Amino acid derivatives. Part 5. Synthesis and anti-HIV activity of new sebacoyl 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]

[a]Department of Chemistry, College of Science, University of Basrah, Basrah, Iraq
[b]Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium
E-mail: najim.al-masoudi@gmx.de

DOI: http://dx.doi.org/10.3998/ark.5550190.0011.918

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 NH_4SCN 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 Br_2 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.

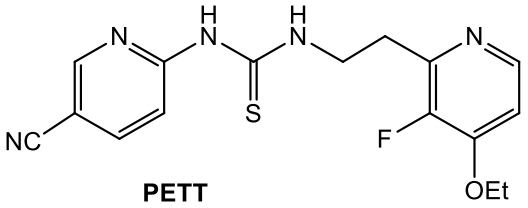
Keywords: Amino acids, anti-HIV activity, phthalimide, sebacoyl chloride

Introduction

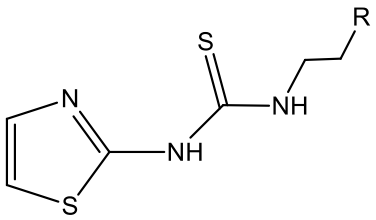
HIV-1 reverse transcriptase is a key enzyme in the HIV replication as well as a key target for developing anti-HIV drugs. Two types of reverse transcriptase inihibitors have been developed[1,2]: nucleoside reverse transcriptase inihibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTI). Three NNRTIs, nevirapine,[3] delaviridine,[4] and efavirenz[5] 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 activity[8-12] 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



PETT



thiazole thiourea

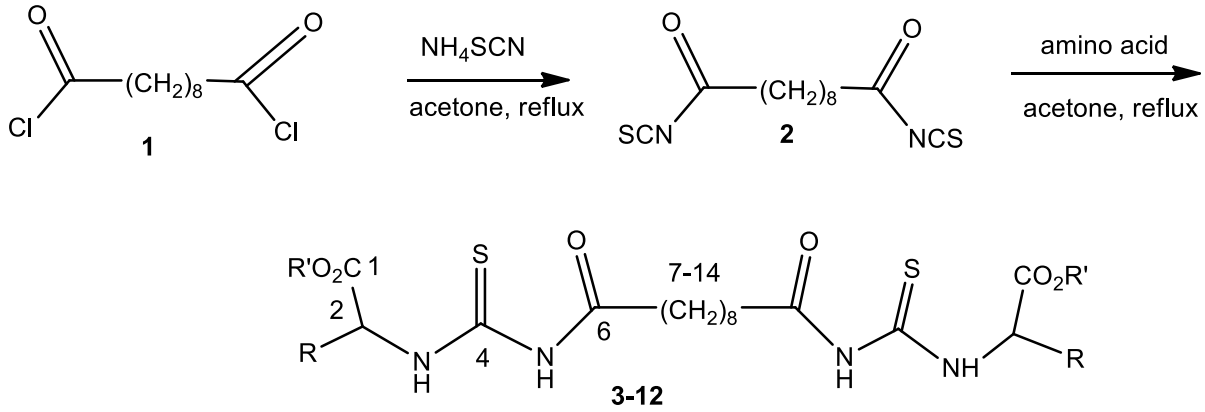
Results and Discussion

In our present work, sebacoyl chloride (octane-1,8-dicarboxylic acid dichloride) **1** has been selected as a spacer building block[28] 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 CSNH*CO* residues. C-2 of the amino acid moieties [*C*H-CO_2H(Me,Et)] appeared in the region δ

66.7-55.9 ppm. The sebacoyl 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-COSY[31] spectrum, where the doublet of H^2_{alanin} at δ 3.41 ppm was found to correlate with CO_2H-C^2_{alanin}-H) at δ_C 55.9 ppm. In the ^{1}H 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 (CH_2-7 + CH_2-14) and (CH_2-8 + CH_2-13), respectively, by spin decoupling experiment. Similary, the methylene protons (CH_2-9 - CH_2-12) 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 HMBC[33] spectrum of **11**, H^2_{alanin} proton at δ_H 3.41 ppm showed two $^2J_{C,H}$ couplings: one with CO_2H at δ_C 173.0 ppm, and the other with Me_{alanin} at δ_C 17.3 ppm.

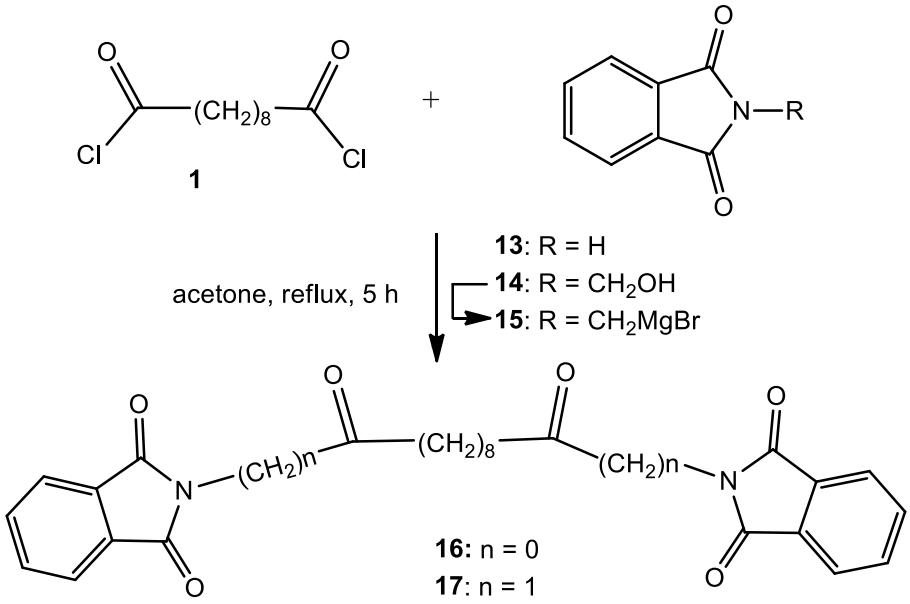


	R	R'	Amino acid
3	CH_2CO_2H	H	L-aspartic acid
4	$(CH_2)_2CO_2H$	H	L-glutamic acid
5	$CH(CH_3)_2$	Me	L-valin-Me-ester
6	$(CH_2)_4NH_2$	Et	L-lysine-Et-ester
7	CH_2SH	H	L-cysteine
8	CH_2-3-indole	H	L-tryptophane
9	CH_2-3-imidazole	H	L-histidine
10	$(CH_2)_3$-guanidine	H	L-arginine
11	CH_3	H	L-alanine
12	$(CH_2)_4NH_2$	H	L-lysine

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

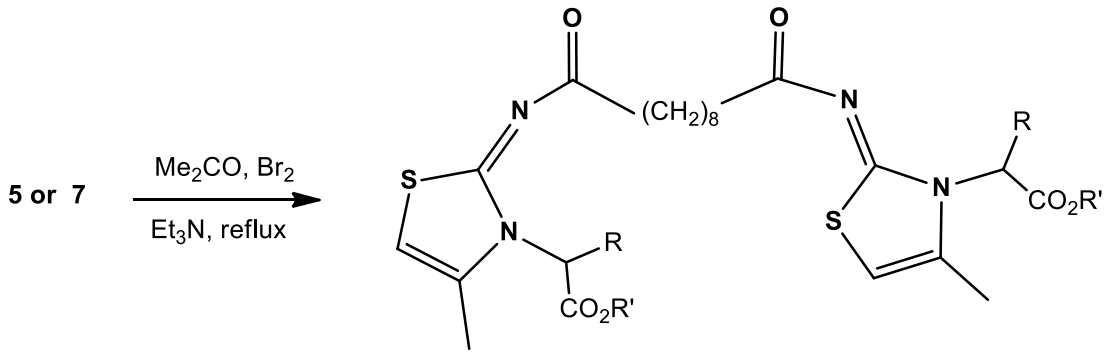
Next, sebacoyl chloride **1** was treated with phthalimide **13** or *N*-(phthalimido)methylmagnesium bromide **15**, prepared from hydroxymethyl-phthalimide **14**,[34] in refluxing acetone afforded after purification the sebacoyl-*N*,*N*-bis-phthalimide **16** and the

methylphthalimide analogue **17** in 83 and 86% yield, respectively (scheme 2). The structures of **16** and **17** were assigned by the ^{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 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 sebacoyl 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 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 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 gradient[33] selected HMBC spectra. H-5 of the thiazole ring at δ_H 5.87 and 5.92 ppm showed $^{2}J_{C,H}$ couplings with C-4 of the thiazole ring at δ_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 δ_C 163.8 and 163.6 ppm, respectively.



	R	R'	Amino acid
18	$(CH(Me)_2$	Me	L-valin-Me-ester
19	CH_2SH	H	L-cystein

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 IC_{50} lower than the CC_{50} 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 (^{13}C) 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-^{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_4SCN (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 vigrous 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 ºC. ^{1}H NMR (DMSO-d_6): δ 3.77 (dd, 2H, $J_{H2\text{-}aspar,H3a\text{-}aspar.}$= 3.4 Hz, $J_{H2\text{-}aspar.,H3b\text{-}aspar.}$= 11.4 Hz, CO_2H-H^2_{aspar}); 3.17 (br s., 1H, NH); 2.75 (dd, 1H, $J_{H3a,H3b\text{-}aspar.}$= 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): δ 184.9 (C=S); 174.3 (CSNH*CO* + CO_2H); 137.1, 127.3, 123.3, 119.8, 11.2, 109.9 ($C_{trypt.}$); 66.7 (CO_2H-*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 $C_{20}H_{30}N_4O_{10}S_2$ (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 ºC. ^{1}H NMR (DMSO-d_6): δ 11.08 (br s., 2H, CO_2H); 3.86 (br s., 1H, NH); 3.59 (dd, 2H, $J_{H2\text{-}glutamic,H3a\text{-}glutamic}$= 3.5 Hz, $J_{H2\text{-}glutamic,H3b\text{-}glutamic}$= 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_2-8 + CH_2-13); 1.31-1.21 (m, 8H, CH_2-9 + CH_2-10 + CH_2-11 + CH_2-12). ^{13}C NMR (DMSO-d_6): δ 185.7 (C=S); 177.5 (CO_2H); 174.7 (CSNH*CO* + CO_2H); 61.9 (CO_2H-*CH*); 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 $C_{22}H_{34}N_4O_{10}S_2$ (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 ºC. ^{1}H NMR (DMSO-d_6): δ 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_2-10 + CH_2-11); 1.08 (m, 12H, 4xCH_3). ^{13}C NMR (DMSO-d_6): δ 187.1 (C=S); 174.3 (CSNH*CO*); 170.8 (*CO*Et); 61.8 (CO_2Me-*CH*); 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 $C_{24}H_{42}N_4O_6S_2$ (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 ºC. ^{1}H 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, 2xOCH_2CH_3); 3.92 (t, 2H, $J_{H2\text{-}lysin,H3\text{-}a,b)}$ = 6.1 Hz, 2xH^2_{lysin}); 2.72 (br s., 8H, 2xCH_2-NH_2+2xNH_2); 1.82-1.77 (m, 8H, 2xCH_2-3_{lysin}+CH_2-7 + CH_2-14); 1.59 (m, 6H, 2xCH_2-5_{lysin} + 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): δ 187.9 (C=S); 174.1 (CSNH*CO*); 170.6 (*CO*Et); 61.7 (O$CH_2$$CH_3$ + CO_2Et-*CH*); 51.1 (CH_2NH_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_2CH_3). Anal. calc. for $C_{28}H_{52}N_6O_6S_2$ (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 215-217ºC. ^{1}H NMR (DMSO-d_6): δ 4.03 (dd, 2H, $J_{H2\text{-}cystein,H3\text{-}a)}$ = 7.1 Hz, $J_{H2\text{-}cystein,H3\text{-}b)}$= 14.2 Hz 2x$H^2_{cystein}$); 3.16 (br s., 4H, 2x$H^{3a}_{cystein}$ + 2x$H^{3b}_{cystein}$); 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): δ 188.8 (C=S); 175.7 (CSNH*CO*); 174.9 (CO_2H); 63.9 (CO_2H-*CH*); 36.4 (C-7 + C-14); 32.0 (C-10 + C-11); 28.9 (C-9 + C-12); 27.2 (CH_2SH); 25.0 (C-8 + C-13). Anal. calc. for $C_{18}H_{30}N_4O_6S_4$ (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 ºC. ^{1}H NMR (DMSO-d_6): δ 10.90 (s, 1H, CO_2H); 7.20 (1H, d, $J_{2,NH}$ = 2.2 Hz, $H^2_{trypt.}$); 7.56 (d, 1H, J = 7.8 Hz, H^7_{trypt}); 7.34 (d, 1H, = 8.0 Hz, H^4_{trypt}); 7.07 (t, 1H, J= 8.0 Hz, H^5_{trypt}); 6.98 (t, 1H, J= 7.8 Hz, H^6_{trypt}). 3.43 (dd, 2H, $J_{2,\ CH2a\text{-}trypt.}$= 4.0 Hz, $J_{2,CH2b\text{-}trypt.}$= 9.0 Hz, CO_2H-2x$H^2_{trypt.}$); 3.31 (dd, 1H, CH_2a-trypt); 2.93 (dd, 1H, $J_{Ha,Hb\text{-}trypt.}$= 15.0 Hz, CH_2b-trypt.); 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): δ 184.9 (C=S); 174.3 (CSNH*CO* + CO_2H); 137.1, 127.3, 123.3, 119.8, 111.2, 109.9 ($C_{trypt.}$); 62.7 (CO_2H-*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 $C_{34}H_{40}N_6O_6S_2$ (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 ºC. ^{1}H NMR (DMSO-d_6): δ 7.38 (s, 1H, $H^2_{imidazol}$); 6.37 (s, 1H, $H^5_{imidazol}$); 3.64 (dd, 2H, $J_{2',3'a(histidin)}$= 7.5 Hz, $J_{2',3'ba(histidin)}$ = 13.5 Hz 2x$H^2_{histidin}$); 3.10 (m., 4H, 2x$H^{3a}_{hisidin}$ + 2x$H^{3b}_{histidin}$); 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): δ 184.2 (C=S); 177.7 (CSNH*CO*); 174.0 (CO_2H); 135.4, ($C^2_{imidazol}$); 132.7 ($C^4_{imidazol}$); 120.3 ($C^5_{imidazol}$); 61.9 (CO_2H-*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 $C_{24}H_{34}N_8O_6S_2$ (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-guanidino)pentanoic acid (10). From L-arginine (1.04 g). Yield: 1.64 g (86%); mp 120-122 ºC. ^{1}H NMR (DMSO-d_6 + D_2O): δ 3.69 (dd, 2H, $J_{H2\text{-}arginin,H3a\text{-}arginin}$= 3.6 Hz, $J_{H2\text{-}arginin,H3b\text{-}arginin}$= 11.6 Hz, CO_2H-$H^2_{arginin}$); 2.69 (m, 4H; 2xCH_2-$5_{arginin}$); 1.81 (m, 4H, 2xCH_2-$3_{arginin}$); 1.91 (m, 4H, CH_2-7 + CH_2-14); 1.61 (m, 8H, 2xCH_2-$4_{arginin}$ + 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_2O): δ 184.7 (C=S); 175.2 (CONH); 174.4 (CSNH*CO*); 157.8 (C=NH); 61.9 (CO_2D-*CH*); 36.1 (C-7 + C-14 + 2x$C^5_{arginin}$); 28.8 (C-9 + C-10, C-11, C-12 + 2x$C^3_{arginin}$); 26.2 (C-8 + C-13 + 2x$C^4_{arginin}$). Anal. calc. for $C_{24}H_{44}N_{10}O_6S_2$ (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 ºC. ^{1}H NMR (DMSO-d_6): δ 3.41 (d, 2H, $J_{H2\text{-}alanin,CH3\text{-}alanin)}$ = 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 - CH_2-12); 1.24 (t, 6H, *J* = 7.0 Hz, Me_{alanin}) ^{13}C NMR (DMSO-d_6): δ 186.7 (C=S); 175.7 (CSNH*CO*); 173.0 (CO_2H); 55.9 (CO_2H-*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 $C_{18}H_{30}N_4O_6S_2$ (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%); mp230-232 °C. ^1H NMR (DMSO-d_6): δ 8.02 (br s., 2H, 2xNH); 3.67 (t, 2H, $J_{H2\text{-}lysin,H3\text{-}a,b)}$ = 5.5 Hz, 2xH^2_{lysin}); 2.76 (m., 4H, 2xCH_2-NH_2); 1.78-1.71 (m, 8H, 2xCH_2-3_{lysin}+CH_2-7 + CH_2-14); 1.57 (m, 4H, 2xCH_2-4_{lysin}); 1.45 (m, 4H, CH_2-8 + CH_2-13); 1.38 (m, 4H, CH_2-9 + CH_2-12); 1.23 (m, 4H, CH_2-10 + CH_2-11). ^{13}C NMR (DMSO-d_6): δ 187.1 (C=S); 175.8 (CSNH*CO* +CO_2H); 63.5 (CO_2H-*CH*); 40.0 (CH_2NH_2); 38.0 (C-7 + C-14); 29.2-27.4 (C^3_{lysin} + C^4_{lysin} + C-9 + C-10 + C-11 + C-12); 26.1 (C-8 + C-13). Anal. calc. for $C_{24}H_{44}N_6O_6S_2$ (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, CH_2-2 + CH_2-9); 1.52 (m, 4H, CH_2-3 + CH_2-8); 1.27 (m, 8H, CH_2-4 - CH_2-7). ^{13}C NMR (DMSO-d_6): δ 172.1 (CH_2-*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 $C_{26}H_{24}N_{26}O_6$ (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, 2xCH_2-phthal.); 2.17 (t, 4H, *J* = 7.3 Hz, CH_2-3 + CH_2-10); 1.47 (m, 4H, CH_2-4 + CH_2-9); 1.24 (m, 8H, CH_2-5 - CH_2-8). ^{13}C NMR (DMSO-d_6): δ 174.5 (CH_2-*C*=*O*); 167.4 ($C^{phthal.}$=O); 134.7, 131.5, 123.7 (Ar-C); 60.1 (*CH_2*-C=O); 38.9 (C-3 + C-10); 28.5 (C-5 – C-8); 24.4 (C-4 + C-9). Anal. calc. for $C_{28}H_{28}N_2O_6$ (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 Et_3N (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, 2x$H^5_{thiazol}$); 3.68 (s, 3H, CO_2*Me*); 3.48 (dd, 2H, $J_{2,3(valin)}$= 7.3 Hz, 2xH^2_{valin}); 2.75 (m, 2H, 2xH^3_{valin}); 2.13 (m, 4H, 2xCO*$CH_{2sebacoyl}$*); 1.70 (s, 6H, 2x$C^4_{triazol}$-*CH_3*); 1.55 (m, 4H, 2x$COCH_2$*$CH_{2sebacoyl}$*); 1.30 (m, 8H, 4x$CH_{2sebacoyl}$); 1.07 (m, 12H, 4xCH_{3valin}). ^{13}C NMR (DMSO-d_6): δ 173.1 (2x$C^{sebacoyl}$=O); 171.5 (2x*CO_2*Me); 163.8 (C=N); 132.9 ($C^4_{thiazol}$); 100.1 ($C^5_{thiazol}$); 60.5 (2xCO_2Me-*CH*); 52.4 (2xCO_2*Me*); 34.1 (2xCO*$CH_{2sebacoyl}$*);

30.2-25.8 (C^3_{valin} + 6x$CH_{2sebacoyl}$); 18.1 ((2x$C^4_{thiazol}$-*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. ^{1}H NMR (DMSO-d_6): δ 5.92 (s, 2H, 2x$H^5_{thiazol}$); 3.90 (dd, 2H, $J_{H2\text{-}cystein,H3\text{-}a)}$= 7.0 Hz, $J_{H2\text{-}cystein,H3\text{-}b)}$= 13.9 Hz 2x$H^2_{cystein}$); 3.10 (m., 4H, 2x$H^{3a}_{cystein}$ + 2x$H^{3b}_{cystein}$); 2.38 (m, 4H, +2xCO*$CH_{2sebacoyl}$*); 1.68 (s, 6H, 2x$C^4_{triazol}$-*CH_3*); 1.58 (m, 4H, 2x$COCH_2$*$CH_{2sebacoyl}$*); 1.28 (m, 8H, 4x$CH_{2sebacoyl}$). ^{13}C NMR (DMSO-d_6): δ 173.3 (2x$C^{sebacoyl}$=O); 163.6 (C=N); 132.7 ($C^4_{thiazol}$); 99.8 ($C^5_{thiazol}$); 62.7 (CO_2H-*CH*); 31.8 (2xCO*$CH_{2sebacoyl}$*); 28.5 (4x$CH_{2sebacoyl}$); 25.3 (2x$COCH_2$*$CH_{2sebacoyl}$*); 24.1 (2xCH_2SH); 18.2 (2x$C^4_{thiazol}$-*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 $[M+H]^+$.

Acknowledgments

We thank Mr. U. Haunz of chemistry department, University of Konstanz, Germany for the NMR experiments.

References

1. De Clercq, E. *Med. Chem. Res.* **2004**, *13*, 439.
2. Barbaro, G.; Scozzafava, A.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Pharm. Des.* **2005**, *11*, 1805.
3. Koup, R. A.; Merluzzi, V. J.; Hargrave, J. L. *J. Infect. Dis.* **1991**, *163*, 966.
4. Freimuth, W. W. *Adv. Exp. Med. Biol.* **1996**, *394*, 279.
5. Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Olsen, D. B.; Carroll, S. S.; Pettibone, D. J.; Obrien, J. A.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, I. W.; Schleif, W. A.; Sardana, V. V.; Long, W. J.; Byrnes, V. W.; Emini, E. A. *Antimicrob. Agents Chemother.* **1995**, *39*, 2602.
6. Wainberg, M. A.; Sawyer, J. P.; Montaner, J. S.; Murphy, R. L.; Kuritzkes, D. R.; Raffi, F. *Antiviral Ther.* **2005**, *10*, 13.
7. Imamichi, T. *Curr. Pharm. Des.* **2004**, *10*, 4039.
8. Amajaour, H. A. S.; Al-Soud, Y. A.; Al-Sa'doni, H.; Al-Masoudi, N. A. *Z. Naturforsch. (J. Chem. Sci).* **2007**, *62b*, 523.
9. Al-Masoudi, N. A.; Al-Soud, Y. A.; Kalogerakis, A.; De Clercq, E.; Paneccoque, C. *Chem. Biodiver.* **2006**, *3*, 515.
10. Y. A. Al-Soud, N. A. Al-Masoudi, E. De Clercq and C. Paneccoque, *Heteroatom Chem.* **2007**, *4*, 333.

11. Al-Soud, Y. A.; Al-Masoudi, N. A.; De Clercq, E.; Paneccoque, C. *Antiviral Chem. Chemother*. **2007**, *18*, 191.
12. Al-Soud, Y. A.; Al-Masoudi**,** N. A.; Gh. Hassan, H.; Gh.; De Clercq, E.; Pannecouque, C. *Acta Pharm.* **2007**, *57*, 379.
13. Ahgren, C.; Backro, K.; Bell, F. W.; Cantrell, A. S.; Clemens, M.; Colacino, J.; Deeter, M. J. B.; Engelhardt, J. A.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C. L.; Kasher, J. S.; Kinnick, M. D.; Lind, P.; Lopez, C.; Morin, J. M.; Muesing, M. A.; Noreen, R.; Oberg, B.; Paget, C. J.; Palkowitz, J. A.; Parrish, C.; Pranc, P.; Rippy, M. K.; Rydergard, C.; Sahlberg, C.; Swanson, S.; Ternansky, R.; Unge, J.; Vasileff, T. R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X. X. *Antimicrob. Agents Chemother*. **1995**, *39*, 1329.
14. Heinisch, G.; Matuszczak, B.; Pachler, S.; Rakowitz, D. *Antivir. Chem. Chemother*. **1997**, *8*, 443.
15. Ren, J.; Diprose, J.; Warren, J.; Esnouf, R. M.; Bird, L. E.; Ikemizu, S.; Slater, M.; Milton, J.; Balzarini, J.; Stuart, D. I; Stammers, D. K. *J. Biol. Chem.* **2000,** *275*, 5633.
16. Ahgren, C.; Backro, K.; Bell, F. W.; Cantrell, S.; Clemens, M.; Colacino, J. M.; Deeter, M. J. B.; Engelhardt, J. A.; Hogberg, M.; Jaskunas, S. R. *Antimicrob. Agents Chemother.* **1995**, *39*, 1329.
17. Uckun, F. M.; Venkatachalam, T. K. United States Patent 2005, 6960606.
18. Fathalla, W.; Pazdera, P. *Arkivoc* **2007**, (*i)*, 236.
19. Fathalla, W.; Ali, I. A. I. *Heteroatom Chem.* **2007**, *18*, 637.
20. Fathalla, W.; El Rayes, S. M.; Ali, I. A. I. *Arkivoc* **2007**, (*xvi)*, 173.
21. El Rayes, S. M.; Ali, I. A. I.; Fathalla, W. *Arkivoc* **2008**, (*xi)*, 86.
22. Fathalla, W.; Pazdera, P. *Arkivoc* **2007**, (*i)*, 236.
23. 23.. Fathalla, W. *Arkivoc* **2008**, *(xii)*, 245.
24. Ali, I. A. I.; Al-Masoudi, I. A.; Saeed, B.; Al-Masoudi; N. A.; La Colla, P. *Heteroatom Chem.* **2005**, *16*, 148.
25. Al-Masoudi, N. A.; Al-Masoudi, I. A.; Ali, I . A. I.; Saeed, B.; La Colla, P. *Heteroatom Chem.* **2005**, *16*, 576**.**
26. Ali, I. A. I.; Al-Masoudi, I. A.; Al-Soud, Y. A.; Saeed, B.; Al-Masoudi, N. A.; La Colla, P.*Acta Pharm.* **2006**, *56*, 175.
27. Hamad, N.S.; Al-Haidari, N. H.; Al-Masoudi, **I. A.;** Sabri, M.; Sabri, L.; Al-Masoudi, N. A. *Arch. Pharmazie- life Science* **2010**, *in press*.
28. Masllorens, J.; Pla-Quintana, A.; Parella,T.; Roglans, A. *Arkivoc* **2010**, (*ii)*, 203.
29. Koenig, K.-H.; Kuge, M.; Kaul, L.; Pletsch, H.-J. *Chem. Ber*. **1987**, *120*, 1251.
30. Kabbani, A. T.; Ramadan, H.; Hammud, H. H.; Ghannoum, A. M.; Mouneimne, Y. *J. Uni. Chem. Techn. Metal.* **2005**, *40*, 339.
31. Al-Masoudi, N A.; Al-Soud, Y. A.; Geyer, A. *Spectroscopy Lett.* **1998**, *31*, 1031.
32. Bax, A.; Griffey, R. H.; Hawkins, B. L. Correlation *J. Magn. Reson.* **1983**, *55*, 301
33. Willker, W.; Leibfritz, D.; Kerssebaum, R.; Bermel, W. *Mag. Reson.* **1993**, *Chem. 31*, 287.
34. Hong, S. I.; Kim, C. K.; Kim, Y. J. *Bull. Korean Chem. Soc.* **1983**, *4*, 171.

35. R. Pauwels, J. Balzarini, M. Baba, R. Snoeck, D. Schols, P. Herdewijn, J. Desmyter, E. De Clercq, *J. Virol. Methods* **1988**, *20*, 309.
36. K. D. Hargrave, J. R. Proudfoot, K. G. Grozinger, E. Cullen, S. R. Kapadia, U. R. Patel, V. U. Fuchs, S. C. Mauldin, J. Vitous, M. L. Behnke, J. M. Klunder, K. Pal, J. W. Skiles, D. W. McNeil, J. M. Rose, G. C. Chow, M. T. Skoog, J. C. Wu, G. Schmidt, W. W. Engel, W. G. Eberlein, T. D. Saboe, S. J. Campbell, A. S. Rosenthal, J. Adam, *J. Med. Chem.* **1991**, *34*, 2231.
37. Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrmann, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D.W.; Broder, S. *Proc Natl Acad Sci USA* **1985**, *82*, 7096.

