CH_3); HPLC t_R = 11.21 (54%) and 12.18 (39%) min; Negative ion Electrospray MS: Calculated: $C_{32}H_{42}N_4O_8S_2$ *m/z* 683.4 (M − H), Found: *m/z* 683.4 (M − H).

34. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-alaninyl-L-aspartic acid (2 diastereomers): 15.8 mg; ^{1}H NMR (DMSO-d_6) δ 7.88−8.40 (m, 4, NH), 5.17 (t, 1, J = 7.5 and 8.4 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.38−4.54 (m, 2, α CH), 4.20−4.34 (m, 2, α CH), 3.10−3.24 (m, 2, allylic CH_2S), 2.50−2.80 (m, 4, CH_2S and CH_2CO), 1.86−2.10 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.84 (s, 3, $COCH_3$), 1.60−1.63 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.20 (m, 3, CH_3); HPLC t_R = 9.30 (65%) and 10.25 (35%) min; Negative ion Electrospray MS: Calculated: $C_{30}H_{48}N_4O_8S_1$ *m/z* 623.4 (M − H), Found: *m/z* 623.4 (M − H).

35. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-isoleucinyl-L-aspartic acid (2 diastereomers): 32.9 mg; ^{1}H NMR (DMSO-d_6) δ 8.10−8.40 (m, 3, NH), 7.64−7.76 (m, 1, NH), 5.16 (t, 1, J = 7.2 and 7.8 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.38−4.54 (m, 2, α CH), 4.26−4.38 (m, 1, α CH), 4.14−4.24 (m, 1, α CH), 3.10−3.24 (m, 2, allylic CH_2S), 2.50−2.80 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.65−1.78 (m, 1, CH), 1.58−1.64 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.32−1.50 (m, 1, diastereotopic CH_2), 1.14−1.24 (m, 3, CH_3), 0.92−1.14 (m, 1, diastereotopic CH_2), 0.74−0.86 (m, 6, CH_3); HPLC t_R = 11.68 (57%) and 12.43 (37%) min; Negative ion Electrospray MS: Calculated: $C_{33}H_{54}N_4O_8S_1$ *m/z* 665.4 (M − H), Found: *m/z* 665.5 (M − H).

36. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-glutaminyl-L-aspartic acid (2 diastereomers): 12.8 mg; ^{1}H NMR (DMSO-d_6) δ 7.86−8.40 (m, 4, NH), 7.16−7.28 (m, 1, diastereotopic $CONH_2$), 6.76 (s, 1, diastereotopic $CONH_2$), 5.17 (t, 1, J = 7.2 and 7.8 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.38−4.56 (m, 2, α CH), 4.16−4.32 (m, 2, α CH), 3.10−3.25 (m, 2, allylic CH_2S), 2.50−2.82 (m, 6, CH_2S and CH_2CO), 1.88−2.14 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.84 (s, 3, $COCH_3$), 1.65−1.76 (m, 2, CH_2), 1.60−1.64 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.16−1.26 (m, 3, CH_3); HPLC t_R = 8.01 (89%) and 8.86 (11%) min; Negative ion Electrospray MS: Calculated: $C_{32}H_{51}N_5O_9S_1$ *m/z* 680.4 (M − H), Found: *m/z* 680.4 (M − H).

37. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-prolinyl-L-alanine (2 diastereomers): 13.9 mg; ^{1}H NMR (DMSO-d_6) δ 8.02−8.38 (m, 4, NH), 5.16 (t, 1, J = 6.9 and 8.1 Hz, olefinic H), 5.00−5.10 (m, 2, olefinic H), 4.38−4.56 (m, 2, α CH), 4.25−4.36 (m, 1, α CH), 4.08−4.22 (m, 1, α CH), 3.40−3.65 (m, 2, NCH_2), 3.10−3.22 (m, 2, allylic CH_2S), 2.25−2.80 (m, 4, CH_2S), 1.88−2.10 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.60−1.64 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.12−1.32 (m, 8, CH_3 and proline CH_2); HPLC t_R = 11.09 (62%) and 11.48 (36%) min; Positive ion Electrospray MS: Calculated: $C_{31}H_{51}N_4O_6S_1$ *m/z* 607.4 (M + H), $C_{31}H_{50}N_4O_6S_1Na_1$ 629.4 (M + Na). Found: *m/z* 607.4 (M + H), 629.4 (M + Na).

38. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-valinyl-L-methionine (2 diastereomers): 16.4 mg; ^{1}H NMR (DMSO-d_6) δ 7.70−8.40 (m, 4, NH), 5.16 (t, 1, J = 7.8 Hz, olefinic H), 5.00−5.10 (m, 2, olefinic H), 4.08−4.52 (m, 4, α CH), 3.16 (d, 2, J = 7.5 Hz, allylic CH_2S), 2.62−2.80 (m, 1, CH_2S), 2.40−2.60 (m, 3, CH_2S partially obscured by the DMSO-d_6 signal), 1.70−2.10 (m, 11, allylic CH_2, β CH and CH_2), 2.01 (s, 3, SCH_3), 1.84 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.60−1.66 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.16−1.24 (m, 3, CH_3), 0.78−0.88 (m, 6, CH_3); HPLC t_R = 14.68 (50%) and 15.15 (34%) min; Positive ion Electrospray MS: Calculated: $C_{33}H_{57}N_4O_6S_2$ *m/z* 669.4 (M + H), $C_{33}H_{56}N_4O_6S_2Na_1$ 691.4 (M + Na). Found: *m/z* 669.7 (M + H), 691.7 (M + Na).

Purified Diastereomers: R_f 0.49 (silica TLC using 1:10 MeOH:$CHCl_3$ plus 2.5% v/v acetic acid): 3.6 mg; ^{1}H NMR (DMSO-d_6) δ 8.12−8.22 (m, 2, NH), 7.87 (d, 1, J = 9.0 Hz, NH), 7.70−7.80 (m, 1, NH), 5.16 (t, 1, J = 7.2 and 8.1 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.30−4.50 (m, 2, α CH), 4.04−4.14 (m, 1, α CH), 3.90−4.00 (m, 1, α CH), 3.15 (d, 2, J = 7.5 Hz, allylic CH_2S), 2.75 (dd, 1, J = 4.8 and 5.4 Hz, CH_2S), 2.30−2.60 (m, 1, CH_2S obscured by the DMSO-d_6 signal), 2.34−2.44 (m, 2, CH_2S), 1.85−2.10 (m, 8, allylic CH_2), 1.99 (s, 3, SCH_3), 1.84 (s, 3, $COCH_3$), 1.63 (s, 3, vinylic CH_3), 1.61 (s, 3, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.16−1.28 (m, 4, β CH and CH_3), 0.82 (t, 6, J = 6.0 Hz, CH_3); HPLC t_R = 14.49 min; Positive ion Electrospray MS: Calculated: $C_{33}H_{57}N_4O_6S_2$ *m/z* 669.4 (M + H), $C_{33}H_{56}N_4O_6S_2Na_1$ 691.4 (M + Na). Found: *m/z* 669.3 (M + H), 691.3 (M + Na).

R_f 0.59 (silica TLC using 1:10 MeOH:$CHCl_3$ plus 2.5% v/v acetic acid): 2.8 mg; ^{1}H NMR (DMSO-d_6) δ 8.30 (d, 1, J = 7.5 Hz, NH), 8.19 (d, 1, J = 8.4 Hz, NH), 7.90 (d, 1, J = 8.7 Hz, NH), 7.70−7.84 (m, 1, NH), 5.16 (t, 1, J = 7.2 and 7.5 Hz, olefinic H), 5.06 (t, 1, J = 7.2 and 5.4 Hz, olefinic H), 4.44−4.54 (m, 1, α CH), 4.30−4.42 (m, 1, α CH), 4.04−4.14 (m, 1, α CH), 3.90−4.02 (m, 1, α CH), 3.17 (d, 2, J = 8.1 Hz, allylic CH_2S), 2.68 (dd, 1, J = 6.0 and 6.6 Hz, CH_2S), 2.46−2.58 (m, 1, CH_2S obscured by the DMSO-d_6 signal), 2.30−2.44 (m, 2, CH_2S), 1.85−2.10 (m, 8, allylic CH_2), 2.00 (s, 3, SCH_3), 1.84 (s, 3, $COCH_3$), 1.63 (s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.30−1.40 (m, 1, β CH), 1.21 (d, 3, J = 7.2 Hz, CH_3), 0.84 (t, 6, J = 4.2 and 6.3 Hz, CH_3); HPLC t_R = 15.10 min; Positive ion Electrospray MS: Calculated: $C_{33}H_{57}N_4O_6S_2$ *m/z* 669.4 (M + H), $C_{33}H_{56}N_4O_6S_2Na_1$ 691.4 (M + Na). Found: *m/z* 669.3 (M + H), 691.3 (M + Na).

39. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-valinyl-L-phenylglycine (2 diastereomers): 34.2 mg; ^{1}H NMR (DMSO-d_6) δ 8.05−8.78 (m, 3, NH), 7.65−7.80 (m, 1, NH), 7.26−7.50 (m, 5, aromatic H), 5.37 (d, 1, J = 7.8 Hz, benzylic CH), 5.27 (d, 1, J = 6.9 Hz, benzylic CH),

5.16 (t, 1, J = 7.8 and 7.5 Hz, olefinic H), 5.00−5.10 (m, 2, olefinic H), 4.24−4.52 (m, 3, α CH), 3.10−3.24 (m, 2, allylic CH_2S), 2.62−2.80 (m, 1, CH_2S), 2.46−2.58 (m, 1, CH_2S partially obscured by the DMSO-d_6 signal), 1.88−2.10 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.84 (s, 3, $COCH_3$), 1.60−1.64 (s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.16−1.22 (m, 3, CH_3), 0.70−0.90 (m, 7, β CH and CH_3); HPLC t_R = 15.12 (35%) and 15.73 (59%) min; Positive ion Electrospray MS: Calculated: $C_{36}H_{55}N_4O_6S_1$ *m/z* 671.4 (M + H), $C_{36}H_{54}N_4O_6S_1Na_1$ 693.4 (M + Na). Found: *m/z* 671.7 (M + H), 693.6 (M + Na).

Purified Diastereomers: R_f 0.36 (silica TLC using 1:10 MeOH:$CHCl_3$ plus 2.5% v/v acetic acid): 2.5 mg; ^{1}H NMR (DMSO-d_6) δ 8.08−8.22 (m, 3, NH), 7.90−8.00 (m, 1, NH), 6.96−7.32 (m, 5, aromatic H), 5.37 (d, 1, J = 7.8, benzylic CH), 5.16 (t, 1, J = 7.8 and 8.1 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.58−4.68 (m, 1, α CH), 4.34−4.54 (m, 2, α CH), 4.06−4.16 (m, 1, α CH), 3.14 (d, 2, J = 8.1 Hz, allylic CH_2S), 2.76 (dd, 1, J = 5.1 Hz, CH_2S), 2.46−2.58 (m, 1, CH_2S obscured by the DMSO-d_6 signal), 1.80−2.12 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.63 (s, 3, vinylic CH_3), 1.62 (s, 3, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.14−1.24 (m, 1, β CH), 1.28 (d, 3, J = 6.9 Hz, CH_3), 0.74−0.84 (m, 6, CH_3); HPLC t_R = 15.27 min; Positive ion Electrospray MS: Calculated: $C_{36}H_{55}N_4O_6S_1$ *m/z* 671.4 (M + H), $C_{36}H_{54}N_4O_6S_1Na_1$ 693.4 (M + Na). Found: *m/z* 671.4 (M + H), 693.3 (M + Na).

R_f 0.46 (silica TLC using 1:10 MeOH:$CHCl_3$ plus 2.5% v/v acetic acid): 1.7 mg; ^{1}H NMR (DMSO-d_6) δ 8.30 (d, 1, J = 7.2 Hz, NH), 8.10−8.20 (m, 2, NH), 8.01 (d, 1, J = 8.1 Hz, NH), 7.12−7.38 (m, 5, aromatic H), 5.27 (d, 1, J = 6.9, benzylic CH), 5.16 (t, 1, J = 7.2 Hz, olefinic H), 5.07 (t, 2, J = 5.1 and 7.2 Hz, olefinic H), 4.82 (br s, 1, α CH), 4.35−4.56 (m, 1, α CH), 4.34−4.44 (m, 1, α CH), 4.10−4.20 (m, 1, α CH), 3.16 (d, 2, J = 8.1 Hz, allylic CH_2S), 2.69 (dd, 1, J = 6.3 Hz, CH_2S), 2.46−2.58 (m, 1, CH_2S obscured by the DMSO-d_6 signal), 1.88−2.10 (m, 8, allylic CH_2), 1.83 (s, 3, $COCH_3$), 1.63 (s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.20−1.30 (m, 1, β CH and CH_3), 0.78−0.86 (m, 6, CH_3); HPLC t_R = 15.82 min; Positive ion Electrospray MS: Calculated: $C_{36}H_{55}N_4O_6S_1$ *m/z* 671.4 (M + H), $C_{36}H_{54}N_4O_6S_1Na_1$ 693.4 (M + Na). Found: *m/z* 671.3 (M + H), 693.2 (M + Na).

40. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-valinyl-L-(N^{ϵ}-carbobenzyloxy)-lysine (2 diastereomers): ^{1}H NMR (DMSO-d_6) δ 8.06−8.40 (m, 3, NH), 7.60−7.74 (m, 1, NH), 7.20−7.42 (m, 5, aromatic H), 5.16 (t, 1, J = 7.5 and 7.8 Hz, olefinic H), 5.02−5.01 (m, 2, olefinic H), 4.99 (s, 2, benzylic CH_2), 4.38−4.52 (m, 1, α CH), 4.28−4.37 (m, 1, α CH), 4.15−4.24 (m, 1, α CH), 4.04−4.14 (m, 1, α CH), 3.10−3.25 (m, 2, allylic CH_2S), 2.90−3.04 (m, 2, CH_2N), 2.62−2.78 (m, 1, CH_2S), 2.50−2.58 (m, 1, CH_2S partially obscured by the DMSO-d_6 signal), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.60−1.78 (m, 6, CH_2 and vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.24−1.46 (m, 4, CH_2), 1.40−1.24 (m, 3, CH_3), 0.76−0.94 (m, 6, CH_3); HPLC t_R = 17.18 (53%) and 17.99 (42%) min; Positive ion Electrospray MS: Calculated: $C_{42}H_{66}N_5O_8S_1$ *m/z* 800.4 (M + H), Found: *m/z* 800.8 (M + H).

41. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-valinyl-L-(*S*-benzyl)-cysteine (2 diastereomers): 46.0 mg; ^{1}H NMR (DMSO-d_6) δ 8.12−8.36 (m, 3, NH), 7.66−7.80 (m, 1, NH), 7.20−7.40 (m, 5, aromatic H), 5.16 (t, 1, J = 7.8 Hz, olefinic H), 5.06 (t, 2, J = 5.4 and 6.9 Hz, olefinic H), 4.18−4.54 (m, 4, α CH), 3.70−3.82 (m, 2, benzylic CH_2), 3.10−3.20 (m, 2, allylic CH_2S), 2.50−2.96 (m, 4, CH_2S), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.58−1.66 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.25−1.44 (m, 1, β CH), 1.16−1.24 (m, 3, CH_3), 0.78−0.90 (m, 6, CH_3); HPLC t_R = 17.86 (48%) and 18.28 (44%) min; Positive ion Electrospray MS: Calculated: $C_{38}H_{60}N_4O_6S_2$ *m/z* 731.4 (M + H), Found: *m/z* 731.7 (M + H).

42. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-valinyl-L-valine (2 diastereomers): 29.0 mg; ^{1}H NMR (DMSO-d_6) δ 7.64−8.40 (m, 4, NH), 5.16 (t, 1, J = 6.9 and 7.5 Hz, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.20−4.54 (m, 3, α CH), 4.08−4.14 (m, 1, α CH), 3.10−3.24 (m, 2, allylic CH_2S), 2.62−2.78 (m, 1, CH_2S), 2.46−2.60 (m, 1, CH_2S partially obscured by the DMSO-d_6 signal), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.60−1.66 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.14−1.24 (m, 3, CH_3), 0.78−0.92 (m, 12, CH_3); HPLC t_R = 14.47 (54%) and 15.02 (44%) min; Positive ion Electrospray MS: Calculated: $C_{33}H_{47}N_4O_6S_1$ *m/z* 637.4 (M + H), $C_{33}H_{46}N_4O_6S_1Na_1$ 659.4 (M + Na). Found: *m/z* 637.7 (M + H), 659.7 (M + Na).

43. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-valinyl-L-isoleucine (2 diastereomers): 33.0 mg; ^{1}H NMR (DMSO-d_6) δ 7.60−8.40 (m, 4, NH), 5.16 (t, 1, J = 7.8 Hz, olefinic H), 5.00−5.10 (m, 2, olefinic H), 4.08−4.52 (m, 4, α CH), 3.08−3.25 (m, 2, allylic CH_2S), 2.62−2.78 (m, 1, CH_2S), 2.46−2.60 (m, 1, CH_2S partially obscured by the DMSO-d_6 signal), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (br s, 3, $COCH_3$), 1.83 (br s, 3, $COCH_3$), 1.66−1.80 (m, 1, β CH), 1.60−1.66 (s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.32−1.50 (m, 1, diastereotopic CH_2), 1.15−1.25 (m, 4, CH_3 and diastereotopic CH_2), 0.76−0.94 (m, 12, CH_3); HPLC t_R = 16.33 (48%) and 16.79 (46%) min; Positive ion Electrospray MS: Calculated: $C_{34}H_{59}N_4O_6S_1$ *m/z* 651.4 (M + H), $C_{34}H_{58}N_4O_6S_1Na_1$ 673.4 (M + Na). Found: *m/z* 651.8 (M + H), 673.6 (M + Na).

44. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-valinyl-L-proline (2 diastereomers): 18.0 mg; ^{1}H NMR (DMSO-d_6) δ 7.78−8.42 (m, 4, NH), 5.12−5.22 (m, 1, olefinic H), 5.02−5.10 (m, 2, olefinic H), 4.16−4.85 (m, 4, α CH), 3.40−3.80 (m, 2, NCH_2), 3.10−3.22 (m, 2, allylic CH_2S), 2.62−2.80 (m, 1, CH_2S), 2.42−2.60 (m, 1, CH_2S partially obscured by the DMSO-d_6 signal),1.88−2.10 (m, 8, allylic CH_2), 1.80−1.85 (m, 7, $COCH_3$ and proline CH_2), 1.60−1.64 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.12−1.32 (m, 3, CH_3), 0.78−0.94 (m, 6, CH_3); HPLC t_R = 13.07 (15%), 13.49 (27%), 14.16 (50%), and 15.07 (8%) min; Positive ion Electrospray MS: Calculated: $C_{33}H_{55}N_4O_6S_1$ *m/z* 635.4 (M + H), Found: *m/z* 635.7 (M + H).

45. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-valinyl-L-isoleucinyl-L-alanine (2 diastereomers): 75.0 mg; ^{1}H NMR (DMSO-d_6) δ 7.70−8.24 (m, 4, NH), 5.16 (t, 1, J =

7.8 Hz, olefinic H), 5.00−5.10 (m, 2, olefinic H), 4.42−4.64 (m, 1, α CH), 4.08−4.26 (m, 3, α CH), 3.10−3.25 (m, 2, allylic CH_2S), 2.46−2.60 (m, 2, CH_2S), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.66−1.80 (m, 1, *β* CH), 1.60−1.66 (s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.32−1.50 (m, 1, diastereotopic CH_2), 1.24 (d, 3, CH_3), 0.98−1.16 (m, 1, diastereotopic CH_2), 0.74−0.88 (m, 12, CH_3); ^{13}C NMR (DMSO-d_6) *δ* 173.94, 170.54, 170.45, 170.35, 169.20, 169.09, 138.28, 134.56, 130.66, 124.14, 123.68, 120.36, 120.28, 57.63 (m), 56.44 (m), 52.39, 52.20, 47.52, 39.11, 36.72 (m), 32.84 (m), 30.53 (m), 28.94, 28.68, 26.20, 25.92, 25.53, 24.18, 22.46, 19.29, 19.17, 17.98, 17.58, 17.14, 15.82, 15.20, 11.00 ppm; HPLC t_R = 16.01 (67%) and 17.18 (29%) min; Positive ion Electrospray MS: Calculated: $C_{34}H_{59}N_4O_6S_1$ *m/z* 651.4 (M + H), $C_{34}H_{58}N_4O_6S_1Na_1$ *m/z* 673.4 (M + Na); Found: *m/z* 651.8 (M + H), 673.7 (M + Na).

46. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-(*O*-benzyl)-threoninyl-L-phenylalaninyl-L-aspartic acid (2 diastereomers): 9.0 mg; ^1H NMR (DMSO-d_6) *δ* 7.86−8.26 (m, 4, NH), 7.08−7.38 (m, 10, aromatic H), 5.10−5.20 (m, 1, olefinic H), 5.00−5.09 (m, 2, olefinic H), 4.24−4.66 (m, 6, α CH and benzylic CH_2), 3.82−3.94 (m, 1, *β* CH), 3.10−3.20 (m, 4, benzylic CH_2 and allylic CH_2S), 2.50−2.90 (m, 4, CH_2S and CH_2CO), 1.88−2.08 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.63 (s, 3, vinylic CH_3), 1.60 (s, 3, vinylic CH_3), 1.54 (s, 6, vinylic CH_3), 0.98−1.08 (m, 3, CH_3); HPLC t_R = 22.33 (31%) and 23.76 (69%) min; Positive ion Electrospray MS: Calculated: $C_{44}H_{62}N_4O_9S_1$ *m/z* 821.4 (M + H), Found: *m/z* 821.7 (M + H).

47. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-glutamyl-L-phenylalaninyl-L-aspartic acid (2 diastereomers): 82.0 mg; ^1H NMR (DMSO-d_6) *δ* 7.72−8.38 (m, 4, NH), 7.10−7.30 (m, 5, aromatic H), 5.10−5.20 (m, 1, olefinic H), 5.00−5.09 (m, 2, olefinic H), 4.00−4.55 (m, 4, α CH), 3.10−3.30 (m, 4, benzylic CH_2 and allylic CH_2S), 2.10−2.50 (m, 6, CH_2S, CH_2CO), 1.88−2.09 (m, 8, allylic CH_2), 1.84 (br s, 3, $COCH_3$), 1.64−1.82 (m, 4, CH_2), 1.58−1.62 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3); HPLC t_R = 18.40 (53%) and 18.65 (41%) min; Positive ion Electrospray MS: Calculated: $C_{38}H_{57}N_5O_9S_1$ *m/z* 759.4 (M + H), $C_{38}H_{56}N_5O_9S_1K_1$ *m/z* 797.4 (M + K); Found: *m/z* 759.7 (M + H), 797.6 (M + K).

48. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-(*O*-benzyl)-serinyl-L-phenylalaninyl-L-aspartic acid (2 diastereomers): 66.0 mg; ^1H NMR (DMSO-d_6) *δ* 7.64−8.44 (m, 4, NH), 7.10−7.38 (m, 10, aromatic H), 5.00−5.20 (m, 3, olefinic H), 4.30−4.60 (m, 6, α CH and benzylic CH_2), 4.00−4.18 (m, 2, *β* CH_2), 3.10−3.60 (m, 4, benzylic CH_2 and allylic CH_2S), 2.26−2.94 (m, 4, CH_2S and CH_2CO), 1.88−2.08 (m, 8, allylic CH_2), 1.83−1.85 (m, 3, $COCH_3$), 1.58−1.64 (m, 6, vinylic CH_3), 1.54 (s, 6, vinylic CH_3); HPLC t_R = 22.57 (22%) and 23.01 (27%) min; Positive ion Electrospray MS: Calculated: $C_{43}H_{57}N_4O_9S_1$ *m/z* 807.4 (M + H), $C_{43}H_{56}N_4O_9S_1K_1$ *m/z* 845.4 (M + K); Found: *m/z* 807.7 (M + H), 845.6 (M + K).

49. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-(N^{ϵ}-carbobenzyloxy)-lysinyl-L-phenylalaninyl-L-aspartic acid (2 diastereomers): 86.0 mg; ^1H NMR (DMSO-d_6) *δ* 7.70−8.66 (m, 4, NH), 7.08−7.40 (m, 10, aromatic H), 5.10−5.20 (m, 1, olefinic H), 5.00−5.09 (m, 2, olefinic H), 4.99 (s, 2, benzylic CH_2), 4.30−4.50 (m, 2, α CH), 3.95−4.20 (m, 2, α CH), 3.00−3.30 (m, 4, benzylic CH_2 and allylic CH_2S), 2.25−2.95 (m, 6, CH_2N, CH_2S and CH_2CO), 1.86−2.08 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.62 (s, 6, vinylic CH_3), 1.50−1.55 (m, 6, vinylic CH_3), 1.10−1.45 (m, 4, CH_2); HPLC t_R = 21.31 (43%) and 21.91 (43%) min; Positive ion Electrospray MS: Calculated: $C_{47}H_{67}N_5O_{10}S_1$ *m/z* 892.4 (M + H), $C_{47}H_{66}N_5O_{10}S_1Na_1$ 914.4 (M + Na), $C_{47}H_{66}N_5O_{10}S_1K_1$ 930.4 (M + K), Found: *m/z* 892.6 (M + H), 914.6 (M + Na), 930.6 (M + K); Negative ion electrospray MS: Calculated: $C_{47}H_{65}N_5O_{10}S_1$ *m/z* 890.4 (M − H), Found: *m/z* 890.6 (M − H).

50. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-phenylalaninyl-L-aspartic acid (2 diastereomers): 68.0 mg; ^1H NMR (DMSO-d_6) *δ* 7.92−8.34 (m, 4, NH), 7.12−7.26 (m, 5, aromatic H), 5.10−5.20 (m, 1, olefinic H), 5.00−5.09 (m, 2, olefinic H), 4.14−4.52 (m, 4, α CH), 2.92−3.30 (m, 4, allylic CH_2S and benzylic CH_2), 2.40−2.86 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.84−1.85 (m, 3, $COCH_3$), 1.59−1.65 (m, 6, vinylic CH_3), 1.55 (br s, 6, vinylic CH_3), 1.10−1.18 (m, 3, CH_3); HPLC t_R = 19.09 (49%) and 19.84 (43%) min; Positive ion Electrospray MS: Calculated: $C_{36}H_{54}N_4O_8S_1$ *m/z* 701.4 (M + H), $C_{36}H_{53}N_4O_8S_1K_1$ *m/z* 739.4 (M + K); Found: *m/z* 701.6 (M + H), 739.5 (M + K).

51. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-serinyl-L-phenylalaninyl-L-aspartic acid (2 diastereomers): 58.0 mg; ^1H NMR (DMSO-d_6) *δ* 7.92−8.20 (m, 4, NH), 7.10−7.30 (m, 5, aromatic H), 5.10−5.20 (m, 1, olefinic H), 5.00−5.09 (m, 2, olefinic H), 4.18−4.56 (m, 4, α CH), 3.40−3.60 (m, 2, *β* CH_2), 3.00−3.30 (m, 4, benzylic CH_2 and allylic CH_2S), 2.40−2.86 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.84−1.86 (m, 3, $COCH_3$), 1.59−1.65 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3); HPLC t_R = 18.31 (32%) and 18.73 (38%) min; Positive ion Electrospray MS: Calculated: $C_{36}H_{54}N_4O_9S_1$ *m/z* 717.4 (M + H), $C_{36}H_{53}N_4O_9S_1K_1$ *m/z* 755.4 (M + K); Found: *m/z* 717.6 (M + H), 755.5 (M + K).

52. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-prolinyl-L-phenylalaninyl-L-aspartic acid (2 diastereomers): 52.0 mg; ^1H NMR (DMSO-d_6) *δ* 7.64−8.50 (m, 4, NH), 7.12−7.32 (m, 5, aromatic H), 5.10−5.25 (m, 1, olefinic H), 5.00−5.09 (m, 2, olefinic H), 4.20−4.80 (m, 4, α CH), 3.40−3.80 (m, 2, NCH_2), 2.40−3.20 (m, 12, benzylic CH_2, allylic CH_2S, CH_2S, proline CH_2 and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.87 (s, 3, $COCH_3$), 1.82 (s, 3, $COCH_3$), 1.63 (s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3); HPLC t_R = 19.31 (52%) and 21.61 (46%) min; Positive ion Electrospray MS: Calculated: $C_{38}H_{56}N_4O_8S_1$ *m/z* 727.4 (M + H), $C_{38}H_{55}N_4O_8S_1Na_1$ *m/z* 749.4 (M + Na); Found: *m/z* 727.5 (M + H), 749.6 (M + Na).

53. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-aspartate-L-phenylalaninyl-L-aspartic acid (2 diastereomers): 85.0 mg; ^1H NMR (DMSO-d_6) *δ* 7.10−8.30 (m, 4, NH), 7.10−7.30 (m, 5, aromatic H), 5.10−5.20 (m, 1, olefinic H), 5.00−5.09 (m, 2, olefinic H), 4.30−4.60 (m, 4, α CH), 2.90−3.30 (m, 4, allylic CH_2S and benzylic CH_2), 2.30−2.86 (m,

6, CH_2S and CH_2CO), 1.87−2.10 (m, 8, allylic CH_2), 1.80−1.86 (m, 3, $COCH_3$), 1.58−1.65 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3); HPLC t_R = 17.71 min; Positive ion Electrospray MS: Calculated: $C_{37}H_{54}N_4O_{10}S_1$ *m/z* 745.4 (M + H), Found: *m/z* 745.6 (M + H).

54. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-phenylglycyl-L-phenylalaninyl-L-aspartic acid (2 diastereomers): 34.0 mg; ^{1}H NMR (DMSO-d_6) δ 8.12−8.78 (m, 4, NH), 7.04−7.34 (m, 10, aromatic H), 5.40−5.60 (m, 1, α CH), 5.00−5.20 (m, 3, olefinic H), 4.30−4.70 (m, 3, α CH), 2.80−3.50 (m, 4, allylic CH_2S and benzylic CH_2), 2.40−2.75 (m, 6, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.82−1.87 (m, 3, $COCH_3$), 1.55−1.65 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3); HPLC t_R = 21.88 (59%) and 22.27 (21%) min; Positive ion Electrospray MS: Calculated: $C_{41}H_{56}N_4O_8S_1$ *m/z* 763.4 (M + H), Found: *m/z* 763.6 (M + H).

Library Compounds − Pure Monobenzyl Esters: 55. *N*-Acetyl-(*S-E,E*-farnesyl)-(D,L)-cysteinyl-L-alaninyl-L-methioninyl-L-aspartic acid monobenzyl ester (2 diastereomers): ^{1}H NMR (DMSO-d_6) δ 7.84−8.42 (m, 4, NH), 7.28−7.42 (m, 5, aromatic H), 5.16 (t, 1, J = 7.2 Hz, olefinic H), 5.02−5.10 (m, 4, benzylic and olefinic H), 4.55−4.65 (m, 1, α CH), 4.20−4.48 (m, 3, α CH), 3.10−3.20 (m, 2, allylic CH_2S), 2.50−2.90 (m, 4, CH_2S and CH_2CO), 2.36−2.48 (m, 2, CH_2S), 1.86−2.10 (m, 8, allylic CH_2), 2.02 (s, 3, SCH_3), 2.01 (s, 3, SCH_3), 1.84 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.60−1.64 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.20 (d, 3, J = 6.9 Hz, CH_3); HPLC t_R = 16.98 (60%) and 17.62 (34%) min; Negative ion Electrospray MS: Calculated: $C_{39}H_{47}N_4O_8S_1$ *m/z* 773.4 (M − H), Found: *m/z* 773.4 (M − H).

56. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-alaninyl-L-aspartic acid monobenzyl ester (2 diastereomers): ^{1}H NMR (DMSO-d_6) δ 7.86−8.40 (m, 4, NH), 7.28−7.42 (m, 5, aromatic H), 5.17 (m, 1, olefinic H), 5.02−5.10 (m, 4, benzylic and olefinic H), 4.52−4.64 (m, 1, α CH), 4.38−4.48 (m, 1, α CH), 4.20−4.34 (m, 2, α CH), 3.14−3.20 (m, 2, allylic CH_2S), 2.50−2.90 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.60−1.64 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.16−1.24 (m, 6, CH_3); HPLC t_R = 15.80 (68%) and 16.44 (32%) min; Negative ion Electrospray MS: Calculated: $C_{37}H_{53}N_4O_8S_1$ *m/z* 713.4 (M − H), Found: *m/z* 713.4 (M − H).

57. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-isoleucinyl-L-aspartic acid monobenzyl ester (2 diastereomers): ^{1}H NMR (DMSO-d_6) δ 8.12−8.40 (m, 3, NH), 7.64−7.76 (m, 1, NH), 7.28−7.42 (m, 5, aromatic H), 5.16 (t, 1, J = 7.2 and 7.8 Hz, olefinic H), 5.02−5.10 (m, 4, benzylic and olefinic H), 4.52−4.64 (m, 1, α CH), 4.38−4.48 (m, 1, α CH), 4.26−4.22 (m, 1, α CH), 4.14−4.22 (m, 1, α CH), 3.10−3.20 (m, 2, allylic CH_2S), 2.50−2.90 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.84 (s, 3, $COCH_3$), 1.83 (s, 3, $COCH_3$), 1.65−1.80 (m, 1, CH), 1.58−1.64 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.32−1.46 (m, 1, diastereotopic CH_2), 1.14−1.24 (m, 3, CH_3), 0.96−1.10 (m, 1, diastereotopic CH_2), 0.72−0.84 (m, 6, CH_3); HPLC t_R = 18.03 (68%) and 18.33 (32%) min; Positive ion Electrospray MS: Calculated: $C_{40}H_{61}N_4O_8S_1$ *m/z* 757.4 (M + H), $C_{40}H_{60}N_4O_8S_1Na_1$ *m/z* 779.4 (M + Na); Found: *m/z* 757.5 (M + H), 779.5 (M + Na).

58. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-glutaminyl-L-aspartic acid monobenzyl ester (2 diastereomers): ^{1}H NMR (DMSO-d_6) δ 7.86−8.40 (m, 4, NH), 7.10−7.40 (m, 5, aromatic H), 7.20−7.26 (m, 1, diastereotopic $CONH_2$), 6.77 (s, 1, diastereotopic $CONH_2$), 5.16 (t, 1, J = 8.4 and 9.0 Hz, olefinic H), 5.02−5.10 (m, 4, benzylic and olefinic H), 4.52−4.64 (m, 1, α CH), 4.38−4.50 (m, 1, α CH), 4.16−4.32 (m, 2, α CH), 3.14−3.20 (m, 2, allylic CH_2S), 2.50−2.88 (m, 6, CH_2S and CH_2CO), 1.86−2.14 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.84 (s, 3, $COCH_3$), 1.65−1.76 (m, 2, CH_2), 1.60−1.64 (m, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.16−1.26 (m, 3, CH_3); HPLC t_R = 12.85 (66%) and 13.76 (34%) min; Positive ion Electrospray MS: Calculated: $C_{39}H_{58}N_5O_9S_1$ *m/z* 772.4 (M + H), $C_{39}H_{57}N_5O_9S_1Na_1$ *m/z* 794.4 (M + Na); Found: *m/z* 772.5 (M + H), 794.5 (M + Na).

Library Compounds Derived by Partial Saponification of Benzyl Ester Protecting Groups − Mixtures: 59. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-aspartate-L-aspartic acid (2 diastereomers) *plus 15% monobenzyl ester*: 30.9 mg; ^{1}H NMR (DMSO-d_6) δ 7.98−8.46 (m, 4, NH), trace of 7.30−7.40 (m, 5 aromatic H from the monobenzyl ester), 5.12−5.22 (m, 1, olefinic H), 5.02−5.10 (m, 1, olefinic H), 4.37−4.64 (m, 3, α CH), 4.20−4.34 (m, 1, α CH), 3.10−3.24 (m, 2, allylic CH_2S), 2.50−2.82 (m, 6, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.63 (s, 3, vinylic CH_3), 1.62 (s, 3, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.14−1.24 (m, 3, CH_3); HPLC t_R = Triacid product at 9.19 (44.29%) and 9.82 (34.38%) min, t_R = Monobenzyl ester at 12.87 (6.68%) and 13.57 (8.01%) min; Positive ion Electrospray MS: Calculated: triacid $C_{31}H_{49}N_4O_{10}S_1$ *m/z* 669.4 (M + H), monobenzyl ester $C_{38}H_{55}N_4O_{10}S_1$ *m/z* 759.4 (M + H); Found: triacid *m/z* 669.4 (M + H), monobenzyl ester *m/z* 759.4 (M + H).

60. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-phenylalaninyl-L-aspartic acid (2 diastereomers) *plus 48% mono benzyl ester*: 12.8 mg; ^{1}H NMR (DMSO-d_6) δ 7.84−8.40 (m, 4, NH), 7.12−7.40 (m, 10, aromatic H, monobenzyl ester and phenylalanine), 5.12−5.20 (m, 1, olefinic H), 5.11 (s, 2, benzylic H from monobenzyl ester), 5.02−5.09 (m, 2, olefinic H), 4.37−4.66 (m, 3, α CH), 4.14−4.26 (m, 1, α CH), 3.00−3.24 (m, 4, allylic CH_2S and phenylalanine benzylic CH_2), 2.50−2.90 (m, 4, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.85 (s, 3, $COCH_3$), 1.84 (s, 3, $COCH_3$), 1.59−1.64 (m, 6, vinylic CH_3), 1.55 (br s, 6, vinylic CH_3), 1.08−1.16 (m, 3, CH_3); HPLC t_R = Diacid product at 12.31 (23.6%) and 13.21 (25.6%) min, t_R = Monobenzyl ester at 16.46 (25.4%) and 16.91 (22.9%) min; Negative ion Electrospray MS: Calculated: diacid $C_{36}H_{52}N_4O_8S_1$ *m/z* 699.4 (M − H), monobenzyl ester $C_{43}H_{58}N_4O_8S_1$ *m/z* 789.4 (M − H); Found: diacid *m/z* 669.4 (M − H), monobenzyl ester *m/z* 789.4 (M − H).

61. *N*-Acetyl-(*S*-(*E,E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-(*S*-benzyl)-cysteinyl-L-aspartic acid (2 diastereomers) *plus 42% monobenzyl ester*: 13.0 mg; ^{1}H NMR (DMSO-d_6) δ 8.00−8.46 (m, 4, NH), 7.20−7.40 (m, 10,

aromatic H, monobenzyl ester and *S*-benzyl ether), 5.12−5.20 (m, 1, olefinic H), 5.09 (s, 2, benzylic H from monobenzyl ester), 5.02−5.09 (m, 2, olefinic H), 4.40−4.66 (m, 3, α CH), 4.24−4.36 (m, 1, α CH), 3.74 (s, 2, *S*-benzylic CH_2), 3.12−3.24 (m, 2, allylic CH_2S), 2.50−2.92 (m, 6, CH_2S and CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.80−1.86 (m, 3, $COCH_3$), 1.59−1.64 (m, 6, vinylic CH_3), 1.55 (br s, 6, vinylic CH_3), 1.18−1.26 (m, 3, CH_3); HPLC t_R = Diacid product at 12.54 (29.4%) and 13.29 (28.3%) min, t_R = Monobenzyl ester at 16.61 (23.8%) and 16.88 (18.4%) min; Negative ion FABMS using the matrix glycerol/*n*-butanol: Calculated: diacid $C_{37}H_{53}N_4O_8S_2$ *m*/*z* 745 (M − H), monobenzyl ester $C_{44}H_{59}N_4O_8S_2$ *m*/*z* 835 (M − H); Found: diacid *m*/*z* 745 (M − H), monobenzyl ester *m*/*z* 835 (M − H).

62. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-(D,L)-cysteinyl)-L-alaninyl-L-valinyl-L-glutamic acid (2 diastereomers) *plus 34% monobenzyl ester*: 13.0 mg; ^{1}H NMR (DMSO-d_6) δ 7.64−8.40 (m, 4, NH), 7.28−7.40 (m, 5, aromatic H), 5.16 (t, 1, J = 7.2 and 7.5 Hz, olefinic H), 5.02−5.10 (m, 4, benzylic and olefinic H), 3.98−4.52 (m, 4, α CH), 3.10−3.20 (m, 2, allylic CH_2S), 2.62−2.80 (m, 1, CH_2S), 2.50−2.60 (m, 1, CH_2S partially obscured by the DMSO-d_6 signal), 2.20−2.45 (m, 2,CH_2CO), 1.88−2.10 (m, 8, allylic CH_2), 1.80−1.86 (m, 3, $COCH_3$), 1.66−1.80 (m, 2, CH_2), 1.63 (br s, 6, vinylic CH_3), 1.55 (s, 6, vinylic CH_3), 1.14−1.24 (m, 3, CH_3), 0.76−0.90 (m, 6, CH_3); HPLC t_R = Diacid product at 11.98 (25%) and 12.83 (18%) min, t_R = Monobenzyl ester at 17.98 (20%) and 18.53 (13%) min; Positive ion Electrospray MS: Calculated: diacid $C_{33}H_{55}N_4O_8S_1$ *m*/*z* 667.4 (M + H), monobenzyl ester $C_{40}H_{61}N_4O_8S_1$ *m*/*z* 757.4 (M + H); Found: diacid *m*/*z* 667.7 (M + H), monobenzyl ester *m*/*z* 757.7 (M + H).

63. *N*-Acetyl-(*S*-(*E*,*E*-farnesyl)-(D,L)-cysteinyl)-L-(*S*-benzyl)-cysteinyl-L-phenylalaninyl-L-aspartic acid (2 diastereomers) *plus 30% monobenzyl ester*: 14.0 mg; ^{1}H NMR (DMSO-d_6) δ 7.96−8.46 (m, 4, NH), 7.10−7.40 (m, 5, aromatic H), 5.00−5.12 (m, 3, olefinic H), 4.20−4.70 (m, 4, α CH), 3.62−3.80 (m, 2, benzylic CH_2), 3.00−3.60 (m, 4, allylic CH_2S and benzylic CH_2), 2.40−2.96 (m, 6, CH_2S and CH_2CO), 1.88−2.08 (m, 8, allylic CH_2), 1.86 (s, 3, $COCH_3$), 1.85 (s, 3, $COCH_3$), 1.58−1.64 (m, 6, vinylic CH_3), 1.54 (s, 6, vinylic CH_3); HPLC t_R = Diacid product at 22.47 (21%) and 23.35 (31%) min, t_R = Monobenzyl ester at 25.97 (11%) and 26.77 (11%) min; Positive ion Electrospray MS: Calculated: diacid $C_{43}H_{59}N_4O_8S_2$ *m*/*z* 823.4 (M + H), monobenzyl ester $C_{50}H_{65}N_4O_8S_2$ *m*/*z* 913.4 (M + H); Found: diacid *m*/*z* 823.6 (M + H), monobenzyl ester *m*/*z* 913.7 (M + H).

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