

Amino acid derivatives. Part 5. Synthesis and anti-HIV activity of new sebacyl precursor derived thioureido-amino acid and phthalimide derivatives

Najim A. Al-Masoudi,^{a*} Nahed Al-Haidery,^a Naeem T. Faili^a and C. Pannecouque^b

^aDepartment of Chemistry, College of Science, University of Basrah, Basrah, Iraq

^bRega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium

E-mail: najim.al-masoudi@gmx.de

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Abstract

A series of sebacyl *N,N*-bis(substituted-alkyl-2-thioureido)alkyl carboxylic acid or ester derivatives **3-12** bearing an amino acid ester residue were prepared by a *one-pot* sequential reaction of sebacyl chloride **1** with NH₄SCN and amino acid or their ester hydrochlorides. Analogously, the sebacyl-phthalimido derivatives **16** and **17** were prepared from treatment of **1** with phthalimide precursors. Treatment of **5** and **7** with Br₂ in acetone furnished the imino-thiazole analogues **18** and **19**, respectively. Compounds **5**, **6**, **8-11** and **16** have been selected for their inhibitory activity screening against HIV-1 and HIV-2 in MT-4 cells.

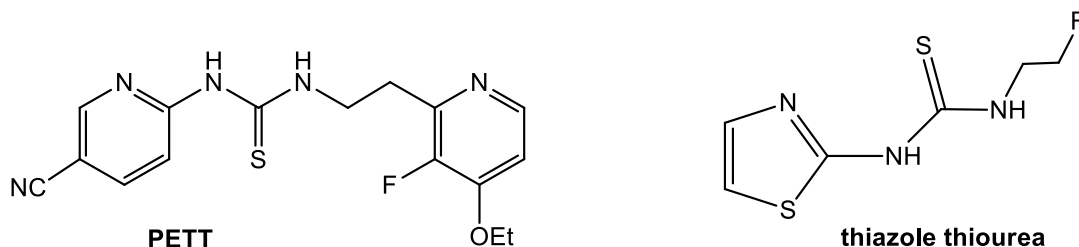
Keywords: Amino acids, anti-HIV activity, phthalimide, sebacyl chloride

Introduction

HIV-1 reverse transcriptase is a key enzyme in the HIV replication as well as a key target for developing anti-HIV drugs. Two types of reverse transcriptase inhibitors have been developed^{1,2}: nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTI). Three NNRTIs, nevirapine,³ delaviridine,⁴ and efavirenz⁵ have been approved by FDA for the treatment of HIV infection. However, significant resistance has been developed against the current NNRTI and there is an urgent need to develop new anti-HIV agents that are effective against these resistance mutants.^{6,7} We have reported recently the synthesis of new nitroimidazoles with remarkable anti-HIV activity⁸⁻¹² as NNRTIs candidates. Several heterocyclic thioureas have been reported as a new class of potent non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as phenethylthiazolyl-thiourea (PETT) derivatives.¹³⁻¹⁶ Uckun *et al.*¹⁷ described the synthesis of a series of thiazole thioureas with alkyl, aryl, heteroaryl substituents as newly identified NNRTI of HIV, including mutant strains of HIV,

and effective in the treatment of multi-drug resistant HIV infection. The synthesis of biologically active amino acid coupled derivatives was considered to be of a major interest.¹⁸⁻²¹ Recently, Fathalla *et al.*^{22,23} reported new quinazoline thioureas derivatives bearing an amino acid ester residue based on domino reaction of *N*-(2-cyanophenyl)benzimidoyl isothioyanate with amino acid methyl ester hydrochlorides.

In continuation of our work on amino acid derivatives,²⁴⁻²⁷ we described here the development of a new series of thioureas bearing amino acids or their ester analogues which can be used as potent NNRTI's



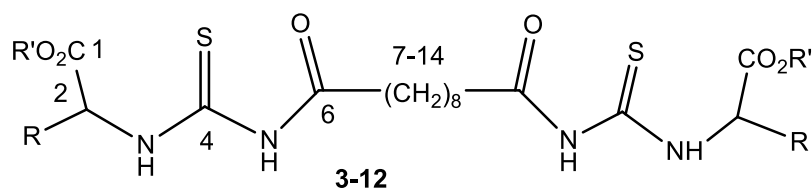
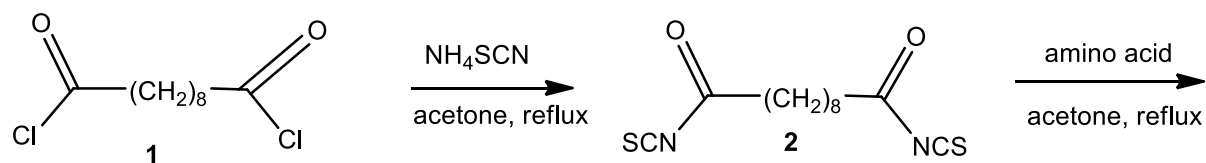
Results and Discussion

In our present work, sebacoyl chloride (octane-1,8-dicarboxylic acid dichloride) **1** has been selected as a spacer building block²⁸ for the synthesis of new derivatives of sebacoyl-*N,N*-bis(substituted-alkyl-2-thioureido)alkyl carboxylic acid or ester aiming for evaluation of their anti-HIV activity. Koenig *et al.*²⁹ have used **1** for the synthesis of 3,3,3',3'-tetraethyl-1,1'-sebacoyl-bis(thiourea) and other analogues *via* the sebacoyl dithiocyanate derivative **2**. Compound **2** was the key intermediate for synthesis of the compounds investigated in our work. Thus, treatment of **1** with NH_4SCN in acetone, following Kabbani approach,³⁰ afforded **2** which was directly treated with the desired amino acid derivatives to give, after purification, the sebacoyl-thioureido-amino acid derivatives in 63-86% yield. The synthetic reactions are summarized in scheme 1.

The structures of **3-12** were determined by their ^1H , ^{13}C NMR and by mass spectra. The sebacoyl protons showed almost a similar pattern. H-7 and H-14 protons appeared as multiplets in the region δ 2.61-1.78 ppm, while H-8 and H-13 proton signals are oriented as multiplets in the region δ 1.81-1.45 ppm. H-9 - H-12 were appeared as multiplets in the region δ H-2 of the amino acid moieties are oriented in the region δ with different multiplicities, depending on the functional group adjacent to H-2. The other protons of the amino acids or esters were fully analyzed. The ^{13}C NMR spectra of **3-12** contained almost similar resonance signals of the sebacoyl C-7 - C-14 and thioureido carbon atoms. The chemical shifts between δ 188.8 and 184.25 ppm were assigned to C=S carbon atom of the thioureido moiety (C-4), while the resonances in the range of δ 177.7-174.1 ppm were assigned to the carbonyl groups of the CSNHCO residues. C-2 of the amino acid moieties [CH-CO₂H(Me,Et)] appeared in the region δ

66.7-55.9 ppm. The sebacyl carbon atoms C-7 and C-14 are oriented in the region δ 38.0-35.3, while C-8 and C-13 were appeared in the region δ 26.4-25.0 ppm. The signals between δ 31.5 and 24.7 ppm were attributed to C-9 and C-12.

The proton spin system of **11** was further identified from DFQ-COSY³¹ spectrum, where the doublet of H²_{alanin} at δ 3.41 ppm was found to correlate with CO₂H-C²_{alanin}-H) at δ _C 55.9 ppm. In the ¹H NMR (HMQC)³² spectrum of **11**, the multiplets at δ _H 2.25 and 1.51 ppm of carbon atoms resonating at δ _C 35.7 and 25.5 ppm were assigned to (CH₂-7 + CH₂-14) and (CH₂-8 + CH₂-13), respectively, by spin decoupling experiment. Similarly, the methylene protons (CH₂-9 - CH₂-12) at δ _H 1.29 ppm and their carbon atoms (C-9 + C-12) (δ _C 30.2) and (C-10 + C-11) (δ _C 28.2 ppm) have been identified. From the gradient selected HMBC³³ spectrum of **11**, H²_{alanin} proton at δ _H 3.41 ppm showed two ²J_{C,H} couplings: one with CO₂H at δ _C 173.0 ppm, and the other with Me_{alanin} at δ _C 17.3 ppm.

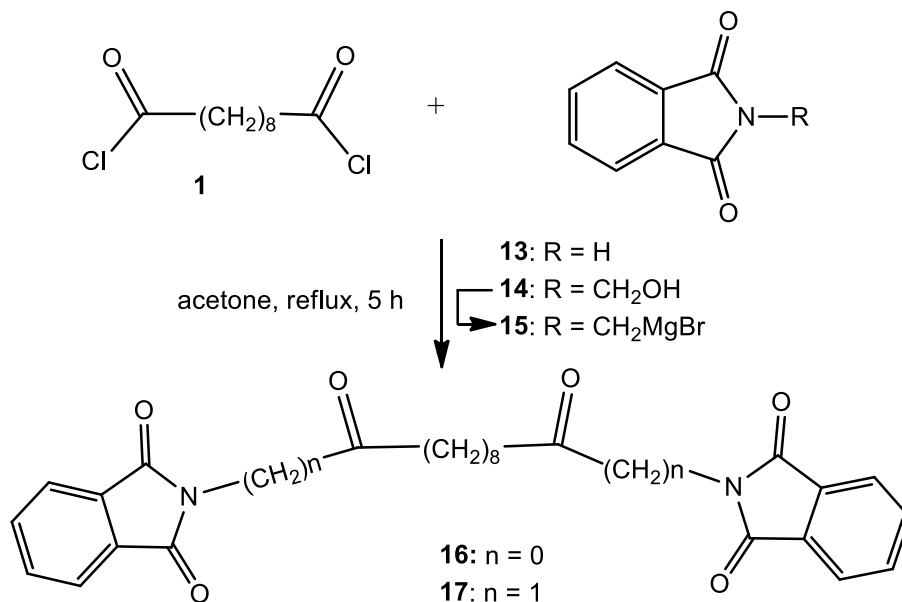


	R	R'	Amino acid
3	CH ₂ CO ₂ H	H	L-aspartic acid
4	(CH ₂) ₂ CO ₂ H	H	L-glutamic acid
5	CH(CH ₃) ₂	Me	L-valin-Me-ester
6	(CH ₂) ₄ NH ₂	Et	L-lysine-Et-ester
7	CH ₂ SH	H	L-cysteine
8	CH ₂ -3-indole	H	L-tryptophane
9	CH ₂ -3-imidazole	H	L-histidine
10	(CH ₂) ₃ -guanidine	H	L-arginine
11	CH ₃	H	L-alanine
12	(CH ₂) ₄ NH ₂	H	L-lysine

Scheme 1. Synthesis of sebacyl N,N-bis(substituted-alkyl-2-thioureido)alkyl carboxylic acid or ester derivatives.

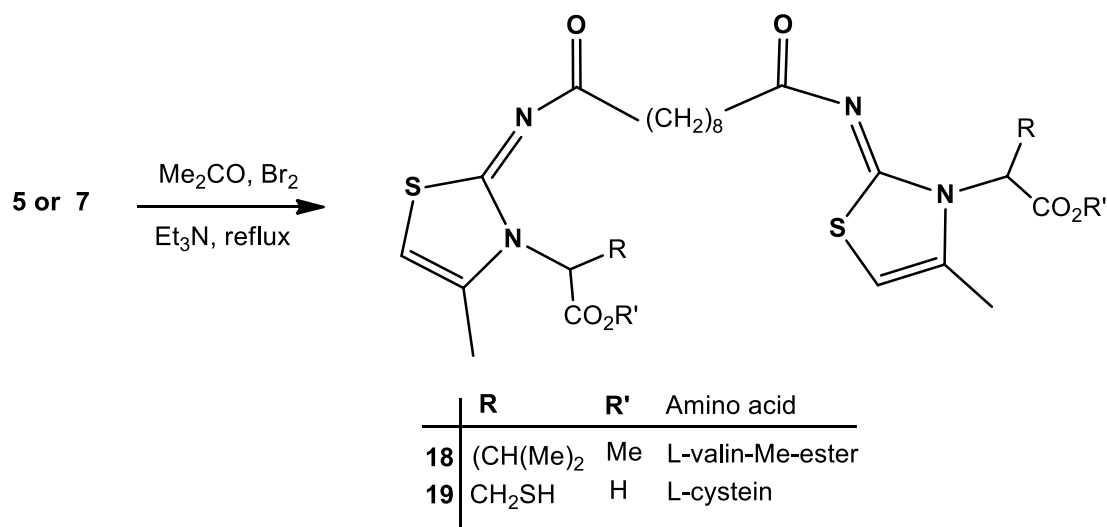
Next, sebacyl chloride **1** was treated with phthalimide **13** or *N*-(phthalimido)methylmagnesium bromide **15**, prepared from hydroxymethyl-phthalimide **14**,³⁴ in refluxing acetone afforded after purification the sebacyl-*N,N*-bis-phthalimide **16** and the

methylphthalimide analogue **17** in 83 and 86% yield, respectively (scheme 2). The structures of **16** and **17** were assigned by the ^1H , ^{13}C NMR and mass spectra. The ^1H NMR spectra showed rather similar patterns for the sebacyl (CH_2) protons for those of **3-12**, meanwhile, the singlet at δ 4.96 ppm was attributed to the ethylene group adjacent to the phthalimide precursor. In the ^{13}C NMR spectra of **16** and **17**, the higher-field resonances at δ 172.1 and 174.5 ppm were attributed to C=O group of the sebacyl moiety, while the resonances at δ 167.3 and 167.4 ppm were assigned to C=O of the phthalimide residue.



Scheme 2. Synthesis of sebacyl-N,N-bis-phthalimide and methyl analogue.

Further, our work was modified by selecting **5** and **7** as precursors for the synthesis of new analogues of sebacyl-2-imino-thiazole. Thus, treatment of **5** and **7** with acetone and bromine under reflux led to cyclization of the thioureido residue furnishing the 2-imino-thiazole derivatives **18** and **19** in 65 and 71% yields, respectively (Scheme 3). The structures of **18** and **19** were determined from their ^1H -, ^{13}C NMR and mass spectra. The sebacyl protons showed rather similar pattern for the sebacyl (CH_2) protons for those of **16** and **17**. The singlets at δ 5.87 and 5.92 ppm were assigned to H-5 of the thiazole ring, respectively, while the singlets at δ 1.70 and 1.68 ppm were attributed to the methyl groups at C-4 of the thiazole moiety. In the ^{13}C NMR of **18** and **19**, the resonances at δ 163.8 and 163.6 ppm, were attributed to C=N (C-2), respectively, whereas the signals at δ 132.9 and 132.7 ppm were assigned to C-4, respectively. C-5 were oriented between δ 100.1 and 99.8 ppm, respectively. The structures of **18** and **19** were further confirmed by the gradient³³ selected HMBC spectra. H-5 of the thiazole ring at δ_{H} 5.87 and 5.92 ppm showed $^2J_{\text{C,H}}$ couplings with C-4 of the thiazole ring at δ_{C} 132.9 and 132.7 ppm, as well as $^3J_{\text{C,H}}$ couplings with C=N (C-2) of the thiazole ring at δ_{C} 163.8 and 163.6 ppm, respectively.



Scheme 3. Synthesis of sebacoyl *N,N*-bis-methyl-(alkyl-2-imino-thiazol-3-yl)butanoate or propanoic acid.

In vitro anti-HIV assay

Compounds **5**, **6**, **8-11** and **16** were tested for their *in vitro* anti-HIV-1 (strain III_B) and HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells, based on MTT assay.³⁵ None of the new compounds were found to inhibit HIV-1 and HIV-2 replication, *in vitro*, at IC₅₀ lower than the CC₅₀ in comparison to the antiviral agents Nevirapine (BOE/BIRG587)³⁶ and azidothymidine (AZT).³⁷ In conclusion, the above data showed no selective anti-HIV activity.

Experimental section

General. Melting points are uncorrected and were measured on a Büchi melting point apparatus B-545 (Büchi Labortechnik AG, Switzerland). Microanalytical data were obtained with a Vario, Elemental apparatus (Shimadzu, Japan). NMR spectra were recorded on 400 and 600 MHz (¹H) and on 150.91 MHz (¹³C) spectrometers (Bruker, Germany) with TMS as internal standard and on the δ scale in ppm. Signal assignments for protons were identified by selective proton decoupling or by COSY spectra. Heteronuclear assignments were verified by ¹H-¹³C COSY, or HMBC experiments. Mass spectra were recorded at 70 eV on EI. TLC plates 60 F254 were purchased from Merck.

General procedure of preparation of sebacoyl *N,N*-bis(substituted-alkyl-2-thioureido)alkyl carboxylic acid or ester derivatives (3-12)

A solution of sebacoyl chloride (0.72 g, 3.0 mmol) and NH₄SCN (0.46 g, 6.0 mmol) in acetone (20 mL) was heated under reflux for 1 h. After

cooling and filtration, a solution of the desired free amino acid or the ester analogue (6.0 mmol) in dry acetone (15 mL) was added and the mixture was heated under reflux for 6 h. After cooling, an excess of crushed ice was pouted on the mixture with vigorous stirring. The resulting result was collected, washed with acetone and recrystallized from EtOH or DMF-ether.

Sebacyl-*N,N*-bis(2-thioureido)succinic acid (3). From L-aspartic acid (0.80 g), Yield: 1.0 g (61%); mp 235-236 °C. ¹H NMR (DMSO-*d*₆): δ 3.77 (dd, 2H, $J_{\text{H2-aspar,H3a-aspar}} = 3.4$ Hz, $J_{\text{H2-aspar,H3b-aspar}} = 11.4$ Hz, CO₂H- H^2_{aspar}); 3.17 (br s., 1H, NH); 2.75 (dd, 1H, $J_{\text{H3a,H3b-aspar}} = 15.0$ Hz, H^{3a}_{aspar}); 2.72 (dd, 1H, H^{3b}_{aspar}); 2.61 (m, 2H, CH₂-7 + CH₂-14); 1.69 (m, 4H, CH₂-8 + CH₂-13); 1.29-1.23 (m, 8H, CH₂-9 + CH₂-10 + CH₂-11 + CH₂-12). ¹³C NMR (DMSO-*d*₆): δ 184.9 (C=S); 174.3 (CSNHCO + CO₂H); 137.1, 127.3, 123.3, 119.8, 11.2, 109.9 (C_{trypt.}); 66.7 (CO₂H-CH); 35.5 (C-7 + C-14); 31.5 (C10 + C-11); 29.0 (C-9 + C-12); 26.4 (C-8 + C-13). Anal. calc. for C₂₀H₃₀N₄O₁₀S₂ (550.6): C, 43.63; H, 5.49; N, 10.18. Found: C, 43.34; H, 5.41; N, 9.89. MS: m/z (FAB) 551 [M+H]⁺.

Sebacyl-*N,N*-bis(2-thioureido)-L-glutamic acid (4). From L-glutamic acid (0.88 g). Yield: 1.47 g (85%); mp 195-196 °C. ¹H NMR (DMSO-*d*₆): δ 11.08 (br s., 2H, CO₂H); 3.86 (br s., 1H, NH); 3.59 (dd, 2H, $J_{\text{H2-glutamic,H3a-glutamic}} = 3.5$ Hz, $J_{\text{H2-glutamic,H3b-glutamic}} = 11.5$ Hz, CO₂H- H^2_{glutamic}); 2.29 (m, 4H, H^{4a,b}_{glutamic}); 2.14 (m, 4H, CH₂-7 + CH₂-14); 2.11 (m, 4H, H^{3a,b}_{glutamic}); 1.81 (CH₂-8 + CH₂-13); 1.31-1.21 (m, 8H, CH₂-9 + CH₂-10 + CH₂-11 + CH₂-12). ¹³C NMR (DMSO-*d*₆): δ 185.7 (C=S); 177.5 (CO₂H); 174.7 (CSNHCO + CO₂H); 61.9 (CO₂H-CH); 35.7 (C-7 + C-14); 30.8 (C10 + C-11 + C⁴_{glutamic}); 29.2 (C-9 + C-12); 26.4 (C-8 + C-13 + C³_{glutamic}). Anal. calc. for C₂₂H₃₄N₄O₁₀S₂ (578.66): C, 45.66; H, 5.92; N, 9.68. Found: C, 45.35; H, 5.87; N, 9.42. MS: m/z (FAB) 579 [M+H]⁺.

Sebacyl *N,N*-bis-methyl(2-thioureido)-3-methylbutanoate (5). From L-valine methyl ester (0.79 g). Yield: 1.04 g (63%); mp 260-262 °C. ¹H NMR (DMSO-*d*₆): δ 8.01 (br s., 1H, NH); 3.71 (s, 3H, CO₂Me); 3.46 (dd, 2H, $J_{2,3(\text{valin})} = 7.5$ Hz, 2xH²_{valin}); 2.76 (m, 2H, 2xH³_{valin}); 2.01 (m, 4H, CH₂-7 + CH₂-14); 1.51 (m, 4H, CH₂-8 + CH₂-13); 1.32 (m, 4H, CH₂-9 + CH₂-12); 1.24 (CH₂-10 + CH₂-11); 1.08 (m, 12H, 4xCH₃). ¹³C NMR (DMSO-*d*₆): δ 187.1 (C=S); 174.3 (CSNHCO); 170.8 (COEt); 61.8 (CO₂Me-CH); 52.1 (CO₂Me); 37.4 (C-7 + C-14); 31.4 (C³_{valin}); 29.8 (C-9 + C-10 + C-11 + C-12); 26.1 (C-8 + C-13); 18.3 (CH₃). Anal. calc. for C₂₄H₄₂N₄O₆S₂ (546.74): C, 52.72; H, 7.74; N, 10.25. Found: C, 52.50; H, 7.68; N, 10.02. MS: m/z (FAB) 547 [M+H]⁺.

Sebacyl-*N,N*-bis-ethyl-(6-amino-2-thioureido)hexanoate (6). From L-lysine ethyl ester dihydrochloride (1.48 g). Yield: 2.14 g (78%), mp 108-110 °C. ¹H NMR (DMSO-*d*₆): δ 8.73, br s., 2H, 2xNH; 8.23 (br s., 2H, 2xNH); 4.22 (q, 4H, J = 7.0 Hz, 2xOCH₂CH₃); 3.92 (t, 2H, $J_{\text{H2-lysin,H3-a,b}} = 6.1$ Hz, 2xH²_{lysin}); 2.72 (br s., 8H, 2xCH₂-NH₂+2xNH₂); 1.82-1.77 (m, 8H, 2xCH₂-3_{lysin}+CH₂-7 + CH₂-14); 1.59 (m, 6H, 2xCH₂-5_{lysin} + 2xNH); 1.47 (m, 4H, CH₂-8 + CH₂-13); 1.38 (m, 4H, CH₂-9 + CH₂-12); 1.23 (m, 10H, 2xOCH₂CH₃ + CH₂-10 + CH₂-11). ¹³C NMR (DMSO-*d*₆): δ 187.9 (C=S); 174.1 (CSNHCO); 170.6 (COEt); 61.7 (OCH₂CH₃ + CO₂Et-CH); 51.1 (CH₂NH₂); 37.8 (C-7 + C-14); 29.2 (C³_{lysin} + C-9 + C-10 + C-11 + C-12); 26.0 (C-8 + C-13); 21.1 (C⁴_{lysin}); 13.9 (OCH₂CH₃). Anal. calc. for C₂₈H₅₂N₆O₆S₂ (632.88): C, 53.14; H, 8.28; N, 13.28. Found: C, 52.94; H, 8.19; N, 13.05. MS: m/z (FAB) 633 [M+H]⁺.

Sebacyl-*N,N*-bis(4-mercapto-2-thioureido)butanoic acid (7). From L-cysteine (0.73 g). Yield: 1.14 g (72%); mp 215-217 °C. ¹H NMR (DMSO-*d*₆): δ 4.03 (dd, 2H, $J_{\text{H2-cystein,H3-a}} = 7.1$ Hz, $J_{\text{H2-cystein,H3-b}} = 14.2$ Hz $2 \times \text{H}^2_{\text{cystein}}$); 3.16 (br s., 4H, $2 \times \text{H}^{3\text{a}}_{\text{cystein}} + 2 \times \text{H}^{3\text{b}}_{\text{cystein}}$); 2.32 (m, 4H, +CH₂-7 + CH₂-14); 1.52 (m, 4H, CH₂-8 + CH₂-13); 1.29 (m, 4H, CH₂-9 + CH₂-12); 1.21 (m, 4H, CH₂-10 + CH₂-11). ¹³C NMR (DMSO-*d*₆): δ 188.8 (C=S); 175.7 (CSNHCO); 174.9 (CO₂H); 63.9 (CO₂H-CH); 36.4 (C-7 + C-14); 32.0 (C-10 + C-11); 28.9 (C-9 + C-12); 27.2 (CH₂SH); 25.0 (C-8 + C-13). Anal. calc. for C₁₈H₃₀N₄O₆S₄ (526.71): C, 41.05; H, 5.74; N, 10.64. Found: C, 40.89; H, 5.75; N, 10.43. MS: m/z (FAB) 527 [M+H]⁺.

Sebacyl-*N,N*-bis(2-thioureido-3-(indol-3-yl))propanoic acid (8). From L-tryptophane (1.23 g). Yield: 1.4 g (67%); mp 255-257 °C. ¹H NMR (DMSO-*d*₆): δ 10.90 (s, 1H, CO₂H); 7.20 (1H, d, $J_{2,\text{NH}} = 2.2$ Hz, H²_{trypt.}); 7.56 (d, 1H, $J = 7.8$ Hz, H⁷_{trypt.}); 7.34 (d, 1H, = 8.0 Hz, H⁴_{trypt.}); 7.07 (t, 1H, $J = 8.0$ Hz, H⁵_{trypt.}); 6.98 (t, 1H, $J = 7.8$ Hz, H⁶_{trypt.}); 3.43 (dd, 2H, $J_{2,\text{CH2a-trypt.}} = 4.0$ Hz, $J_{2,\text{CH2b-trypt.}} = 9.0$ Hz, CO₂H- $2 \times \text{H}^2_{\text{trypt.}}$); 3.31 (dd, 1H, CH₂a-trypt); 2.93 (dd, 1H, $J_{\text{Ha,Hb-trypt.}} = 15.0$ Hz, CH₂b-trypt.); 2.33 (m, 4H, CH₂-7 + CH₂-14); 1.69 (m, 4H, CH₂-8 + CH₂-13); 1.29-1.23 (m, 8H, CH₂-9 + CH₂-10 + CH₂-11 + CH₂-12). ¹³C NMR (DMSO-*d*₆): δ 184.9 (C=S); 174.3 (CSNHCO + CO₂H); 137.1, 127.3, 123.3, 119.8, 111.2, 109.9 (C_{trypt.}); 62.7 (CO₂H-CH); 35.5 (C-7 + C-14); 31.5 (C-10 + C-11); 29.0 (C-9 + C-12); 26.4 (C-8 + C-13). Anal. calc. for C₃₄H₄₀N₆O₆S₂ (692.85): C, 58.94; H, 5.82; N, 12.13. Found: C, 58.72; H, 4.09; N, 11.97. MS: m/z (FAB) 693 [M+H]⁺.

Sebacyl-*N,N*-bis(2-thioureido-3-(imidazol-4-yl))propanoic acid (9). From L-histidine (0.93 g). Yield: 1.43 g (80%); mp 240-242 °C. ¹H NMR (DMSO-*d*₆): δ 7.38 (s, 1H, H²_{imidazol}); 6.37 (s, 1H, H⁵_{imidazol}); 3.64 (dd, 2H, $J_{2',3'\text{a}(\text{histidin})} = 7.5$ Hz, $J_{2',3'\text{b}(\text{histidin})} = 13.5$ Hz $2 \times \text{H}^2_{\text{histidin}}$); 3.10 (m., 4H, $2 \times \text{H}^{3\text{a}}_{\text{histidin}} + 2 \times \text{H}^{3\text{b}}_{\text{histidin}}$); 2.14 (m, 4H, +CH₂-7 + CH₂-14); 1.63 (m, 4H, CH₂-8 + CH₂-13); 1.28 (m, 4H, CH₂-9 + CH₂-12); 1.23 (m, 4H, CH₂-10 + CH₂-11). ¹³C NMR (DMSO-*d*₆): δ 184.2 (C=S); 177.7 (CSNHCO); 174.0 (CO₂H); 135.4, (C²_{imidazol}); 132.7 (C⁴_{imidazol}); 120.3 (C⁵_{imidazol}); 61.9 (CO₂H-CH); 37.4 (C-7 + C-14); 29.9 (C-10 + C-11 + C³_{imidazol}); 28.2 (C-9 + C-12); 26.0 (C-8 + C-13). Anal. calc. for C₂₄H₃₄N₈O₆S₂ (597.71): C, 48.47; H, 5.76; N, 18.84. Found: C, 48.22; H, 5.66; N, 18.67. MS: m/z (FAB) 598 [M+H]⁺.

Sebacyl-*N,N*-bis(2-thioureido-5-guanidino)pentanoic acid (10). From L-arginine (1.04 g). Yield: 1.64 g (86%); mp 120-122 °C. ¹H NMR (DMSO-*d*₆ + D₂O): δ 3.69 (dd, 2H, $J_{\text{H2-arginin,H3a-arginin}} = 3.6$ Hz, $J_{\text{H2-arginin,H3b-arginin}} = 11.6$ Hz, CO₂H- $\text{H}^2_{\text{arginin}}$); 2.69 (m, 4H; $2 \times \text{CH}_2\text{-5}_{\text{arginin}}$); 1.81 (m, 4H, $2 \times \text{CH}_2\text{-3}_{\text{arginin}}$); 1.91 (m, 4H, CH₂-7 + CH₂-14); 1.61 (m, 8H, $2 \times \text{CH}_2\text{-4}_{\text{arginin}} + \text{CH}_2\text{-8} + \text{CH}_2\text{-13}$); 1.31-1.27 (m, 8H, CH₂-9 + CH₂-10 + CH₂-11 + CH₂-12). ¹³C NMR (DMSO-*d*₆ + D₂O): δ 184.7 (C=S); 175.2 (CONH); 174.4 (CSNHCO); 157.8 (C=NH); 61.9 (CO₂D-CH); 36.1 (C-7 + C-14 + $2 \times \text{C}^5_{\text{arginin}}$); 28.8 (C-9 + C-10, C-11, C-12 + $2 \times \text{C}^3_{\text{arginin}}$); 26.2 (C-8 + C-13 + $2 \times \text{C}^4_{\text{arginin}}$). Anal. calc. for C₂₄H₄₄N₁₀O₆S₂ (632.8): C, 45.55; H, 7.01; N, 22.13. Found: C, 45.37; H, 6.93; N, 21.89. MS: m/z (FAB) 633 [M+H]⁺.

Sebacyl-*N,N*-bis(2-thioureido)propanoic acid (11). From L-alanine (0.53 g). Yield: 0.96 (69%); mp 257-260 °C. ¹H NMR (DMSO-*d*₆): δ 3.41 (d, 2H, $J_{\text{H2-alanin,CH3-alanin}} = 3.6$ Hz, $2 \times \text{H}^2_{\text{alanin}}$); 2.25 (m, 4H, +CH₂-7 + CH₂-14); 1.51 (m, 4H, CH₂-8 + CH₂-13); 1.29 (m, 8H, CH₂-

9 - CH₂-12); 1.24 (t, 6H, *J* = 7.0 Hz, Me_{alanin}) ¹³C NMR (DMSO-*d*₆): δ 186.7 (C=S); 175.7 (CSNHCO); 173.0 (CO₂H); 55.9 (CO₂H-CH); 35.7 (C-7 + C-14); 30.2 (C-10 + C-11); 28.2 (C-9 + C-12); 25.5 (C-8 + C-13); 17.3 (Me_{alanin}). Anal. calc. for C₁₈H₃₀N₄O₆S₂ (462.58): C, 46.74; H, 6.54; N, 12.11. Found: C, 46.53; H, 6.47; N, 11.89. MS: *m/z* (FAB) 463 [M+H]⁺.

Sebacoyl-*N,N*-bis(6-amino-2-thioureido)hexanoic acid (12). From L-lysine (0.88 g). Yield: 1.40 g (81%); mp 230-232 °C. ¹H NMR (DMSO-*d*₆): δ 8.02 (br s., 2H, 2xNH); 3.67 (t, 2H, *J*_{H₂-lysine,H₃-a,b}) = 5.5 Hz, 2xH²_{lysine}); 2.76 (m., 4H, 2xCH₂-NH₂); 1.78-1.71 (m, 8H, 2xCH₂-3_{lysine}+CH₂-7 + CH₂-14); 1.57 (m, 4H, 2xCH₂-4_{lysine}); 1.45 (m, 4H, CH₂-8 + CH₂-13); 1.38 (m, 4H, CH₂-9 + CH₂-12); 1.23 (m, 4H, CH₂-10 + CH₂-11). ¹³C NMR (DMSO-*d*₆): δ 187.1 (C=S); 175.8 (CSNHCO + CO₂H); 63.5 (CO₂H-CH); 40.0 (CH₂NH₂); 38.0 (C-7 + C-14); 29.2-27.4 (C³_{lysine} + C⁴_{lysine} + C-9 + C-10 + C-11 + C-12); 26.1 (C-8 + C-13). Anal. calc. for C₂₄H₄₄N₆O₆S₂ (576.77): C, 49.98; H, 7.69; N, 14.57. Found: C, 49.77; H, 7.58; N, 14.33. MS: *m/z* (FAB) 577 [M+H]⁺.

Sebacoyl-*N,N*-bis-phthalimide (16). A solution of sebacoyl chloride **1** (2.39 g, 10.0 mmol) and phthalimide **13** (2.94 g, 20 mmol) in acetone (25 mL) was heated under reflux for 5 h. After cooling the solution was evaporated to dryness to give a crude product followed by washing with water and EtOH. Recrystallization from EtOH afforded **16** (3.82 g, 83%), mp 215-217 °C. ¹H NMR (DMSO-*d*₆): δ 7.96-7.84 (m, 8H, Ar-H); 2.19 (t, 4H, *J* = 7.2 Hz, CH₂-2 + CH₂-9); 1.52 (m, 4H, CH₂-3 + CH₂-8); 1.27 (m, 8H, CH₂-4 - CH₂-7). ¹³C NMR (DMSO-*d*₆): δ 172.1 (CH₂-C=O); 167.3 (C^{phthal.}=O); 134.3, 130.1, 123.9 (Ar-C); 34.9 (C-2 + C-9); 28.4 (C-4 - C-7); 24.6 (C-3 + C-8). Anal. calc. for C₂₆H₂₄N₂O₆ (460.48): C, 67.82; H, 5.25; N, 6.08. Found: C, 67.61; H, 5.17; N, 5.84. MS: *m/z* (FAB) 461 [M+H]⁺.

Sebacoyl-*N,N*-bis-methylphthalimide (17). The compound was prepared in the similar manner of preparation of **16** from hydroxymethyl-phthalimide **14** (3.54 g, 20.0 mmol), *via N*-(phthalimido)methylmagnesium bromide **15**. Yield: 4.20 g (86%); mp 120-122 °C. ¹H NMR (DMSO-*d*₆): δ 7.93-7.86 (m, 8H, Ar-H); 4.96 (s, 4H, 2xCH₂-phthal.); 2.17 (t, 4H, *J* = 7.3 Hz, CH₂-3 + CH₂-10); 1.47 (m, 4H, CH₂-4 + CH₂-9); 1.24 (m, 8H, CH₂-5 - CH₂-8). ¹³C NMR (DMSO-*d*₆): δ 174.5 (CH₂-C=O); 167.4 (C^{phthal.}=O); 134.7, 131.5, 123.7 (Ar-C); 60.1 (CH₂-C=O); 38.9 (C-3 + C-10); 28.5 (C-5 - C-8); 24.4 (C-4 + C-9). Anal. calc. for C₂₈H₂₈N₂O₆ (488.53): C, 68.84; H, 5.78; N, 5.73. Found: C, 68.62; H, 5.69; N, 5.50. MS: *m/z* (FAB) 489 [M+H]⁺.

Sebacoyl-*N,N*-bis-methyl-(3-methyl-2-imino-thiazol-3-yl)butanoate (18). To a stirred solution of **5** (0.55 g, 1.0 mmol) in dry acetone (20 mL) was added Et₃N (1.0 mmol), followed by a dropwise addition of a bromine solution (1.0 mmol) in acetone (10 mL). The reaction mixture was stirred at room temperature for 2 h, then the mixture was evaporated to dryness to give the desired product, which were recrystallized from EtOH to afford **18** (0.41 g, 65%), mp 252-254 °C. ¹H NMR (DMSO-*d*₆): δ 5.87 (s, 2H, 2xH⁵_{thiazol}); 3.68 (s, 3H, CO₂Me); 3.48 (dd, 2H, *J*_{2,3(valin)} = 7.3 Hz, 2xH²_{valin}); 2.75 (m, 2H, 2xH³_{valin}); 2.13 (m, 4H, 2xCOCH₂_{sebacoyl}); 1.70 (s, 6H, 2xC⁴_{thiazol-CH₃}); 1.55 (m, 4H, 2xCOCH₂CH₂_{sebacoyl}); 1.30 (m, 8H, 4xCH₂_{sebacoyl}); 1.07 (m, 12H, 4xCH₃_{valin}). ¹³C NMR (DMSO-*d*₆): δ 173.1 (2xC^{sebacoyl}=O); 171.5 (2xCO₂Me); 163.8 (C=N); 132.9 (C⁴_{thiazol}); 100.1 (C⁵_{thiazol}); 60.5 (2xCO₂Me-CH); 52.4 (2xCO₂Me); 34.1 (2xCOCH₂_{sebacoyl});

30.2-25.8 ($C^3_{\text{valin}} + 6xCH_2\text{sebacoyl}$); 18.1 ($(2xC^4_{\text{thiazol-CH}_3})$). Anal. calc. for $C_{30}H_{46}N_4O_6S_2$ (622.84): C, 57.85; H, 7.44; N, 9.00. Found: C, 57.67; H, 7.34; N, 8.82. MS: m/z (FAB) 623 $[M+H]^+$.

Sebacoyl-N,N-bis-(3-mercapto-2-(4-methyl-2-imino-thiazol-3-yl)propanoic acid (19). The compound was prepared in the similar manner of preparation of **18** from **7** (0.53 g, 1.0 mmol). Yield: 0.43 g (71%); mp 243-246 °C. 1H NMR (DMSO- d_6): δ 5.92 (s, 2H, $2xH^5_{\text{thiazol}}$); 3.90 (dd, 2H, $J_{H2\text{-cystein},H3\text{-a}} = 7.0$ Hz, $J_{H2\text{-cystein},H3\text{-b}} = 13.9$ Hz $2xH^2_{\text{cystein}}$); 3.10 (m., 4H, $2xH^{3a}_{\text{cystein}} + 2xH^{3b}_{\text{cystein}}$); 2.38 (m, 4H, $+2xCOCH_2\text{sebacoyl}$); 1.68 (s, 6H, $2xC^4_{\text{thiazol-CH}_3}$); 1.58 (m, 4H, $2xCOCH_2CH_2\text{sebacoyl}$); 1.28 (m, 8H, $4xCH_2\text{sebacoyl}$). ^{13}C NMR (DMSO- d_6): δ 173.3 ($2xC^{\text{sebacoyl}}=O$); 163.6 (C=N); 132.7 (C^4_{thiazol}); 99.8 (C^5_{thiazol}); 62.7 (CO_2H-CH); 31.8 ($2xCOCH_2\text{sebacoyl}$); 28.5 ($4xCH_2\text{sebacoyl}$); 25.3 ($2xCOCH_2CH_2\text{sebacoyl}$); 24.1 ($2xCH_2SH$); 18.2 ($2xC^4_{\text{thiazol-CH}_3}$). Anal. calc. for $C_{24}H_{34}N_4O_6S_2$ (602.81): C, 47.82; H, 5.69; N, 9.29. Found: C, 47.61; H, 5.59; N, 9.01. MS: m/z (FAB) 603 $[M+H]^+$.

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