# SYNTHESIS OF TWO NEW THIAZOLE-CONTAINING OLIGOPEPTIDES AS POTENTIAL DNA MINOR GROOVE BINDING ANALOGS OF NETROPSIN

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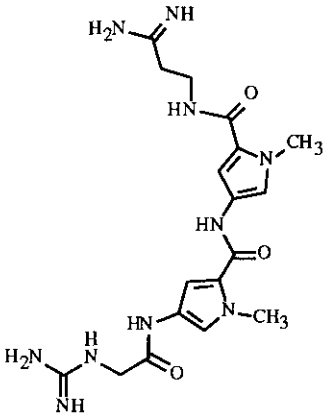
**Abstract** - On the basis of previous studies on synthetic models related to the antibiotic agents Netropsin and Distamycin-A, the design and synthesis of two potential DNA minor groove ligands are described. Methia-Nt and Isothia-Nt were prepared by liquid-phase peptidic synthesis from the key compounds ethyl 2-amino-5-methylthiazole-4-carboxylate (**1**) and ethyl 2-aminothiazole-5-carboxylate (**8**) respectively.

Most of antitumor agents used in clinic are thought to exert their cytotoxic activity by modifying the DNA metabolism.[1] Beside drugs which covalently bind DNA,[2] other compounds are known to induce DNA breakage or inhibit the nucleic acids synthesis by intercalative[3] or non intercalative[4] processes. Among this last class, two natural compounds, the antibiotics Netropsin (Nt) and Distamycin-A (Dst) form highly ordered complexes in the minor groove of DNA and recognize particular nucleotide sequences of double-stranded DNA[4,5] with a high Adenine-Thymine (AT) specificity. These DNA binders could constitute adequate models for the design of synthetic pseudopeptides, referenced as sequence-reading oligopeptides,[6] in order to modify the biological processes of replication and transcription: as such, they can constitute adequate candidates for antiviral and antineoplastic activities.

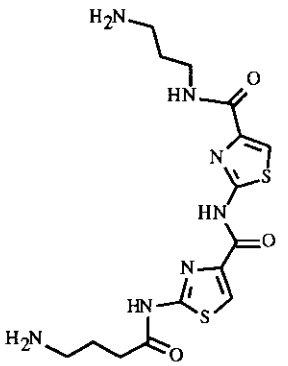
Because of current interest in the control of gene expression, increasing works aim at developing DNA sequence specific agents. For these reasons, it seems particularly interesting to apply the concept of molecules possessing at once strong affinity and specific binding properties to definite nucleotidic sequences. Such molecules would be of great utility when such a recognition is essential on predetermined oligonucleotidic sequence of oncogenes for example.

Thus, in order to delineate the structural, conformational and chemical basis of DNA binding, systematic modifications on Nt and Dst have been fulfilled, implying the different factors responsible for the processes of molecular recognition. In this context, analogs of Nt have been built via replacement of one or two pyrrole units by other heterocyles such as imidazole,[7,8] oxazole[9] or thiazole.[10-14] The consequences of such substitutions in terms of AT specificity alteration and GC acceptance enhancement have been analyzed and, in addition, the influence of the nature and length of the cationic side chain on the specificity of interaction has been proposed.[6,15]

Considering these previous works, we recently report the synthesis and preliminary results about an analog of Nt, namely Thia-Nt (Figure 1), where the implicated heterocycle is the thiazole nucleus and the side chains are simplified primary amines.[11]



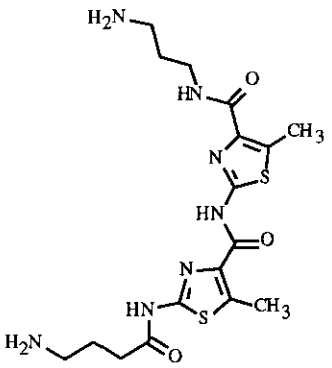
Netropsin



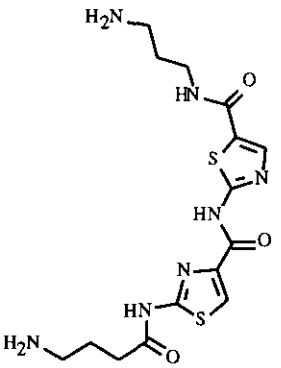
Thia-Nt

Figure 1. Structure of Netropsin and Thia-Nt

Encouraged by the previous results,[14] we decided to investigate systematically the behaviour of new thiazole analogs of Nt in which the heterocyclic part is differently substituted. We report here the efficient and easily reproducible synthesis of oligopeptides Methia-Nt and Isothia-Nt (Figure 2) via a strategic pathway involving the preparation of the key compounds ethyl 2-amino-5-methylthiazole-4-carboxylate and ethyl 2-aminothiazole-5-carboxylate.



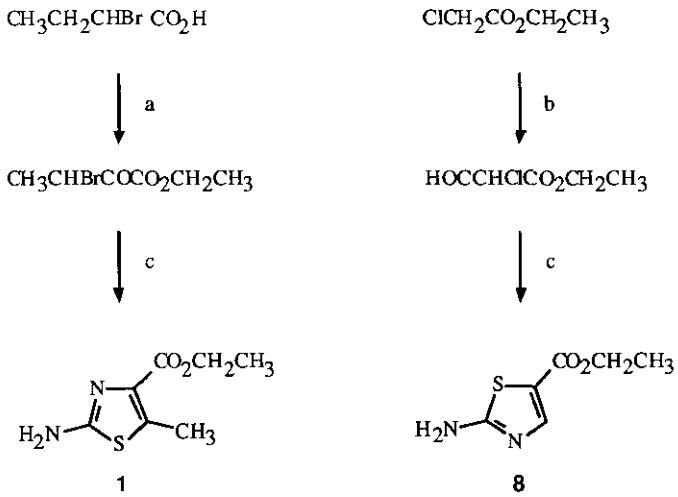
Methia-Nt



Isothia-Nt

Figure 2. Structure of Methia-Nt and Isothia-Nt

The structure of Methia-Nt favors the orientation of the sulfur atoms away from the floor of the double helix, as for Thia-Nt, whereas the methyl group is positioned as for Nt. On the other hand, Isothia-Nt exhibits its two sulfur atoms in opposite orientations, precisely away and toward the axis of DNA. Thia-Nt, Methia-Nt and Isothia-Nt have primary amino iso-length side chains instead of amidine and guanidine residues.

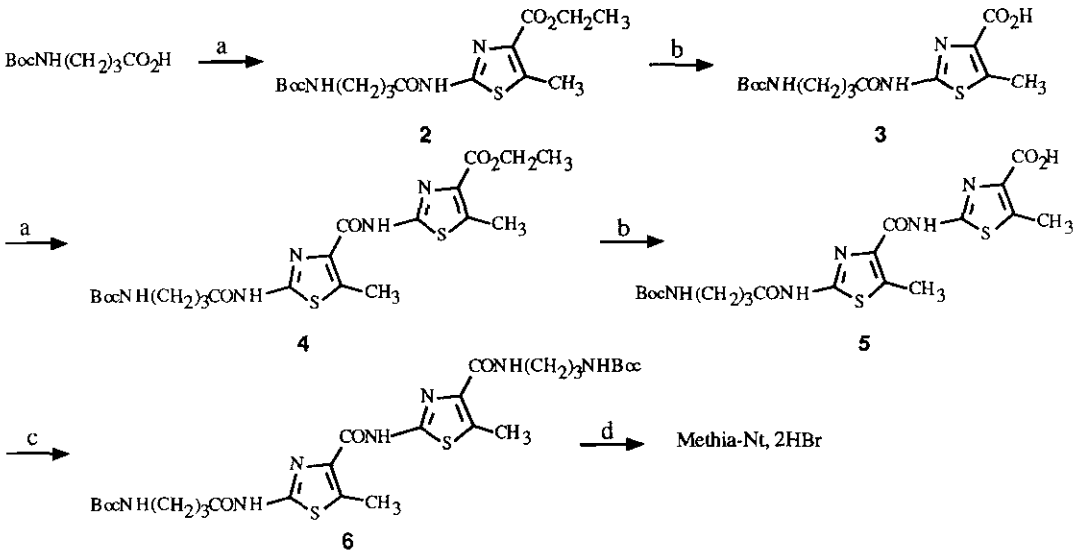



Scheme 1. Reagents : (a) $K_2CO_3/H_2O$, $HCl/C_2H_5OH$, $NBS/CCl_4$ (b) $HCO_2C_2H_5$, $C_2H_5ONa/(C_2H_5)_2O$ (c) $H_2NCSNH_2/H_2O$

The required starting material ethyl 2-amino-5-methylthiazole-4-carboxylate (**1**) was synthetized according to the procedure used for the preparation of ethyl 2-aminothiazole-5-carboxylate (**8**).[16] Cyclising condensation of thiourea with ethyl dl-3-bromo-2-oxobutyrate afforded the heterocycle (**1**), as ethyl formylchloroacetate reacts with thiourea, to furnish the thiazole (**8**)[17] (Scheme 1). Ethyl dl-3-bromo-2-oxobutyrate was prepared following a reported procedure[18] by oxidation with *N*-bromosuccinimide of the intermediate α-hydroxy ester.[19] A classical Claisen reaction between ethyl formate and ethyl chloroacetate allowed us to obtain ethyl formylchloroacetate in accordance with Wislicenus.[20]

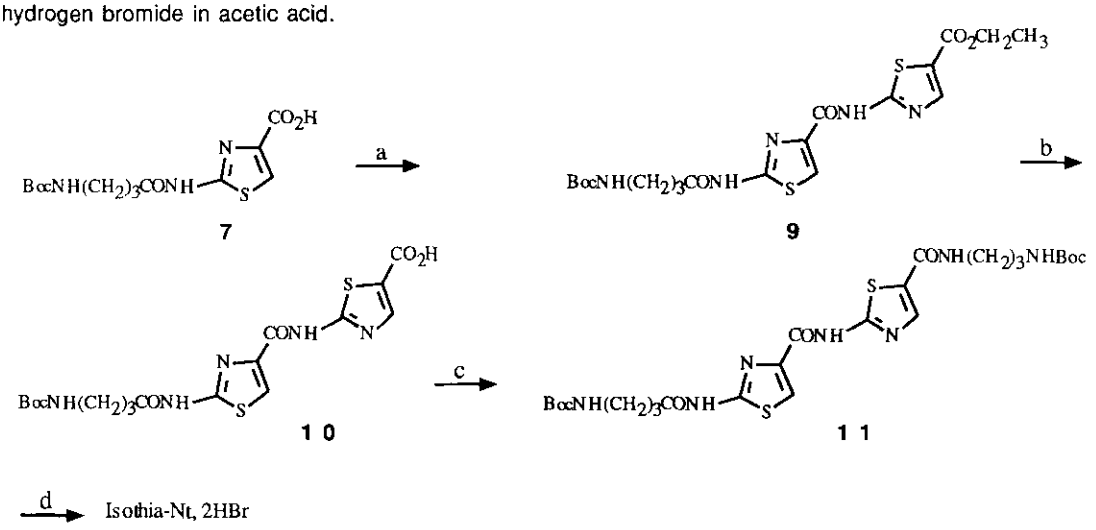
Acylation of the aminothiazole (**1**) with 4-t-butyloxycarbonylaminobutyric acid[21] in the presence of dicyclohexylcarbodiimide (DCC) and 1*H*-hydroxy-1, 2, 3-benzotriazole (HOBt) afforded **2** (Scheme 2).

Alkaline hydrolysis of the ester (**2**) in aqueous methanol gave the acid (**3**). Condensation of ethyl 2-amino-5-methylthiazole-4-carboxylate (**1**) with the acid (**3**) in the above conditions (DCC, HOBt) gave the bisthiazole (**4**). After saponification of the ester group of **4**, the second side chain (4-t-butyloxycarbonyl-aminopropylamine [22]) was coupled, in the presence of DCC and HOBt, with the acid (**5**) to give the protected diamine (**6**). Cleavage of the t-butyloxycarbonyl (Boc) protecting group with hydrogen bromide in acetic acid afforded the desired compound Methia-Nt as dihydrobromide.




Scheme 2. Reagents (a) **1**, HOBt, DCC (b) 4N NaOH/$CH_3OH$
(c) $H_2N(CH_2)_3NHBoc$, HOBt, DCC (d) HBr/$CH_3COOH$

The pseudotetrapeptide Isothia-Nt was synthetized according to Scheme 3. Treatment of ethyl 2-aminothiazole-5-carboxylate (**8**), described above, with acid (**7**)[11] under the conditions used for **4**, afforded compound (**9**) which was hydrolyzed to the corresponding acid (**10**). Conversion of **10** into the *protected pseudotetrapeptide* (**11**) *proceeded satisfactorily under the reaction* conditions described for the synthesis of **6**. The deprotection of compound (**11**) was achieved by treatment with a saturated solution of hydrogen bromide in acetic acid.




Scheme 3. Reagents (a) **8**, HOBt, DCC (b) 4N NaOH /$CH_3OH$ (c) $H_2N(CH_2)_3NHBoc$, HOBt, DCC
(d) HBr/$CH_3COOH$

## EXPERIMENTAL

Melting points were taken on a Tottoli Büchi 510 apparatus and are uncorrected. The ir spectra were recorded with a Perkin Elmer 1310 spectrophotometer using potassium bromide pellets. The $^1H$ nmr spectra were recorded on a Bruker WP80 SY spectrometer. Chemical shifts are reported in ppm from tetramethylsilane as an internal standard and are given in δ units. The EI mass spectra were recorded on a Ribermag R10.10 (combined with Riber 400 data system) mass spectrometer at 70 eV by using direct insertion. FAB mass spectra were determined on a Kratos MS-50 RF mass spectrometer. Thin layer chromatography (tlc) was carried out using silica gel 60F-254 Merck, in system solvent chloroform-methanol (80/20, v : v). Spots were visualized by inspection under uv light at 254 nm and after exposure to vaporized $I_2$ and/or ninhydrin.

### Ethyl 2-amino-5-methylthiazole-4-carboxylate (1)

2-Bromobutyric acid was hydrolysed to 2-hydroxybutyric acid using potassium carbonate and was esterified with absolute ethanol and dry hydrogen chloride to give ethyl 2-hydroxybutyrate. To a solution of 2.6 g (20 mmol) of the hydroxy ester in 40 ml of carbon tetrachloride were added 7.12 g (40 mmol) of *N*-bromosuccinimide. The mixture was refluxed for 5 h, cooled and the succinimide was filtered. The filtrate was dried over anhydrous sodium sulfate, concentrated and distilled *in vacuo* to yield 3.0 g (70 %) of ethyl dl-3-bromo-2-oxobutyrate, bp 92-110° C (12 mm Hg).

A mixture of 1.1 g (14.3 mmol) of thiourea and 3.0 g (14.3 mmol) of ethyl dl-3-bromo-2-oxobutyrate in 20 ml of water was heated gradually until boiling under stirring (15 min) and then allowed to react for 12 h at room temperature. The base was precipitated by addition of 20 % ammonia, then resolubilized in 1 N hydrochloric acid and finally reprecipitated with 20 % ammonia. The crude product was filtered and recrystallized from water-ethanol (90/10, v : v) to give **1** in a 57 % yield, mp 164-166° C; $R_f$ 0.76; ir : 1600 (NH), 1680 (CO ester); $^1H$ nmr ($CDCl_3$) : δ 5.6 (m, 2H, $NH_2$), 4.3 (q, J = 6.5 Hz, 2H, $CH_2$), 2.6 (s, 3H, $CH_3$ thiazole), 1.3 (t , J = 6.5 Hz, 3H, $CH_3$); ms (m/z, I %) : 186 ($M^+$, 71). Anal. Calcd for $C_7H_{10}N_2O_2S$ : C, 45.15; H, 5.41; N, 15.04. Found : C, 45.08; H, 5.50; N, 15.12.

### Ethyl 2-(4-t-butyloxycarbonylaminobutyryl)amino-5-methylthiazole-4-carboxylate ( 2 )

Cold solutions of 906 mg (4.4 mmol) of DCC and 674 mg (4.4 mmol) of HOBt in 10 ml of a mixture of dichloromethane-dimethylformamide (1/1, v : v) was added to a solution of 812 mg (4 mmol) of 4-t-butyloxycarbonylaminobutyric acid in 10 ml of dichloromethane-dimethylformamide (1/1, v : v) at 0° C for 1 h under stirring. A cold solution of 744 mg (4 mmol) of **1** in 5 ml of a mixture of dichloromethane-dimethyformamide (1/1, v : v) was added and stirring was continued for 2 h at 0° C and 12 h at room temperature. The solvent was evaporated and the residue was taken up with dichloromethane, providing dicyclohexylurea (DCU) which was filtered. The organic solution was washed successively with 1 N hydrochloric acid, water and 1 M sodium bicarbonate. After drying over anhydrous sodium sulfate, the solvent was removed *in vacuo*. The remaining DCU was discarded by precipitation with acetone, the resulting material was recrystallised from a mixture of ethanol-petroleum ether giving pure **2** (1.47 g, 99 % yield), mp 132-134° C; $R_f$ 0.89; ir : 1720 (CO amide), 1680 (CO ester); $^1H$ nmr ($CDCl_3$) : δ 11.4 (m,

1H, NH), 5.0 (m, 1H, NHBoc), 4.4 (q, J = 6.5 Hz, 2H, $CH_2$), 3.2 (m, 2H, $C\underline{H}_2NH$), 2.6 (s, 3H, $CH_3$ thiazole), 2.5 (t, J = 6.7 Hz, 2H, $CH_2CO$), 1.9 (m, 2H, $CH_2$), 1.4 (m, 12H, $CH_3$); ms (m/z, I %) : 371 ($M^+$, 1.6), 228 (100). Anal. Calcd for $C_{16}H_{25}N_3O_5S$ : C, 51.74; H, 6.78; N, 11.31. Found : C, 51.89; H, 6.89; N, 11.47.

**2-(4-t-Butyloxycarbonylaminobutyryl)amino-5-methythiazole-4-carboxylic acid (3)**

A solution of 742 mg (2 mmol) of **2** and 2 ml (8 mmol) of 4N sodium hydroxide in 3 ml of methanol was stirred at room temperature. The progress of the reaction was monitored by tlc and was thereby judged to be complete after 6 h. The solvent was evaporated, the residue was taken up in water and impurities were extracted with dichloromethane (2 x 10 ml). The acid (**3**) was then precipitated by cautious acidification to pH 3-4 with cold 1N hydrochloric acid to yield 520 mg (76%) of pure **3** as ascertained by tlc, mp 186-188° C; $R_f$ 0.52; $^1H$ nmr (DMSO-$d_6$) : δ 12.3 (m, 1H, NH), 6.8 (m, 1H, NHBoc), 3.0 (m, 2H, $C\underline{H}_2NH$), 2.6 (s, 3H, $CH_3$ thiazole), 2.4 (t, J = 6.7 Hz, 2H, $CH_2CO$), 1.7 (m, 2H, $CH_2$), 1.4 (s, 9H, $CH_3$); ms (FAB+) : 344 ($M^+$+1). Anal. Calcd for $C_{14}H_{21}N_3O_5S$ : C, 48.97; H, 6.16; N, 12.24. Found : C, 49.05; H, 6.07; N, 12.33.

**Ethyl 2-[2'-(4-t-butyloxycarbonylaminobutyryl)amino-5'-methylthiazole-4'-carboxamido]-5-methylthiazole-4-carboxylate (4)**

The acid (**3**) (343 mg, 1 mmol) was reacted with 186 mg (1 mmol) of the amine (**1**) using 227 mg (1.1 mmol) of DCC and 168 mg (1.1 mmol) of HOBt in 10 ml of dichloromethane-dimethylformamide (1/1, v : v) as described for the preparation of **2**. DCU was removed by precipitation with ethyl acetate and the filtrate was washed with 1 N hydrochloric acid (10 ml), water (10 ml) and 1 M sodium bicarbonate (10 ml), then dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* giving 452 mg (89 % yield) of **4** after recrystallization from a mixture of ethanol-petroleum ether, mp 214-216° C; $R_f$ : 0.93; ir : 1680 (CO ester); $^1H$ nmr ($CDCl_3$) : δ 10.7 (m, 1H, NH), 10.4 (m, 1H, NH), 5.1 (m, 1H, NHBoc), 4.4 (q, J = 6.5 Hz, 2H, $CH_2$), 3.3 (m, 2H, $C\underline{H}_2NH$), 2.75 (s, 3H, $CH_3$ thiazole), 2.65 (s, 3H, $CH_3$ thiazole), 2.6 (m, 2H, $CH_2CO$), 2.0 (m, 2H, $CH_2$), 1.4 (m, 12H, $CH_3$); ms (FAB+) : 512 ($M^+$+1). Anal. Calcd for $C_{21}H_{29}N_5O_6S_2$ : C, 49.30; H, 5.71; N, 13.69. Found : C, 49.07; H, 5.85; N, 13.82.

**2-[2'-(4-t-Butyloxycarbonylaminobutyryl)amino-5'-methylthiazole-4'-carboxamido]-5-methylthiazole-4-carboxylic acid (5)**

The ethyl ester (**4**) (255 mg, 0.5 mmol) was totally converted after 6 h to the corresponding acid (**5**), according to the method of preparation of **3**. Compound (**5**) was obtained pure, as ascertained by chromatography, after precipitation by cautious acidification with 1N hydrochloric acid (220 mg, 91 % yield), mp 212-214° C; $R_f$ : 0.25; $^1H$ nmr (DMSO-$d_6$) : δ 12.1 (s, 1H, NH), 11.1 (m, 1H, NH), 6.8 (m, 1H, NHBoc), 3.0 (m, 2H, $C\underline{H}_2NH$), 2.65 (s, 3H, $CH_3$ thiazole), 2.55 (s, 3H, $CH_3$ thiazole), 2.5 (m, 2H, $CH_2CO$), 1.7 (m, 2H, $CH_2$), 1.4 (s, 9H, $CH_3$); ms (FAB+) : 484 ($M^+$+1). Anal. Calcd for $C_{19}H_{25}N_5O_6S_2$ : C, 47.19; H, 5.21; N, 14.48. Found : C, 47.28; H, 5.32; N, 14.31.

**t-Butyl 3-[2-[2'-(4-t-butyloxycarbonylaminobutyryl)amino-5'-methylthiazole-4'-carboxamido]-5-methylthiazole-4-carboxamido]propyl-1-carbamate (6)**

The acid (**5**) (120 mg, 0.25 mmol) was treated with 44 mg (0.25 mmol) of 4-t-butyloxycarbonylaminopropylamine using 57 mg (0.28 mmol) of DCC and 42 mg (0.28 mmol) of HOBt in 5 ml of a mixture of dichloromethane-dimethylformamide (1/1, v : v), according to the procedure described for **2**. Purification of the crude material was accomplished by recrystallization from a mixture of ethanol-petroleum ether to give 141 mg (88 % yield) of compound (**6**), mp 184-187° C; $R_f$ : 0.93; ir : 1680 (CO); $^1H$ nmr ($CDCl_3$) : δ 11.3 (m, 1H, NH), 10.4 (m, 1H, NH), 8.2 (m, 1H, NHCO), 5.0 (m, 1H, NHBoc), 3.4 (m, 6H, $C\underline{H}_2NH$), 2.8 (s, 3H, $CH_3$ thiazole), 2.75 (s, 3H, $CH_3$ thiazole), 2.7 (m, 2H, $CH_2CO$), 1.9 (m, 4H, $CH_2$), 1.4 (m, 18H, $CH_3$); ms (FAB+) : 640 ($M^+$+1). Anal. Calcd for $C_{27}H_{41}N_7O_7S_2$ : C, 50.69; H, 6.46; N, 15.32. Found : 50.43; H, 6.28; N, 15.60.

**3-[2-[2'-(4-Aminobutyryl)amino-5'-methylthiazole-4'-carboxamido]-5-methylthiazole 4-carboxamido]propyl-1-amine dihydrobromide (Methia-Nt)**

A solution of 64 mg (0.1 mmol) of **6** in acetic acid (2 ml) was saturated with dry hydrogen bromide for 3 min and stirring was maintained for 30 min. After evaporation of the solvent under vacuum, the residue was taken up with ether, providing 52 mg (87% yield) of analytically pure Methia-Nt, mp 198-200° C; $R_f$ : 0; $^1H$ nmr ($D_2O$) : δ 3.4 (m, 2H, $C\underline{H}_2NH$), 3.1(m, 4H, $C\underline{H}_2NH_3^+$), 2.65 (m, 2H, $CH_2CO$), 2.55 (s, 3H, $CH_3$ thiazole), 2.5 (s, 3H, $CH_3$ thiazole), 2.0 (m, 4H, $CH_2$); ms (FAB+) : 440 ($M^+$+1). Anal. Calcd for $C_{17}H_{27}N_7O_3S_2Br_2$ : C, 33.95; H, 4.52; N, 16.30. Found : C, 40.13; H, 4.53; N, 16.47.

**Ethyl 2-aminothiazole-5-carboxylate (8)**

Potassium (8 g, 0.20 mol) was added to 50 ml of dry ethanol under stirring and nitrogen atmosphere. After complete reaction of potassium and cooling, 100 ml of dry ether were added, then a solution of 19 ml (0.22 mol) of ethyl formate and 24 ml (0.22 mol) of ethyl chloroacetate in 100 ml of dry ether was added slowly and the mixture was stirred overnight. The potassium salt was filtered, washed carefully with ether and dissolved in water. The aqueous solution was acidified cautiously to pH 4 with 10 N hydrochloric acid in a cold bath and extracted with ether (4 x 50 ml). After drying over anhydrous sodium sulfate, the organic solution was concentrated *in vacuo* to give 7.5 g (0.05 mol) of ethyl formylchloroacetate which were treated with 3.8 g (0.05 mol) of thiourea in 50 ml of water, as described for the preparation of **1**. The base was precipitated by addition of ammonia; this procedure was repeated after dissolution in 1 N hydrochloric acid and the precipitate was recrystallized from a mixture of water-ethanol (9/1, v : v) to give **8** in a 67% yield, mp 156-158° C; $R_f$ : 0.70; ir : 1650 (NH), 1680 (CO ester); $^1H$ nmr ($CDCl_3$) : δ 7.7 (s, 1H, CH thiazole), 5.5 (s, 2H, $NH_2$), 4.3 (q, J = 6.5 Hz, 2H, $CH_2$), 1.3 (t, J = 6.5 Hz, 3H, $CH_3$); ms (m/z, I %) : 172 ($M^+$, 58). Anal. Calcd for $C_6H_8N_2O_2S$ : C, 41.85; H, 4.68; N, 16.27. Found : C, 41.66; H, 4.64; N, 16.39.

**Ethyl 2-[2'-(4-t-butyloxycarbonylaminobutyryl)aminothiazole-4'-carboxamido]-thiazole-5-carboxylate (9)**

The acid (**7**) (99 mg, 0.30 mmol) was allowed to react with 52 mg (0.30 mmol) of the amine (**8**) using 68 mg (0.33 mmol) of DCC and 50 mg (0.33 mmol) of HOBt in 10 ml of a mixture of dichloromethane-dimethylformamide (1/1, v : v) according to the procedure described for **4**, giving 140 mg of **9** (96% yield) after recrystallization from ethanol, mp 224-226° C; $R_f$ : 0.90; ir : 1720 (CO amide), 1680 (CO ester); $^1H$ nmr ($CDCl_3$) : δ 8.2 (s, 1H, CH thiazole), 8.0 (s, 1H, CH thiazole), 4.9 (m, 1H, NHBoc), 4.3 (m, 2H, $CH_2$), 3.3 (m, 2H, $C\underline{H}_2NH$), 2.6 (m, 2H, $CH_2CO$), 1.8 (m, 2H, $CH_2$), 1.5 (m, 12H, $CH_3$); ms (FAB+) : 484 ($M^+$+1). Anal. Calcd for $C_{19}H_{25}N_5O_6S_2$ : C, 47.19; H, 5.21; N, 14.48. Found : C, 47.44; H, 5.45; N, 14.37.

**2-[2'-(4-t-Butyloxycarbonylaminobutyryl)aminothiazole-4'-carboxamido]thiazole-5-carboxylic acid (10)**

The ester (**9**) (97 mg, 0.20 mmol) was converted to the corresponding acid (**10**) according to the method of preparation of **7**. The yield of crude and chromatographically pure product was 66% (60 mg), mp > 250° C; $R_f$ : 0.16; $^1H$ nmr (DMSO-$d_6$) : δ 15.5 (s, 1H, OH), 8.2 (s, 1H, CH thiazole), 8.0 (s, 1H, CH thiazole), 6.8 (m, 1H, NHBoc), 3.2 (m, 2H, $C\underline{H}_2NH$), 2.5 (m, 2H, $CH_2CO$), 1.9 (m, 2H, $CH_2$), 1.4 (s, 9H, $CH_3$); ms (FAB+) : 478 ($M^+$+Na). Anal. Calcd for $C_{17}H_{21}N_5O_6S_2$ : C, 44.83; H, 4.65; N, 15.37. Found : C, 44.78; H, 4.73; N, 15.28.

**t-Butyl 3-[2-[2'-(4-t-butyloxycarbonylaminobutyryl)aminothiazole-4'-carboxamido]-thiazole-5-carboxamido]propyl-1-carbamate (11)**

The procedure used for the preparation of **11** is strictly identical to that of **6** (57 % yield). An authentic sample was recrystallized from ethyl acetate, mp 177-181° C; $R_f$ : 0.79; ir : 1680 (CO); $^1H$ nmr ($CDCl_3$) : δ 11.4 (m, 1H, NH), 8.3 (m, 1H, NHCO), 8.2 (s, 1H, CH thiazole), 7.9 (s, 1H, CH thiazole), 5.1 (m, 1H, NHBoc), 3.4 (m, 6H, $C\underline{H}_2NH$), 2.7 (m, 2H, $CH_2CO$), 1.9 (m, 4H, $CH_2$), 1.4 (m, 18H, $CH_3$); ms (FAB+) : 612 ($M^+$+1). Anal. Calcd for $C_{25}H_{37}N_7O_7S_2$ : C, 49.09; H, 6.10; N, 16.03. Found : C, 48.88; H, 6.05; N, 16.20.

**3-[2-[2'-(4-Aminobutyryl)aminothiazole-4'-carboxamido]thiazole-5-carboxamido]-propyl-1-amine dihydrobromide (Isothia-Nt)**

The compound (**11**) was totally converted into the corresponding deprotected compound Isothia-Nt according to the method of preparation of Methia-Nt (87 % yield of crude and pure product), mp 196-201° C; $R_f$ : 0; $^1H$ nmr ($D_2O$) : δ 8.1 (s, 1H, CH thiazole), 7.7 (s, 1H, CH thiazole), 3.3 (m, 2H, $C\underline{H}_2NH$), 3.1 (m, 4H, $C\underline{H}_2NH_3^+$), 2.5 (m, 2H, $CH_2CO$), 2.0 (m, 4H, $CH_2$); ms (FAB+) : 412 ($M^+$+1). Anal. Calcd for $C_{15}H_{23}N_7O_3S_2Br_2$ : C, 31.42; H, 4.04; N, 17.10. Found : C, 31.26; H, 4.13; N, 17.32.

## ACKNOWLEDGEMENTS

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