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

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Abstract
A series of sebacoyl 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 sebacoyl chloride 1 with NH4SCN and amino acid or their ester hydrochlorides. Analogously, the sebacoyl-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, sebacoyl 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 developed1,2: nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Three NNRTIs, nevirapine,3 delavirdine,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 NNRTI 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. Recently, Fathalla et al.\textsuperscript{22,23} reported new quinazoline thioureas derivatives bearing an amino acid ester residue based on domino reaction of \textit{N}-(2-cyanophenyl)benzimidoyl isothiocyante with amino acid methyl ester hydrochlorides.

In continuation of our work on amino acid derivatives,\textsuperscript{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.

![PETT](Image)

\textit{Results and Discussion}

In our present work, sebacoyl chloride (octane-1,8-dicarboxylic acid dichloride) 1 has been selected as a spacer building block\textsuperscript{28} for the synthesis of new derivatives of sebacoyl-\textit{N,N}-bis(substituted-alkyl-2-thioureido)alkyl carboxylic acid or ester aiming for evaluation of their anti-HIV activity. Koenig \textit{et al.}\textsuperscript{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\textsubscript{4}SCN in acetone, following Kabbani approach,\textsuperscript{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 \textsuperscript{1}H, \textsuperscript{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 \(\delta\) 2.61-1.78 ppm, while H-8 and H-13 proton signals are oriented as multiplets in the region \(\delta\) 1.81-1.45 ppm. H-9 - H-12 were appeared as multiplets in the region \(\delta\) H-2 of the amino acid moieties are oriented in the region \(\delta\) 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 \textsuperscript{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 \(\delta\) 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 \(\delta\) 177.7-174.1 ppm were assigned to the carbonyl groups of the CSNHCO residues. C-2 of the amino acid moieties [CH-CO\textsubscript{2}H(Me,Et)] appeared in the region \(\delta\)
The sebacoyl carbon atoms C-7 and C-14 are oriented in the region \( \delta \) 38.0-35.3, while C-8 and C-13 were appeared in the region \( \delta \) 26.4-25.0 ppm. The signals between \( \delta \) 31.5 and 24.7 ppm were attributed to C-9 and C-12.

The proton spin system of \( \mathbf{11} \) was further identified from DFQ-COSY\(^{31}\) spectrum, where the doublet of \( H^2_{\text{alanin}} \) at \( \delta \) 3.41 ppm was found to correlate with \( CO_2H - C^2_{\text{alanin}} - H \) at \( \delta \)C 55.9 ppm. In the \( ^1H \) NMR (HMOC)\(^{32}\) spectrum of \( \mathbf{11} \), the multiplets at \( \delta \)H 2.25 and 1.51 ppm of carbon atoms resonating at \( \delta \)C 35.7 and 25.5 ppm were assigned to (CH\(_2\)-7 + CH\(_2\)-14) and (CH\(_2\)-8 + CH\(_2\)-13), respectively, by spin decoupling experiment. Similarly, the methylene protons (CH\(_2\)-9 - CH\(_2\)-12) at \( \delta \)H 1.29 ppm and their carbon atoms (C-9 + C-12) (\( \delta \)C 30.2) and (C-10 + C-11) (\( \delta \)C 28.2 ppm) have been identified. From the gradient selected HMBC\(^{33}\) spectrum of \( \mathbf{11} \), \( H^2_{\text{alanin}} \) proton at \( \delta \)H 3.41 ppm showed two \( ^2J_{C,H} \) couplings: one with \( CO_2H \) at \( \delta \)C 173.0 ppm, and the other with Me\(_{\text{alanin}} \) at \( \delta \)C 17.3 ppm.

![Scheme 1](image)

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

Next, sebacoyl chloride \( \mathbf{1} \) was treated with phthalimide \( \mathbf{13} \) or \( N \)- (phthalimido)methylmagnesium bromide \( \mathbf{15} \), prepared from hydroxymethyl-phthalimide \( \mathbf{14} \), \(^{34}\) in refluxing acetone afforded after purification the sebacoyl-N,N-bis-phthalimide \( \mathbf{16} \) and the
methylphthalimide analogue 17 in 83 and 86% yield, respectively (scheme 2). The structures of 16 and 17 were assigned by the $^1$H, $^{13}$C NMR and mass spectra. The $^1$H NMR spectra showed rather similar patterns for the sebacoyl (CH$_2$) protons for those of 3-12, meanwhile, the singlet at $\delta$ 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 $\delta$ 172.1 and 174.5 ppm were attributed to C=O group of the sebacoyl moiety, while the resonances at $\delta$ 167.3 and 167.4 ppm were assigned to C=O of the phthalimide residue.

Scheme 2. Synthesis of sebacoyl-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 sebacoyl-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 $^1$H-, $^{13}$C NMR and mass spectra. The sebacoyl protons showed rather similar pattern for the sebacoyl (CH$_2$) protons for those of 16 and 17. The singlets at $\delta$ 5.87 and 5.92 ppm were assigned to H-5 of the thiazole ring, respectively, while the singlets at $\delta$ 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 $\delta$ 163.8 and 163.6 ppm, were attributed to C=N (C-2), whereas the signals at $\delta$ 132.9 and 132.7 ppm were assigned to C-4, respectively. C-5 were oriented between $\delta$ 100.1 and 99.8 ppm, respectively. The structures of 18 and 19 were further confirmed by the gradient$^{33}$ selected HMBC spectra. H-5 of the thiazole ring at $\delta_H$ 5.87 and 5.92 ppm showed $^2$J$_{C,H}$ couplings with C-4 of the thiazole ring at $\delta_C$ 132.9 and 132.7 ppm, as well as $^3$J$_{C,H}$ couplings with C=N (C-2) of the thiazole ring at $\delta_C$ 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 IIIb) and HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells, based on MTT assay.\(^5\) None of the new compounds were found to inhibit HIV-1 and HIV-2 replication, in vitro, at IC\(_{50}\) lower than the CC\(_{50}\) in comparison to the antiviral agents Nevirapine (BOE/BIRG587)\(^6\) and azidothymidine (AZT).\(^7\) 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 \((^{13}C)\) spectrometers (Bruker, Germany) with TMS as internal standard and on the \(\delta\) scale in ppm. Signal assignments for protons were identified by selective proton decoupling or by COSY spectra. Heteronuclear assignments were verified by \(^1H-^{13}C\) 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 NH\(_2\)SCN (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.

**Sebacoyl-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-\( d_6 \)): \( \delta \) 3.77 (dd, 2H, \( J_{H2-aspar.H3a-aspar.} = 3.4 \) Hz, \( J_{H2-aspar.H3b-aspar.} = 11.4 \) Hz, \( CO_2H-H^2辞aspar. \)); 3.17 (br s., 1H, NH); 2.75 (dd, 1H, \( J_{H3a.H3b-aspar.} = 15.0 \) Hz, \( H^{3a-aspar.} \)); 2.72 (dd, 1H, \( H^{3b-aspar.} \)); 2.61 (m, 2H, \( CH_2-7 + CH_2-14 \)); 1.69 (m, 4H, \( CH_2-8 + CH_2-13 \)); 1.29-1.23 (m, 8H, \( CH_2-9 + CH_2-10 + CH_2-11 + CH_2-12 \)). \( ^{13}C \) NMR (DMSO-\( d_6 \)): \( \delta \) 184.9 (C=S); 174.3 (CSNHC0 + CO\(_2\)H); 137.1, 127.3, 123.3, 119.8, 11.2, 109.9 (C\(_{trypt.}\)); 66.7 (CO\(_2\)H-C\(_{H}\)); 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 C\(_{20}\)H\(_{30}\)N\(_4\)O\(_{10}\)S\(_2\) (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]+.

**Sebacoyl-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-\( d_6 \)): \( \delta \) 11.08 (br s., 2H, CO\(_2\)H); 3.86 (br s., 1H, NH); 3.59 (dd, 2H, \( J_{H2-glutamic.H3a-glutamic} = 3.5 \) Hz, \( J_{H2-glutamic.H3b-glutamic} = 11.5 \) Hz, \( CO_2H-H^2 glutamic \)); 2.29 (m, 4H, \( H^{4a,b glutamic} \)); 2.14 (m, 4H, \( CH_2-7 + CH_2-14 \)); 2.11 (m, 4H, \( H^{3a,b glutamic} \)); 1.81 (CH-8 + CH-13); 1.31-1.21 (m, 8H, \( CH_2-9 + CH_2-10 + CH_2-11 + CH_2-12 \)). \( ^{13}C \) NMR (DMSO-\( d_6 \)): \( \delta \) 185.7 (C=S); 177.5 (CO\(_2\)H); 174.7 (CSNHC0 + CO\(_2\)H); 61.9 (CO\(_2\)H-C\(_{H}\)); 35.7 (C-7 + C-14); 30.8 (C10 + C-11 + C\(^4\) glutamic); 29.2 (C-9 + C-12); 26.4 (C-8 + C-13 + C\(^3\) glutamic). Anal. calc. for C\(_{22}\)H\(_{34}\)N\(_4\)O\(_{10}\)S\(_2\) (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]+.

**Sebacoyl 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-\( d_6 \)): \( \delta \) 8.01 (br s., 1H, NH); 3.71 (s, 3H, CO\(_2\)Me); 3.46 (dd, 2H, \( J_{2,3(valin)} = 7.5 \) Hz, \( 2xH^2_valin \)); 2.76 (m, 2H, \( 2xH^3_valin \)); 2.01 (m, 4H, \( CH_2-7 + CH_2-14 \)); 1.51 (m, 4H, \( CH_2-8 + CH_2-13 \)); 1.32 (m, 4H, \( CH_2-9 + CH_2-12 \)); 1.24 (CH-10 + CH-11); 1.08 (m, 12H, \( 4xCH_3 \)). \( ^{13}C \) NMR (DMSO-\( d_6 \)): \( \delta \) 187.1 (C=S); 174.3 (CSNHC0); 170.8 (COEt); 61.8 (CO\(_2\)Me-C\(_{H}\)); 52.1 (CO\(_2\)Me); 37.4 (C-7 + C-14); 31.4 (C\(^3\) valin); 29.8 (C-9 + C-10 + C-11 + C-12); 26.1 (C-8 + C-13); 18.3 (CH\(_3\)). Anal. calc. for C\(_{24}\)H\(_{32}\)N\(_4\)O\(_{10}\)S\(_2\) (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]+.

**Sebacoyl-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-\( d_6 \)): \( \delta \) 8.73, \( J_{H2-lysin,H3-a,b} = 6.1 \) Hz, \( 2xH^2_lysin \)); 2.72 (br s., 8H, \( 2xCH_2-NH_2+2xNH_2 \)); 1.82-1.77 (m, 8H, \( 2xCH_2-3lysin+CH_2-7 + CH_2-14 \)); 1.59 (m, 6H, \( 2xCH_2-5lysin + 2xNH \)); 1.47 (m, 4H, \( CH_2-8 + CH_2-13 \)); 1.38 (m, 4H, \( CH_2-9 + CH_2-12 \)); 1.23 (m, 10H, \( 2xOCH_2CH_3 + CH_2-10 + CH_2-11 \)). \( ^{13}C \) NMR (DMSO-\( d_6 \)): \( \delta \) 187.9 (C=S); 174.1 (CSNHC0); 170.6 (COEt); 61.7 (OCH\(_2\)CH\(_3\) + CO\(_2\)Et-CH\(_3\)); 51.1 (CH\(_2\)NH\(_2\)); 37.8 (C-7 + C-14); 29.2 (C\(^3\) lysin + C-9 + C-10 + C-11 + C-12); 26.0 (C-8 + C-13); 21.1 (C\(^4\) lysin); 13.9 (OCH\(_2\)CH\(_3\)). Anal. calc. for C\(_{28}\)H\(_{32}\)N\(_4\)O\(_{10}\)S\(_2\) (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]+.
Sebacoyl-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. $^1$H NMR (DMSO-d$_6$): $\delta$ 4.03 (dd, 2H, $J_{H2-cystein,H3-a} = 7.1$ Hz, $J_{H2-cystein,H3-b} = 14.2$ Hz 2xH$_2$ cystein); 3.16 (br s., 4H, 2xH$_{3a}$ cystein + 2xH$_{3b}$ cystein): 2.32 (m, 4H, +CH$_2$-7 + CH$_2$-14); 1.52 (m, 4H, CH$_2$-8 + CH$_2$-13)); 1.29 (m, 4H, CH$_2$-9 + CH$_2$-12); 1.21 (m, 4H, CH$_2$-10 + CH$_2$-11). $^{13}$C NMR (DMSO-d$_6$): $\delta$ 188.8 (C=S); 175.7 (CSNHC0); 174.9 (CO$_2$H); 63.9 (CO$_2$H-CH); 36.4 (C-7 + C-14); 32.0 (C-10 + C-11); 28.9 (C-9 + C-12); 27.2 (CH$_2$SH); 25.0 (C-8 + C-13). Anal. calc. for C$_{18}$H$_{30}$N$_4$O$_6$S$_4$ (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]$^+$.  

Sebacoyl-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. $^1$H NMR (DMSO-d$_6$): $\delta$ 10.90 (s, 1H, CO$_2$H); 7.20 (1H, d, $J_{2,2NH} = 2.2$ Hz, H$_2$tryp); 7.56 (d, 1H, $J = 7.8$ Hz, H$_2$tryp); 7.34 (d, 1H, $J_{1,2H} = 8.0$ Hz, H$_1$tryp); 7.07 (t, 1H, $J = 8.0$ Hz, H$_2$tryp); 6.98 (t, 1H, $J = 7.8$ Hz, H$_1$tryp). 3.43 (dd, 2H, $J_{2,2,2H2,2tryp} = 4.0$ Hz, $J_{2,2,2H2,2tryp} = 9.0$ Hz, CO$_2$H-2xH$_2$tryp); 3.31 (dd, 1H, CH$_2$a-tryp); 2.93 (dd, 1H, $J_{1,2a,3b-tryp} = 15.0$ Hz, CH$_2$b-tryp); 2.33 (m, 4H, CH$_2$-7 + CH$_2$-14); 1.69 (m, 4H, CH$_2$-8 + CH$_2$-13); 1.29-1.23 (m, 8H, CH$_2$-9 + CH$_2$-10 + CH$_2$-11 + CH$_2$-12). $^{13}$C NMR (DMSO-d$_6$): $\delta$ 184.9 (C=S); 174.3 (CSNHC0 + CO$_2$H); 137.1, 127.3, 123.3, 119.8, 111.2, 109.9 (C(tryp)); 62.7 (CO$_2$H-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 C$_{34}$H$_{40}$N$_6$O$_6$S$_2$ (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]$^+$.  

Sebacoyl-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. $^1$H NMR (DMSO-d$_6$): $\delta$ 7.38 (s, 1H, H$_5$imidazo); 6.37 (s, 1H, H$_5$imidazo); 3.64 (dd, 2H, $J_{2,2,a(histidin)} = 7.5$ Hz, $J_{2,2,b(histidin)} = 13.5$ Hz 2xH$_2$histidin); 3.10 (m, 4H, 2xH$_3$hisidin + 2xH$_3$hisidin); 2.14 (m, 4H, +CH$_2$-7 + CH$_2$-14); 1.63 (m, 4H, CH$_2$-8 + CH$_2$-13); 1.28 (m, 4H, CH$_2$-9 + CH$_2$-12); 1.23 (m, 4H, CH$_2$-10 + CH$_2$-11). $^{13}$C NMR (DMSO-d$_6$): $\delta$ 184.2 (C=S); 177.7 (CSNHC0); 174.0 (CO$_2$H); 135.4, (C$_4$imidazol); 132.7 (C$_4$imidazol); 120.3 (C$_5$imidazol); 61.9 (CO$_2$H-CH); 37.4 (C-7 + C-14); 29.9 (C-10 + C-11 + C$_3$imidazol); 28.2 (C-9 + C-12); 26.0 (C-8 + C-13). Anal. calc. for C$_{24}$H$_{34}$N$_6$O$_6$S$_2$ (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]$^+$.  

Sebacoyl-N,N-bis(2-thioureido-5-pentanido)pentanoic acid (10). From L-arginine (1.04 g). Yield: 1.64 g (86%); mp 120-122 °C. $^1$H NMR (DMSO-d$_6$ + D$_2$O): $\delta$ 3.69 (dd, 2H, $J_{H2-arginin,H3a-arginin} = 3.6$ Hz, $J_{H2-arginin,H3b-arginin} = 11.6$ Hz, CO$_2$H-H$_2$arginin); 2.69 (m, 4H, 2xCH$_2$-5arginin); 1.81 (m, 4H, 2xCH$_2$-3arginin); 1.91 (m, 4H, CH$_2$-7 + CH$_2$-14); 1.61 (m, 8H, 2xCH$_2$-4arginin + CH$_2$-8 + CH$_2$-13); 1.31-1.27 (m, 8H, CH$_2$-9 + CH$_2$-10 + CH$_2$-11 + CH$_2$-12). $^{13}$C NMR (DMSO-d$_6$ + D$_2$O): $\delta$ 184.7 (C=S); 175.2 (CONH); 174.4 (CSNHC0); 157.8 (C=NH); 61.9 (CO$_2$D-CH); 36.1 (C-7 + C-14 + 2xC$_3$arginin); 28.8 (C-9 + C-10, C-11, C-12 + 2xC$_3$arginin); 26.2 (C-8 + C-13 + 2xC$_4$arginin). Anal. calc. for C$_{24}$H$_{44}$N$_{10}$O$_6$S$_2$ (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]$^+$.  

Sebacoyl-N,N-bis(2-thioureido)propanoic acid (11). From L-alanine (0.53 g). Yield: 0.96 (69%); mp 257-260 °C. $^1$H NMR (DMSO-d$_6$): $\delta$ 3.41 (d, 2H, $J_{H2-alamin,CH3-alamin} = 3.6$ Hz, 2xH$_2$alanin); 2.25 (m, 4H, +CH$_2$-7 + CH$_2$-14); 1.51 (m, 4H, CH$_2$-8 + CH$_2$-13)); 1.29 (m, 8H, CH$_2$-
9 - CH₂-12); 1.24 (t, 6H, J = 7.0 Hz, Me₂alanin) ¹³C NMR (DMSO-d₆): δ 186.7 (C=S); 175.7 (CSNHCOC); 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 (Me₂alanin). Anal. calc. for C₁₈H₃₀N₂O₈S₂ (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-d₆): δ 8.02 (br s., 2H, 2xNH); 3.67 (t, 2H, Jₙ₂ₙ₃₋₄ = 5.5 Hz, 2xH⁻¹₂₅₇₅₈₉₁₀); 2.76 (m., 4H, 2xCH₂-NH₂); 1.78-1.71 (m, 8H, 2xCH₂-3lysin+CH₂-7 + CH₂-14); 1.57 (m, 4H, 2xCH₂-4lysin); 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-d₆): δ 187.1 (C=S); 175.8 (CSNHCOC+CO₂H); 63.5 (CO₂H-CH); 40.0 (CH₂NH₂); 38.0 (C-7 + C-14); 29.2-27.4 (C³lysin + C⁴lysin + C-9 + C-10 + C-11 + C-12); 26.1 (C-8 + C-13). Anal. calc. for C₁₂₆H₁₄₄N₁₀O₁₆S₂ (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-d₆): 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-d₆): δ 172.1 (CH₂-C=O); 167.3 (C³phthalamide); 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 C₁₂₆H₁₄₄N₁₀O₁₆S₂ (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-d₆): δ 7.93-7.86 (m, 8H, Ar-H); 4.96 (s, 4H, 2xCH₂-phthalamide); 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-d₆): δ 174.5 (CH₂-C=O); 167.4 (C³phthalamide); 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 C₁₂₆H₁₄₄N₁₀O₁₆S₂ (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-d₆): δ 5.87 (s, 2H, 2xH³thiazol); 3.68 (s, 3H, CO₂Me); 3.48 (dd, 2H, J₂₃,₂₄ = 7.3 Hz, 2xH²valin); 2.75 (m, 2H, 2xH³valin); 2.13 (m, 4H, 2xCOCH₂sebacoyl); 1.70 (s, 6H, 2xC¹thiazol-CH₃); 1.55 (m, 4H, 2xCOCH₂CH₂sebacoyl); 1.30 (m, 8H, 4xCH₂sebacoyl); 1.07 (m, 12H, 4xCH₃valin). ¹³C NMR (DMSO-d₆): δ 173.1 (2xSebacoyl-O)= 171.5 (2xCO₂Me); 163.8 (C=N); 132.9 (C¹thiazol); 100.1 (C⁵thiazol); 60.5 (2xCO₂Me-CH); 52.4 (2xCO₂Me); 34.1 (2xCOCH₂sebacoyl);
30.2-25.8 (C$_{3}$valin + 6xCH$_{2}$sebacoyl); 18.1 ((2xC$_{4}$thiazol-CH$_{3}$). Anal. calc. for C$_{30}$H$_{46}$N$_{4}$O$_{6}$S$_{2}$ (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. $^{1}$H NMR (DMSO-d$_{6}$): δ 5.92 (s, 2H, 2xH$_{3}$thiazol); 3.90 (dd, 2H, J$_{H2}$-cystein,H$_{3}$-a)$^{=} = 7.0$ Hz, J$_{H2}$-cystein,H$_{3}$-b)$^{=} = 13.9$ Hz 2xH$_{2}$cystein); 3.10 (m, 4H, 2xH$_{3}$cystein + 2xH$_{3}$cystein); 2.38 (m, 4H, +2xCOCH$_{2}$sebacoyl); 1.68 (s, 6H, 2xC$_{4}$thiazol-CH$_{3}$); 1.58 (m, 4H, 2xCOCH$_{2}$CH$_{2}$sebacoyl); 1.28 (m, 8H, 4xCH$_{2}$sebacoyl). $^{13}$C NMR (DMSO-d$_{6}$): δ 173.3 (2xC$_{4}$sebacoyl=O); 163.6 (C=N); 132.7 (C$_{4}$thiazol); 99.8 (C$_{5}$thiazol); 62.7 (CO$_{2}$H-CH); 31.8 (2xCOCH$_{2}$sebacoyl); 28.5 (4xCH$_{2}$sebacoyl); 25.3 (2xCOCH$_{2}$CH$_{2}$sebacoyl); 24.1 (2xCH$_{2}$SH); 18.2 (2xC$_{4}$thiazol-CH$_{3}$). Anal. calc. for C$_{24}$H$_{34}$N$_{4}$O$_{6}$S$_{2}$ (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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References

