Synthesis of Heteroaryl Substituted α-Mercapto Acids from Thiomalic Acid Using Hexafluoroacetone as Protecting and Activating Reagent

Ksenia Pumpor, Elisabeth Windeisen and Klaus Burger*

Department of Organic Chemistry, University of Leipzig, Johannisalle 29, D-04103 Leipzig, Germany

Received January 10, 2003

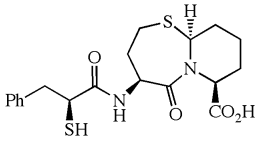
The synthesis of heterocyclic α-mercapto acids starting from (*RS)*-thiomalic acid using hexafluoroacetone as protecting and activating agent is described. The new compounds are useful building blocks for peptide and depsipeptide modification as well as for drug design.

J. Heterocyclic Chem., **40**, 435 (2003).

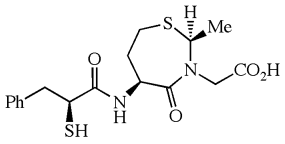
Introduction.

α-Hydroxy acids, besides α-amino acids and carbohydrates, belong to the most important and abundant representatives of low molecular compounds of the naturally occurring chiral pool [1]. In contrary, mercapto carboxylic acids are rare. They were found as constituents of natural products, for example in biologically active natural peptides [2]. However, mercapto acids as well as acylmercapto acids are interesting building blocks for medicinal chemistry. A β-mercapto acid is a subunit of *Captopril*, a classical drug for treating hypertension [3], an α-mercapto acid subunit is present in *Omapatrilat* and *Gemopatrilat*. Both are vasopeptidase inhibitors that are currently under clinical evaluation [4]. They all belong to a class of oligomers called peptide hybrides. Compounds containing the mercapto or the mercaptoacyl [5] moiety often exhibit strong inhibitory effects on metal-containing enzymes (metallozymes) [6], similar to hydroxamic acids [7]. Some of the zinc-containing angiotensine converting enzymes (ACE) possess the α-mercaptoacyl substructure [8].

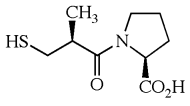
Scheme 1



Omapatrilat



Gemopatrilat



Captopril

A growing number of reports focus on peptidomimetic compounds built from two or more different types of monomers [9]. Consequently, the development of new methodology for the synthesis of new types of amino [10], hydroxy [11], keto [12] and mercapto acids [13-15] and their incorporation into peptide and depsipeptide hybrides is an area of current interest [9].

Heterocyclic compounds, especially thiazole derivatives, exhibit a broad range of biological activities. The thiazole substructure is present in numerous natural products, drugs, and pesticides [16]. Some of the natural occurring thiazole derivatives exhibiting antibiotic activity are amino acids. As the first representative of this class of compounds 3-amino-3-(thiazol-2-yl)propanoic acid was isolated from the antibiotic bottromycin (*Streptomyces bottropensis*) [17]. Naturally occurring thiazole-substituted hydroxy acids, like 4-amino-4-(4-carboxythiazol-2-yl)-2-hydroxybutanoic acid, isolated from the macrocycle nosiheptide, are rare [18]. Thiazole-substituted mercapto acids are unknown to the best of our knowledge.

Subsequently, we report on a preparatively simple route to this class of compounds starting from (*RS*) thiomalic acid.

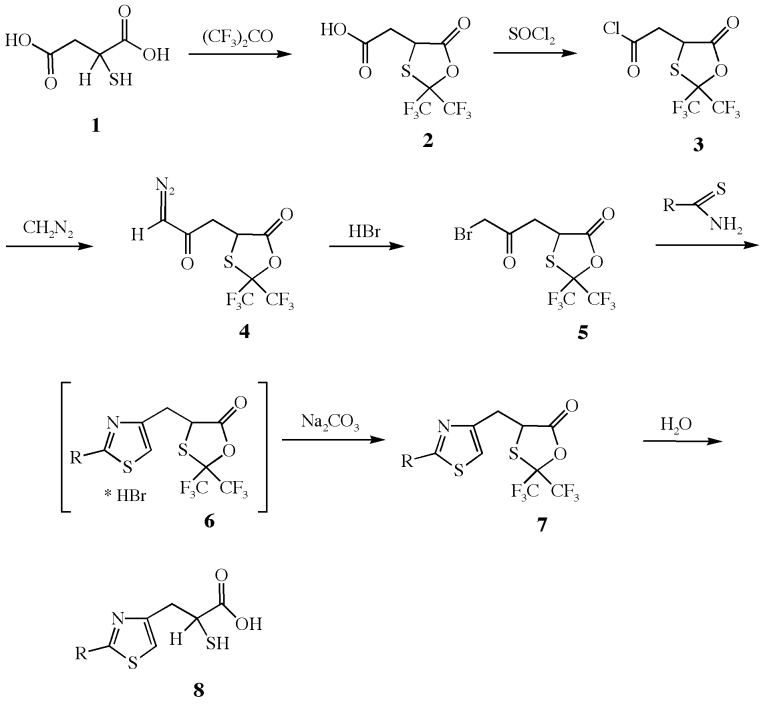
Results and Discussion.

We found that a recently described protection/activation concept for the regioselective derivatization of multifunctional α-amino [19] and α-hydroxy acids [20] can also be applied to α-mercapto acids. Hexafluoroacetone reacts readily with α-mercapto acids in DMSO at room temperature to give 2,2-bis(trifluoromethyl)-1,3-oxathiolan-5-ones in 80 - 90% yield [21]. In one step, protection of the α-mercapto and the adjacent carboxy group is achieved. Concomitantly, the α-carboxy group is activated towards nucleophiles and can be regioselectively derivatized. A variety of functional groups present in the side-chain are tolerated by the above protection/activation procedure and therefore, can be derivatized regioselectively. On exclusion of moisture 2,2-bis(trifluoromethyl)-1,3-oxathiolan-5-ones can be stored in a refrigerator over months without any decomposition.

In this context, compound **2** a derivative of thiomalic acid is a synthetically useful intermediate, because the carboxylic group of the side chain can be regioselectively functionalized after separate activation. Another advantage, protection and α-activation and on the other hand α-derivatization and deblocking of the mercapto function occur in one step. Therefore, the hexafluoroacetone concept saves steps compared to conventional strategies.

On heating **2** with an excess of thionyl chloride, the corresponding acid chloride is formed in excellent yields.

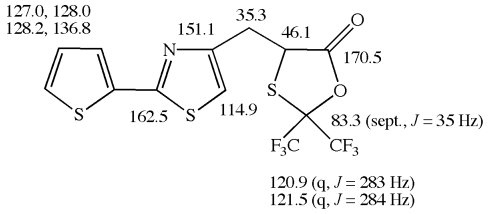
Scheme 2



7a: R = 2-thienyl
7b: R = p-fluorophenyl
7c: R = p-chlorophenyl
7d: R = 2-(p-tolyl)-4-trifluoromethyl-5-thiazolyl

With an excess of diazomethane (> 2 equivalents) **3** is converted into diazoketone **4**, which is a preparatively versatile building block [22]. For example, when **4** is treated with conc. HBr or conc. HCl at - 78 °C within minutes the corresponding haloketones **5** are formed in up to 90% yield, which can be subjected to the *Hantzsch* reaction without further purification [23, 24]. Dry acetone proved to be the best solvent for the reaction of **5** with thioamides, selenamides and thioureas. When a reaction mixture of **5** and the corresponding thioamide is heated up to 50 °C, within minutes the HX-salts **6** start to crystallize. On stirring in a two-phase system (aqueous $NaHCO_3$ solution/diethyl ether) the salts **6** were converted into the thiazoles (**6** → **7**). After separation of the organic phase and drying with $MgSO_4$, products **7** obtained after evaporation of the solvent *in vacuo* are already analytically pure. The structure of the new compounds was proved by ir and nmr spectroscopy. An ir absorption in the region of 1815 - 1800 cm^{-1} unequivocally reveals the presence of a lactone moiety, whereas the ^{13}C nmr spectra show resonance signals of an unchanged 1,3-oxathiolan-5-one and a newly formed thiazole ring system.

Scheme 3



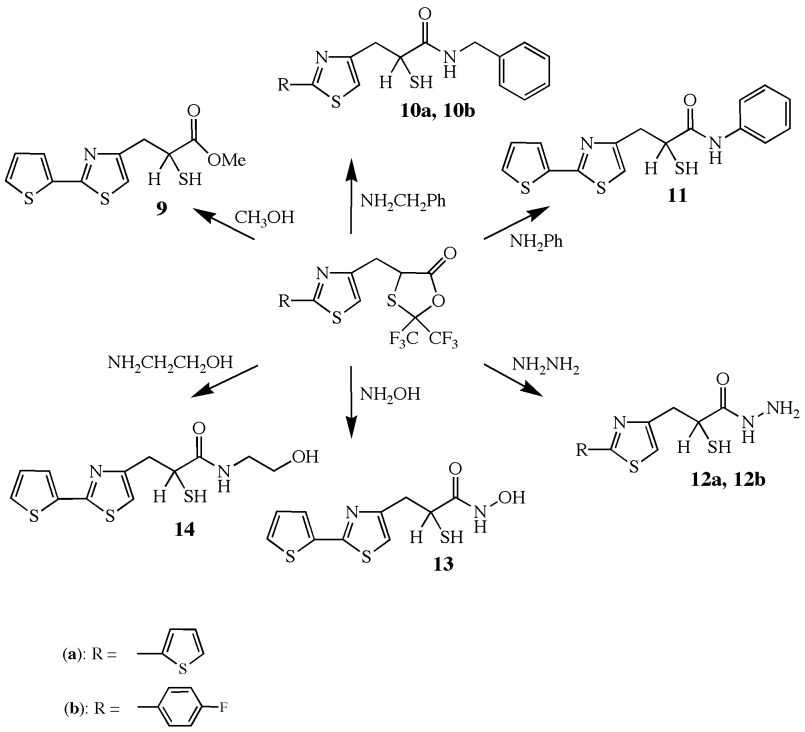
^{13}C chemical shifts (ppm) of **7a**

Deprotection of compounds **7** to give the α-mercapto acids **8** can be achieved by heating up to 50 °C in a THF/water mixture. In Scheme 4, some synthetically useful reactions are summarized: Esters **9** are obtained on heating in the presence of an excess of the corresponding alcohols. Reaction of **7** with amines, hydrazine and hydroxyl amine at room temperature provides ready access to a variety of α-mercapto acid derivatives **10 - 14.**

Because of their broad spectrum of biological activities, the development of synthetic routes to new types of hydroxamic acid derivatives is of current interest [25,26]. Compounds **11** represent a new ligand system to form metal chelates, having two interesting coordination sites, namely a mercapto and an *N*-hydroxyamide moiety. Reaction of **7** with *C*-terminal protected amino acids or N-protected amino acid hydrazides offers a preparatively simple access to new types of peptide hybrides (**15 - 17**) [27]. The option to derivatize the deblocked HS-group subsequently, increases the synthetic potential of this reaction sequence considerably.

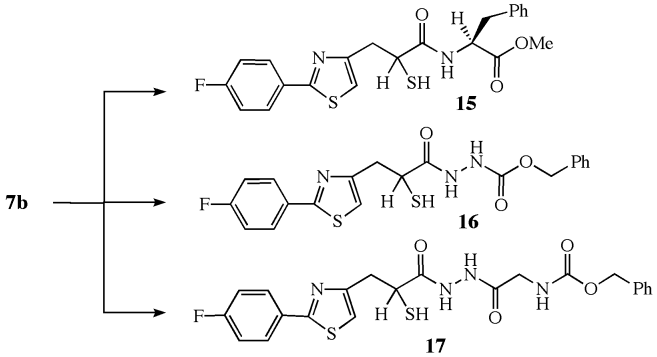
Aminolytic ring opening reactions of the lactones **7** occur efficiently when the resulting products are poorly soluble in

Scheme 4



the solvent used and therefore spontaneously crystallize from the reaction mixture. In most cases the compounds obtained are already analytically pure. The progress of the reactions can be monitored by ^{19}F NMR spectroscopy.

Scheme 5



The above described synthetic sequence is well suited for the generation of libraries of peptide and depsipeptide surrogates with new sequence motifs, which could be of interest to pharmaceutical industry. Oxidation on air of the mercapto group of compounds **8** - **17** is a slow process. Nevertheless, the experiments should be performed under inert gas. On further applications of α-mercapto acids for drug synthesis, including glycosylation and disulfide formation, we report elsewhere.

EXPERIMENTAL

General.

Solvents were purified prior to use. Reagents were used as purchased. Melting points were determined on a Boetius heating table. For C,H,N analyses a CHNO-Rapid-Elemental-Analyser (Heraeus) was used. Mass spectra were recorded on a VG 12-250 (Masslab) electron ionization spectrometer (EI = 70 eV). Ir spectra were obtained using a Specord spectrometer (Carl-Zeiss, Jena) and Genesis Series FTIR ATI Mattson spectrometer. Nmr spectra were recorded on Varian GEMINI 200 (^1H 199.96; ^{13}C 50.29 MHz), GEMINI 2000 (^1H 200.04; ^{13}C 50.31 MHz) and GEMINI 300 (^1H 300.08: ^{13}C 75.46 MHz) instruments. Chemical shifts are reported in ppm relative to tetramethylsilane. For ^{19}F nmr spectra, external trifluoroacetic acid is used as reference. Thin-layer chromatography was performed on Merck (Darmstadt, Germany) Kieselgel $60F_{254}$ precoated plates. Reactions were carried out under dry argon.

[2,2-Bis(trifluoromethyl)-5-oxo-1,3-oxathiolan-4-yl]acetic acid (**2**).

In a closed system, equipped with a dry ice condenser and sealed with a bubbler, a suspension of racemic thiomalic acid (15.0 g, 100 mmol) in 50 ml of DMSO was treated with an excess (> 2 equivalents) of hexafluoroacetone. After the reaction was complete, the reaction mixture was poured into 300 ml of an ice/water mixture and extracted with 200 ml CH_2Cl_2. The aqueous phase was extracted with 100 ml of CH_2Cl_2 (3x). The combined organic phase was washed (3x) with 100 ml portions of an ice/water mixture, dried with $MgSO_4$ and evaporated to dryness *in vacuo*. The solid residue was recrystallized from benzene/pentane. Yield: 25.6 g (86%) **2**, mp 84 °C, white crystals; ir

(KBr): ν 3300-2700, 1830, 1720 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.02 (dd, 1H, J = 18.0 Hz, J = 10.0 Hz), 3.36 (dd, 1H, J = 18.0 Hz, J = 4.0 Hz), 4.51 (dd, 1H, J = 10.0 Hz, J = 4.0 Hz, 1H), 10.63 ppm (s. br., 1H); ^{13}C nmr ($CDCl_3$): δ 37.9, 41.6, 83.5 (sept., J = 35 Hz), 120.8 (q, J = 284 Hz), 121.3 (q, J = 284 Hz), 169.8, 175.6 ppm; ^{19}F nmr ($CDCl_3$): δ 0.11 (q, J = 9.0 Hz, 3F), 1.28 ppm (q, J = 9.0 Hz, 3F); ms (EI) m/z = 298 $[M]^+$, 280 $[M - H_2O]^+$, 252 [280 - CO]$^+$, 69 $[CF_3]^+$.

Anal. Calcd. for $C_7H_4F_6O_4S$ (298.17): C, 28.19; H, 1.35. Found: C, 28.09; H, 1.42.

[2,2-Bis(trifluoromethyl)-5-oxo-1,3-oxathiolan-4-yl]acetyl chloride (**3**).

Compound **2** (25.0 g, 83.8 mmol) was heated with 20 ml freshly distilled thionyl chloride under reflux for 6 h. After removal of the excess of thionyl chloride, the remaining liquid was distilled *in vacuo*. Yield: 24.4 g (88%) **3**, bp 80 °C/6 torr, slightly yellow liquid; mp ca. 15 °C; ir (film): ν 1800 br., 1385 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.47 (dd, 1H, J = 19.0 Hz, J = 10.0 Hz), 3.86 (dd, 1H, J = 19.0 Hz, J = 4.0 Hz), 4.55 ppm (dd, 1H, J = 10.0 Hz, J = 4.0 Hz); ^{13}C nmr ($CDCl_3$): δ 41.6, 49.8, 83.9 (sept., J = 35 Hz), 120.9 (q, J = 284 Hz), 121.4 (q, J = 285 Hz), 169.1, 171.5 ppm; ^{19}F nmr ($CDCl_3$): δ 1.60 (q, J = 9.0 Hz, 3F), 2.40 ppm (q, J = 9.0 Hz, 3F); ms (EI) m/z = 316/318 $[M]^+$, 281 [M - Cl]$^+$, 252 [M - CO, - HCl]$^+$, 182 $[CF_3CSCF_3]^+$, 113 $[CF_3CS]^+$, 87 [281 - CO, - CF_3COCF_3]$^+$, 69 $[CF_3]^+$.

Anal. Calcd. for $C_7H_3ClF_6O_3S$ (316.60): C, 26.55; H, 0.95. Found: C, 26.74; H, 1.09.

4-(3-Diazo-2-oxopropyl)-2,2-bis(trifluoromethyl)-1,3-oxathiolan-5-one (**4**).

To a stirred solution of diazomethane (100 mmol) in 200 ml of diethyl ether, **3** (11.78 g, 37.2 mmol) in 50 ml of diethyl ether was slowly added with cooling (0 °C). After 30 minutes the solvent was evaporated and the residue was distilled under reduced pressure. Yield: 11.15 g (93%) **4**, bp 86 °C/0.1 torr, mp 30 °C, yellow crystals; ir ($CHCl_3$): ν 2095, 1805, 1635 cm^{-1}; ^1H nmr ($DCCl_3$): δ 2.90 (dd, 1H, J = 17.0 Hz, J = 11.0 Hz), 3.38 (dd, 1H, J = 17.0 Hz, J = 3.0 Hz), 4.51 (dd, 1H, J = 11.0 Hz, J = 3.0 Hz), 5.44 ppm (s, 1H); ^{13}C nmr ($CDCl_3$): δ 41.3, 43.8, 55.8, 83.8 (sept, J = 34 Hz), 121.0 (q, J = 284 Hz), 121.4 (q, J = 286 Hz), 170.9, 188.9 ppm; ^{19}F nmr ($CDCl_3$): δ 1.60 (q, J = 9.0 Hz, 3F), 2.34 ppm (q, J = 9.0 Hz, 3F); ms (EI) m/z = 322 $[M]^+$, 294 $[M - N_2]^+$, 252 [M - CO, - CH_2N_2]$^+$, 225 [294 - CF_3], 113 $[CF_3CS]^+$, 69 $[CF_3]^+$, 55 $[CH_2COCH]^+$.

Anal. Calcd. for $C_8H_4F_6N_2O_3S$ (322.18): C, 29.82; H, 1.25; N, 8.69. Found: C, 30.46; H, 1.53; N, 7.60.

4-(3-Bromo-2-oxopropyl)-2,2-bis(trifluoromethyl)-1,3-oxathiolan-5-one (**5a**).

To a stirred solution of freshly prepared diazoketone **4** (10.0 g, 31 mmol) in THF (70 ml) at - 78 °C, conc. HBr (25 ml) was added dropwise. After gas formation ceased, the mixture was warmed up to 0 °C and the solvents and the excess of HBr were distilled off *in vacuo*. The residue was dissolved in 100 ml of $CHCl_3$, washed with cold $NaHCO_3$ solution, and dried with $MgSO_4$. The solvent was evaporated *in vacuo* and the remaining liquid was purified by distillation under reduced pressure. Slightly yellow oil, crystallizing on storage in a refrigerator. Yield: 9.55 g (82%) **5a**, bp 86 °C/0.2 torr, mp 40 °C; ir (KBr): ν 1815, 1735 cm^{-1}; ^1H nmr (acetone-d_6): δ 3.45 (dd, 1H, J = 19.0 Hz, J = 10.0 Hz), 3.92 (dd, 1H, J = 19.0 Hz, J = 3.0 Hz), 4.38 (d, 2H, J = 2.0 Hz), 4.87 ppm (dd, 1H, J = 10.0 Hz, J = 3.0 Hz); ^{13}C nmr (acetone-d_6): δ 34.8, 41.6, 44.0, 84.0 (sept., J = 34 Hz), 122.1 (q, J = 284 Hz), 122.5 (q, J = 284 Hz), 171.2, 199.2 ppm; ^{19}F nmr (acetone-d_6): δ 0.24 (q, J = 10.0 Hz, 3F), 1.14 ppm (q, J = 10.0 Hz, 3F); ms (EI) m/z = 376 $[M]^+$, 295 [M - Br]$^+$, 281 [M - CH_2Br]$^+$, 253[M - $COCH_2Br$]$^+$, 87 [253 - CF_3COCF_3]$^+$.

Anal. Calcd. for $C_6H_5BrF_6O_3S$ (375.08): C, 25.61; H, 1.34. Found: C, 25.89; H, 1.41.

4-(3-Chloro-2-oxopropyl)-2,2-bis(trifluoromethyl)-1,3-oxathiolan-5-one (**5b**).

To a stirred solution of freshly prepared diazoketone **4** (3.22 g, 10.0 mmol) in 25 ml of THF at - 78 °C, conc. HCl (7 ml) was added dropwise. After gas formation ceased, the mixture was warmed up to 0 °C and the solvents and the excess of HCl were evaporated *in vacuo*. For working-up procedure see **5a**. After evaporation of the solvent the residue was recrystallized from pentane/$CHCl_3$. Yield: 2.68 g (81%) **5b**, mp 51 °C, white crystals; ir (KBr): ν 1806, 1755 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.22 (dd, 1H, J = 19.0 Hz, J = 11.0 Hz), 3.75 (d, 1H, J = 19.0 Hz, J = 3.0 Hz), 4.21 (s, 2H), 4.49 ppm (dd, 1H, J = 11.0 Hz, J = 3.0 Hz); ^{13}C nmr ($CDCl_3$): δ 40.8, 44.3, 47.4, 83.9 (sept., J = 35 Hz), 121.0 (q, J = 284 Hz), 121.5 (q, J = 285 Hz), 170.8, 199.4 ppm; ^{19}F nmr ($CDCl_3$): δ 1.65 (q, J = 9.0 Hz, 3F), 2.34 ppm (q, J = 9.0 Hz, 3F); ms (EI) m/z = 332/330 $[M]^+$, 294 [M - HCl]$^+$, 281 [M - CH_2Cl]$^+$, 253 [M - $COCH_2Cl$]$^+$, 87 [253 - CF_3COCF_3]$^+$, 79/77 $[COCH_2Cl]^+$.

Anal. Calcd. for $C_8H_5ClF_6O_3S$ (330.63): C, 29.06; H, 1.52. Found: C, 29.10; H, 1.08.

4-(Thiazol-4-ylmethyl)-2,2-bis(trifluoromethyl)-1,3-oxathiolan-5-one (**7**).

General Procedure.

To a stirred solution of **5a** (10 mmol) in 10 ml of acetone, the corresponding thioamide (10 mmol), dissolved in 10 ml of acetone, was added dropwise. Then the reaction mixture was heated under reflux for 4 hours. The solvent was removed *in vacuo*, and the residue was suspended in diethyl ether (100 ml) and washed with ice-cold $NaHCO_3$ solution. The aqueous phase was extracted with diethyl ether (3x 50 ml). The combined organic layer was washed with ice-cold water (3x 50 ml) and dried with $MgSO_4$. After evaporation of the solvent under reduced pressure the residue was recrystallized from hexane/$CHCl_3$.

4-[2-(2-Thienyl)-thiazol-4-ylmethyl]-2,2-bis(trifluoromethyl)-1,3-oxathiolan-5-one (**7a**).

Compound **5a** (3.75 g, 10 mmol) was reacted with thiophene thioamide (1.43 g, 10 mmol) in 20 ml of acetone. Yield: 3.73 g (89%) **7a**, mp 65 °C, white crystals; ir ($CHCl_3$): ν 1815 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.26 (dd, 1H, J = 14.9 Hz, J = 11.1 Hz), 3.77 (dd, 1H, J = 15.0 Hz, J = 3.6 Hz), 4.76 (dd, 1H, J = 10.8 Hz, J = 3.9 Hz), 7.05 (s, 1H), 7.13 (m, 1H), 7.46 (m, 1H), 7.56 ppm (m, 1H); ^{13}C nmr ($CDCl_3$): δ 35.3, 46.1, 83.3 (sept., J = 35 Hz), 114.9, 120.9 (q, J = 283 Hz), 121.5 (q, J = 284 Hz), 127.0, 128.0, 128.2, 136.8, 151.1, 162.5, 170.5 ppm; ^{19}F nmr ($CDCl_3$): δ 0.86 (q, J = 9.0 Hz, 3F), 1.86 ppm (q, J = 9.0 Hz, 3F); ms (EI): *m/z* = 419 $[M]^+$, 253 [M - CF_3COCF_3]$^+$, 225 [253 - CO]$^+$, 180 [225 - CSH]$^+$, 71 $[C_3H_3O_2]^+$, 45 $[CSH]^+$.

Anal. Calcd. for $C_{13}H_7F_6NO_2S_3$ (419.39): C, 37.23; H, 1.68; N, 3.34. Found: C, 37.22; H, 1.77; N, 3.39.

4-[2-(4-Fluorophenyl)-thiazol-4-ylmethyl]-2,2-bis(trifluoromethyl)-1,3-oxathiolan-5-one (**7b**).

Compound **5a** (3.75 g, 10 mmol) was reacted with 4-fluorothiobenzamide (1.55 g, 10 mmol) in 20 ml of acetone. Yield: 3.03 g (69%) **7b**, mp 75 °C, white crystals; ir (KBr): ν 3400, 1810 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.32 (dd, 1H, J = 15.0 Hz, J = 10.8 Hz), 3.79 (dd, 1H, J = 15.3 Hz, J = 3.6 Hz), 4.76 (dd, 1H, J = 10.5 Hz, J = 3.6 Hz), 7.11 (s, 1H), 7.19 (m, 2H), 7.96 ppm (m, 2H); ^{13}C nmr ($CDCl_3$): δ 33.5, 45.4, 82.1 (sept., J = 34 Hz), 116.4 (d, J = 22 Hz), 117.6 (d, J = 8.0 Hz), 120.8 (q, J = 284 Hz), 121.4 (q, J = 285 Hz), 128.3, 129.4 (d, J = 3.0 Hz), 151.3, 163.3 (d, J = 248 Hz), 166.0, 170.7 ppm; ^{19}F nmr ($CDCl_3$): δ 0.85 (q, J = 9.3 Hz, CF_3), 1.91 ppm (q, J = 9.0 Hz, CF_3); ms (EI) m/z = 431 $[M]^+$, 412 $[M - F]^+$, 265 $[M - CF_3COCF_3]^+$, 237 $[265 - CO]^+$, 192 $[265 - COCHS]^+$, 122 $[FC_6H_4CNH]^+$.

Anal. Calcd. for $C_{15}H_8F_7NO_2S_2$ (431.34): C, 41.77; H, 1.87; N, 3.35. Found: C, 41.30, H, 2.02; N, 3.35.

4-[2-(4-Chlorophenyl)-thiazol-4-ylmethyl]-2,2-bis(trifluoromethyl)-1,3-oxathiolan-5-one (**7c**).

Compound **5a** (3.75 g, 10 mmol) was reacted with 4-chlorothiobenzamide (1.72 g, 10 mmol) in 20 ml of acetone. Yield: 2.50 g (56%) **7c**, mp 84 °C, white crystals; ir (KBr): ν 1810 cm^{-1}; ^1H nmr (acetone-d_6): δ 3.44 (dd, 1H, J = 15.0 Hz, J = 10.0 Hz), 3.81 (dd, 1H, J = 15.0 Hz, J = 4.0 Hz), 5.15 (dd, 1H, J = 10.0 Hz, J = 4.0 Hz), 7.52 (s, 1H), 7.53 (m, 2H), 7.97 ppm (m, 2H); ^{13}C nmr (acetone-d_6): δ 35.2, 46.6, 83.6 (sept., J = 35 Hz), 117.8, 122.0 (q, J = 283 Hz), 122.7 (q, J = 284 Hz), 128.6, 130.1, 132.9, 136.6, 152.9, 167.5, 181.0 ppm; ^{19}F nmr (acetone-d_6): δ 0.25 (q, J = 9.0 Hz, CF_3), 1.41 ppm (q, J = 9.0 Hz, CF_3); ms (EI) m/z = 447/449 $[M]^+$, 281/283 $[M - CF_3COCF_3]^+$, 253/255 $[M - CF_3COCF_3, - CO]^+$, 208 $[M - CF_3COCF_3, - COCHS]^+$, 71 $[C_3H_3O_2]^+$.

Anal. Calcd. for $C_{15}H_8ClF_6NO_2S_2$ (447.81): C, 40.23; H, 1.80; N, 3.13. Found: C, 40.39; H, 1.86; N, 3.10.

4-[2-(4-Methylphenyl)-thiazol-4-ylmethyl]-2,2-bis(trifluoromethyl)-1,3- oxathiolan-5-one (**7d**).

Compound **5a** 3.75 g (10 mmol) was reacted with 4-methylthiobenzamide (1.51 g, 10 mmol) in 20 ml of acetone. Yield: 2.70 g (63%) **7d**, mp 79 °C, white crystals; ir (KBr): ν 1810, 1790, 1510, 1455, 1210 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.39 (s, 3H), 3.25 (dd, 1H, J = 14.8 Hz, J = 10.6 Hz), 3.75 (dd, 1H, J = 15.0 Hz, J = 3.4 Hz), 4.72 (dd, 1H, J = 10.8 Hz, J = 3.2 Hz), 7.03 (s, 1H), 7.24 (d, 2H, J = 8 Hz), 7.81 ppm (d, 2H, J = 8 Hz); ^{13}C nmr ($CDCl_3$): δ 21.4, 35.5, 46.2, 83.4 (sept., J = 35 Hz), 115.0, 120.9 (q, J = 286 Hz), 121.6 (q, J = 286 Hz), 126.5, 129.7, 130.6, 140.8, 151.3, 169.1, 170.5 ppm; ^{19}F nmr ($CDCl_3$): δ 1.94 (q, J = 9.0 Hz, CF_3), 3.09 ppm (q, J = 9.0 Hz, CF_3); ms (EI) m/z = 427 $[M]^+$, 408 $[M - F]^+$, 233 $[M - (CF_3)_2CO, - CO]^+$, 188 $[M - C_7H_7, - C_4H_3NS]^+$, 118 $[C_7H_7CNH]^+$.

Anal. Calcd. for $C_{16}H_{11}F_6NO_2S_2$ (427.37): C, 44.96; H, 2.59; N, 3.27. Found: C, 45.10; H, 2.78; N, 3.75.

3-[2-(Aryl)-thiazol-4-yl]-(*RS*)-2-mercapto-propanoic Acid (**8**).

General Procedure.

A solution of **7** (5 mmol) in a 1:1-THF/water mixture (50 ml) was heated under reflux for 2 days. After evaporation of the solvents, the residue was dissolved in 100 ml of CH_2Cl_2. The organic layer was washed with water (3x 50 ml) and dried with $MgSO_4$. After evaporation of the solvent *in vacuo* the residue was recrystallized from $CHCl_3$/hexane.

3-[2-(2-Thienyl)-thiazol-4-yl]-(R,S)-2-mercaptopropanoic Acid (**8a**).

Compound **7a** (2.10 g, 5 mmol) was heated in a THF/water mixture. Yield: 1.20 g (88%) **8a**, mp 80 °C, white crystals; ir (KBr): ν 3580-2930, 1710 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.24 (dd, 1H, J = 15 Hz, J = 6.3 Hz), 3.42 (dd, 1H, J = 14.8 Hz, J = 7.5 Hz), 4.04 (dd, 1H, J = 14.0 Hz, J = 7.0 Hz), 6.95 (s, 1H), 6.99 (m, 1H), 7.32 (d, 1H, J = 5.2 Hz), 7.45 (d, 1H, J = 3.6 Hz), 10.40 ppm (s.br., 2H, OH, SH); ^{13}C nmr ($CDCl_3$): δ 32.4, 51.7 (d, J = 61 Hz), 115.7, 127.4, 128.2, 128.3, 136.3, 152.2, 162.4, 175.0 ppm; ms (EI) m/z = 271 $[M]^+$, 253 $[M – H_2O]^+$, 238 $[M - SH]^+$, 226 $[M – CO_2H]^+$, 220 $[253 - SH]^+$, 193 $[226 - SH]^+$, 181 $[226 - CSH]^+$, 111 $[C_5H_5NS]^+$, 83 $[C_4H_3S]^+$, 71 $[C_3H_3O_2]^+$, 39 $[C_3H_3]^+$.

Anal. Calcd. for $C_{10}H_9NO_2S_3$ (271.38): C, 44.26; H, 3.34; N, 5.16. Found: C, 44.20; H, 3.16; N, 4.76.

3-[2-(4-Fluorophenyl)-thiazol-4-yl]-(*RS*)-2-mercaptopropanoic Acid (**8b**).

Compound **7b** (2.16 g, 5 mmol) was heated in a THF/water mixture. Yield: 1.16 g (82%) **8b**, mp 127 °C, white crystals; ir (KBr): ν 3500-2700, 1700, 1605 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.01 (d, 1H, J = 5.8 Hz), 3.03 (dd, 1H, J = 15.0 Hz, J = 7.0 Hz), 3.30 (dd, 1H, J = 14.6 Hz, J = 8.0 Hz), 3.79 (m, 1H), 7.30 (m, 2H), 7.40 (s, 1H), 7.93 ppm (m, 2H); ^{13}C nmr (acetone-d_6): δ 31.8, 55.0, 116.6 (d, J = 22 Hz), 116.6, 129.1 (d, J = 9.0 Hz), 130.7, 154.3, 163.0, 166.9, 172.5 ppm; ms (EI) m/z = 283 $[M]^+$, 250 $[M - SH]^+$, 238 $[M - CO_2H]^+$, 193 $[238 - CSH]^+$, 71 $[C_3H_3O_2]^+$, 45 $[CSH, CO_2H]^+$.

Anal. Calcd. for $C_{12}H_{10}FNO_2S_2$ (283.35): C, 50.87; H, 3.56; N, 4.94.Found: C, 50.61; H, 3.79; N, 4.76.

3-[2-(4-Chlorophenyl)-thiazol-4-yl]-(*RS*)-2-mercaptopropanoic Acid (**8c**).

Compound **7c** (2.24 g, 5 mmol) was heated in a THF/water mixture. Yield: 1.00 g (67%) **8c**; mp 137 °C, yellow crystals; ir (KBr): ν 3400-2800, 1750-1650 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.28 (m, 1H), 3.43 (m, 1H), 4.07 (m, 1H), 7.03 (s, 1H), 7.30 (m, 2H), 7.71 ppm (m, 2H); ^{13}C nmr ($CDCl_3$): δ 32.3, 52.3, 116.4, 127.8, 129.2, 131.3, 136.2, 152.8, 167.4, 174.9 ppm; ms (EI) m/z = 301/299 $[M]^+$, 256/254 $[M - CO_2H]^+$, 211/209 $[254 - CSH]^+$, 71 $[C_3H_3O_2]^+$, 45 $[CSH, CO_2H]^+$.

Anal. Calcd. for: $C_{12}H_{10}ClNO_2S_2$ (299.80): C, 48.08; H, 3.36; N, 4.67. Found: C, 48.02, H, 3.46; N, 4.57.

3-[2-(4-Methylphenyl)-thiazol-4-yl]-(*RS*)-mercaptopropanoic Acid (**8d**).

Compound **7d** (2.14 g, 5 mmol) was heated in a THF/water mixture. Yield: 1.13 g (81%) **8d**, mp 137 °C, white crystals; ir (KBr) ν 3600-2780, 1705 cm^{-1}; ^1H nmr (acetone-d_6): δ 2.34 (s, 3H), 3.39 (m, 2H), 4.22 (m, 1H), 7.28 (m, 3H), 7.79 ppm (m, 2H); ^{13}C nmr (acetone-d_6): δ 21.3, 33.6, 53.0, 115.2, 126.9, 130.3, 131.6, 140.8, 154.1, 168.2, 172.3 ppm; ms (EI) m/z = 279 $[M]^+$, 246 $[M - SH]^+$, 234 $[M - CO_2H]^+$, 188 $[M - C_7H_7]$, 118 $[C_7H_7CNH]^+$, 91 $[HSCHCO_2H]^+$.

Anal. Calcd. for $C_{13}H_{13}NO_2S_2$ (279.37): C, 55.89; H, 4.69; N, 5.01. Found: C, 55.94; H, 4.31; N, 5.19.

Methyl 3-[2-(2-thienyl)-thiazol-4-yl]-(*RS*)-2-mercaptopropionate (**9**).

Compound **7a** (2.10 g, 5 mmol) was heated in dry methanol (25 ml) under reflux for 3 hours. After evaporation of the solvent,

the residue was purified by Kugelrohr distillation *in vacuo*. Yield: 0.75 g (53%) **9**; bp 220 °C/1.5 torr; ir (film): ν 3105, 2950, 1730, 1510 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.19 (d, 1H, J = 9.0 Hz), 3.16 (dd, 1H, J = 15.0 Hz, J = 7.0 Hz), 3.40 (dd, 1H, J = 15.0 Hz, J = 8.0 Hz), 3.74 (s, 3H), 3.90 (m, 1H), 6.92 (s, 1H), 7.03 (m, 1H), 7.36 (m, 1H), 7.46 ppm (m, 1H); ^{13}C nmr ($CDCl_3$): δ 37.2, 40.1, 52.6, 114.7, 126.5, 127.6, 127.8, 137.2, 153.1, 161.5, 173.2 ppm; ms (EI) m/z = 285 $[M]^+$, 254 $[M - OCH_3]^+$, 252 $[M - SH]^+$, 226 [254 - CO]$^+$, 181 [226 - CSH]$^+$, 71 $[C_3H_3O_2]^+$, 45 $[CSH]^+$.

Anal. Calcd. for: $C_{11}H_{11}NO_2S_3$ (285.41): C, 46.29; H, 3.88; N, 4.91. Found: C, 46.04; H, 3.95; N, 5.05.

Aminolysis of 4-(thiazol-4-ylmethyl)-2,2-bis(trifluoromethyl)-1,3-oxathiolan-5-ones (**7**).

General Procedure.

A solution of **7** (5 mmol) in 50 ml of diethyl ether or acetonitrile was reacted at room temperature with an excess of the corresponding amine, aniline, hydrazine hydrate, hydroxylamine, (*S*)-phenylalanine methyl ester, Z-hydrazide and *Z*-glycine hydrazide with stirring. After a few minutes the products began to crystallize. After completion of the reaction (^{19}F NMR analysis) the precipitate was collected by filtration, washed with diethyl ether and dried *in vacuo*.

N-Benzyl 3-[2-(2-thienyl)-thiazol-4yl]-(*RS*)-2-mercaptopropanamide (**10a**).

Compound **7a** (2.10 g, 5 mmol) was treated with benzylamine (1.07 g, 10 mmol) in 50 ml of diethyl ether. Yield: 1.30 g (72%) **10a**, mp 131 °C, white crystals; ir (KBr): ν 3290, 2920, 1630 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.06 (dd; 1H, J = 14.0 Hz, J = 7.0 Hz), 3.32 (dd, 1H, J = 14.0 Hz, J = 8.0 Hz), 3.88 (dd, 1H, J = 8.0 Hz, J = 7.0 Hz), 4.22 (dd; 1H, J = 15.0, J = 6.0 Hz), 4.36 (dd, 1H, J = 15.0 Hz, J = 6.0 Hz), 7.18 (m, 6H), 7.28 (s, 1H), 7.63 (m, 1H), 7.63 (m, 1H), 7.69 (m, 1H), 8.63 ppm (t, 1H, NH, J = 6.0 Hz); ^{13}C nmr (DMSO-d_6): δ 37.4, 40.8, 42.3, 115.9, 126.9, 127.1, 127.2, 128.4, 128.5, 128.7, 136.9, 139.3, 154.0, 160.5, 171.7 ppm; ms (EI) m/z = 360 $[M]^+$, 327 $[M - SH]^+$, 222 [327 - $C_7H_7N]^+$, 194 [222 - CO]$^+$, 181 [194 - CH]$^+$, 106 $[C_7H_7N]^+$, 91 $[C_7H_7]^+$.

Anal. Calcd. for: $C_{17}H_{16}N_2OS_3$ (360.54): C, 56.63; H, 4.47; N, 7.77. Found: C, 56.65; H, 4.55; N, 7.99.

N-Benzyl 3-[2-(4-fluorophenyl)-thiazol-4-yl]-(*RS*)-2-mercaptopropanamide (**10b**).

Compound **7b** (2.16 g, 5 mmol) was reacted with benzylamine (1.07 g, 10 mmol) in 50 ml of diethyl ether. Yield: 1.56 g (84 %) **10b**, mp 147 °C, white crystals; ir (KBr): *ν* 3540-3360, 3300, 1640, 1540 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.04 (d, 1H, J = 9.3 Hz), 3.10 (dd, 1H, J = 14.1 Hz, J = 6.3 Hz), 3.35 (dd, 1H, J = 14.1 Hz, J = 8.7 Hz), 3.93 (m, 1H), 4.19 (dd, 1H, J = 15.6 Hz, J = 5.7 Hz), 4.36 (dd, 1H, J = 15.3 Hz, J = 6.3 Hz), 7.09 (m, 2H), 7.20 (m, 3H), 7.36 (m, 3H), 8.01 (m, 2H), 8.61 ppm (t, 1H, J = 5.9 Hz, NH); ^{13}C nmr (acetone-d_6): δ 37.4, 40.5, 42.0, 115.9, 116.3, 126.6, 126.8, 128.1, 128.2, 128.4, 129.7, 139.0, 154.2, 160.5, 165.2, 165.5, 171.4 ppm; ms (EI): *m/z* = 372 $[M]^+$, 339 [M - SH]$^+$, 234 [339 - $C_7H_7N]^+$, 206 [234 - CO]$^+$, 193 [206 - CH]$^+$, 139 [193 - $C_3H_4N]^+$, 122 [F-C_6H_4-CNH]$^+$, 106 $[C_7H_8N]^+$, 91 $[C_7H_7]^+$, 71 [193 - F-C_6H_4-CNH]$^+$.

Anal. Calcd. for: $C_{19}H_{17}FN_2OS_2$ (372.49): C, 61.27; H, 4.60; N, 7.52. Found: C, 61.30; H, 4.14; N, 7.67.

3-[2-(2-Thienyl)-thiazol-4-yl]-(*RS*)-2-mercaptopropananilide (**11**).

Compound **7a** (2.10 g, 5 mmol) was treated with aniline (0.93 g, 10 mmol) in 50 ml of diethyl ether. Yield: 1.21 g (70%) **11**; mp 158 °C, white crystals; ir (KBr): ν 3545-3285, 1650, 1600, 1540 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.07 (dd, 1H, J = 14.4 Hz, J = 7.5 Hz), 3.14 (d, 1H, J = 9 Hz), 3.37 (dd, 1H, J = 14.4 Hz, J = 7.5 Hz), 3.97 (m, 1H), 7.05 (m, 1H), 7.14 (m, 1H), 7.30 (m, 2H), 7.34 (m, 1H), 7.57 (m, 1H), 7.60 (m, 1H), 7.61 (m, 1H), 7.69 (m, 1H), 10.18 ppm (s, 1H); ^{13}C nmr (DMSO-d_6): δ 36.6, 41.3, 115.7, 119.2, 123.4, 127.0, 128,3, 128.5, 128.7, 136.6, 138.9, 153.6, 160,4, 170.3 ppm; ms (EI) m/z = 346 $[M]^+$, 313 $[M - SH]^+$, 254 $[M – C_6H_6N]^+$, 221 [313 - $C_6H_6N]^+$, 194 [313 - C_6H_5N, - CO]$^+$, 181 [194 - CH]$^+$, 128 [181 – $C_3H_3N]^+$.

Anal. Calcd. for $C_{16}H_{14}N_2OS_3$ (346.49): C, 55.46; H, 4.07; N, 8.08. Found: C, 55.50; H, 4.30; N, 8.25.

3-[2-(2-Thienyl)-thiazol-4-yl]-(*RS*)-2-mercaptopropanhydrazide (**12a**).

Compound **7a** (2.10 g, 5 mmol) and hydrazine hydrate (1.00 g, 20 mmol) were reacted in 50 ml of diethyl ether. Yield: 1.30 g (91%) **12a**; mp 126 °C, white crystals; ir (KBr): ν 3700-2800, 3310, 1645, 1535 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.02 (dd, 1H, J = 14.6 Hz, J = 7.7 Hz), 3.27 (dd, 1H, J = 14.4 Hz, J = 7.7 Hz), 3.73 (t; 1H, J = 7.6 Hz), 4.17 (s, br., 2H, NH_2), 7.17 (m, 1H), 7.31 (s, 1H), 7.63 (m, 1H), 7.71 (m, 1H), 9.29 ppm (s, br., 1H, NH); ^{13}C nmr (DMSO-d_6): δ 37.0, 39.0, 115.5, 126.9, 128.2, 128.4, 136.6, 153.6, 168.6, 170.8 ppm; ms (EI) m/z = 285 $[M]^+$, 254 [M - $NHNH_2]^+$, 226 [254 - CO]$^+$.

Anal. Calcd. for $C_{10}H_{11}N_3OS_3$ (285.42): C, 42.08; H, 3.88; N, 14.73. Found: C, 41.83; H, 3.64; H, 14.49.

3-[2-(4-Fluorophenyl)-thiazol-4-yl]-(*RS*)-2-mercaptopropanhydrazide (**12b**).

Compound **7b** (2.16 g, 5 mmol) and hydrazine hydrate (1.00 g, 20 mmol) were reacted in 50 ml of diethyl ether. Yield: **12b**; mp 134 °C, white crystals; ir (KBr): *ν* = 3465-3295, 1650, 1510, 1230 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.06 (dd, 1H, J = 14.3 Hz, J = 7.0 Hz), 3.31 (dd, 1H, J = 14.4, J = 7.8 Hz), 3.78 (t, 1H, J = 7.4 Hz), 4.31 (s, br., 2H, NH_2), 7.33 (s, 1H), 7.37 (m, 2H), 7.99 (m, 2H), 9.27 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 39.1, 40.9, 116.0, 116.3, 116.4, 128.3, 128.4, 129.8 (d, J = 3 Hz), 154.2, 163.1 (d, J = 248 Hz), 165.2, 170.9 ppm; ms (EI): *m/z* = 298 $[M + H]^+$, 266 [M - $NHNH_2]^+$, 238 [M - $NHNH_2$, - CO]$^+$, 206 [M - $NHNH_2$, - CO, - S]$^+$.

Anal. Calcd. for $C_{12}H_{12}FN_3OS_2$ (297.38): C, 48.47; H, 4.07; N, 14.13. Found: C, 48.70; H, 4.08; H, 14.40.

N-Hydroxy 3-[2-(2-thienyl)-thiazol-4-yl]-(*RS*)-2-mercaptopropanamide (**13**).

Compound **7a** (2.10 g, 5 mmol) was reacted with hydroxylamine (0.50 g, 15 mmol) in 50 ml of diethyl ether. Yield: 1.15 g (80%) **13**; mp 148 °C, white crystals; ir (KBr): ν 3600-2700, 3230, 1665, 1535 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.02-3.38 (m, 2H), 3.68/3.86 (m, 1H), 7.18 (m, 1H), 7.31/7.33 (s, 1H), 7.64 (m, 1H), 7.72 (m, 1H), 9.17 (m, 1H, NH), 10.77 ppm (s. br., 1H, OH); ^{13}C nmr (DMSO-d_6): δ 32.3, 49.8, 115.5, 126.9, 128.2, 128.4, 136.4, 153.4, 166.1, 168.3 ppm; ms (EI) m/z = 286 $[M]^+$, 253 [M - SH]$^+$, 181 [253 - $C_2H_2O_2N]^+$.

Anal. Calcd. for: $C_{10}H_{10}N_2O_2S_3$ (286.40): C, 41.94; H, 3.52; N, 9.78: Found: C 42,17; H, 3.58; N, 9.65.

N-(2-Hydroxyethyl) 3-[2-(2-thienyl)-thiazol-4-yl]-(*RS*)-2-mercaptopropanamide (**14**).

Compound **7a** (2.10 g, 5 mmol) and ethanolamine (0.92 g, 15 mmol) were reacted in 50 ml of diethyl ether. Yield: 1.07 g (68%) **14**; mp 94 °C, white crystals; ir (KBr): ν 3435-2930, 1640, 1540 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.99 (dd, 1H, J = 14.4 Hz, J = 7.5 Hz), 3.15 (m, 2H), 3.26 (dd, 1H, J = 14.3 Hz, J = 7.5 Hz), 3.39 (m, 2H), 3.78 (t, 1H, J = 7.5 Hz), 7.18 (m, 1H), 7.31 (s, 1H), 7.64 (m, 1H), 7.72 (m, 1H), 8.18 ppm (t, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 37.3, 43.7, 47.8, 62.3, 116.7, 128.0, 129.4, 129.6, 139.0, 155.9, 162.2, 173.5 ppm; ms (EI) m/z = 314 $[M]^+$, 281 $[M - SH]^+$, 253 $[M - NH_2(CH_2)_2OH]^+$, 226 $[M - C(O)NH(CH_2)_2OH]^+$, 193 [226 - $SH]^+$, 181 [226 - $CHS]^+$, 143 [253 - $C_5H_4NS]^+$, 110 $[C_5H_4NS]^+$, 83 $[C_4H_3S]^+$, 71 [181 - $C_5H_4NS]^+$, 40 $[C_3H_4]^+$.

Anal. Calcd. for $C_{12}H_{14}N_2O_2S_3$ (314.45): C, 45.84; H, 4.49; N, 8.91. Found: C 45,80; H, 5.24; N, 8.90.

N-{3-[2-(4-Fluorophenyl)-thiazol-4-yl]-(*RS*)-2-mercaptopropanoyl}-phenylalanine Methylester (**15**).

Compound **7b** (2.16 g, 5 mmol) was reacted with (*S*)-phenylalanine methyl ester (2.69 g, 15 mmol) in of 50 ml diethyl ether. Recrystallization from hexane/$CHCl_3$. Yield: 1.73 g (78 %) **15**; mp 148 °C, white crystals; ir (KBr): ν 3290, 1740, 1645, 1550, 1510 cm^{-1}; ^1H nmr (acetone-d_6): δ 2.43 (d, 1H, J = 9.3 Hz), 3.07 (dd, 1H, J = 13.7 Hz, J = 7.7 Hz), 3.14 (dd, 1H, J = 9.3 Hz, J = 5.8 Hz), 3.19 (dd, 1H, J = 9.3 Hz, J = 5.8 Hz), 3.43 (dd, 1H, J = 14.5 Hz, J = 7.7 Hz), 3.65 (s, 1H), 4.03 (m, 1H), 4.76 (m, 1H), 7.29 (m, 8H), 7.71 (d, 1H, J = 7.8 Hz, NH), 8.05 ppm (m, 2H); ^{13}C nmr (acetone-d_6): δ 38.9, 39.0, 42.7, 53.0, 55.3, 117.2, 117.5 (d, J = 26 Hz), 128.2, 129.8, 130.0, 130.9, 131.9, 138.4, 156.1, 162.7, 167.3, 167.7 ppm; ms (EI) m/z = 444 $[M]^+$, 411 $[M - SH]^+$, 385 $[M - CO_2CH_3]^+$, 265 [385 - $C_7H_7CHNH_2]^+$, 232 [265 - $SH]^+$, 205 [385 - $C_7H_7CHNHCO$, - $SH]^+$, 121 $[FC_6H_4CN]^+$.

Anal. Calcd. for $C_{22}H_{21}FN_2O_3S_2$ (444.55): C, 59.44; H, 4.76; N, 6.30, Found: C, 58.80; H, 5.19; N, 6.87.

N'-{3-[2-(4-Fluorophenyl)-thiazol-4-yl]-2-mercaptopropanoyl}-*N*''-(benzyloxycarbonyl)-hydrazine (**16**).

Compound **7b** (2.16 g, 5 mmol) was reacted with *N*-benzyloxycarbonyl-hydrazine (1.32 g, 10 mmol) in 50 ml of diethyl ether. Yield: 1.60 g (74 %) **17**; mp 152 °C, white crystals; ir (KBr): 3240-3220, 1710, 1680, 1510, 1230 cm^{-1}; ^1H nmr (acetone-d_6): δ 2.50 (d, 1H, J = 8.8 Hz), 3.13 (dd, 1H, J = 14.6 Hz, J = 7.0 Hz), 3.42 (dd, 1H, J = 14.7 Hz, J = 7.0 Hz), 3.94 (dd, 1H, J = 16.3 Hz, J = 7.2 Hz), 5.11 (s, 2H), 7.20 (s, 1H), 7.27 (d, 2H, J = 8.8 Hz), 7.35 (m, 5H), 8.01 (m, 2H), 8.39 (s, br., 1H, NH), 9.33 ppm (s, 1H, NH); ^{13}C nmr (acetone-d_6): δ 39.0, 40.9, 68.0, 117.2, 117.5, 117.6, 129.3, 129.9, 130.0, 131.8, 138.3, 155.8, 157.7, 162.8, 167.3, 173.1 ppm; ms (EI): *m/z* = 431 $[M]^+$, 399 $[M - S]^+$, 323 $[M - PhCH_3O]^+$, 291 [M - F-C_6H_4, -$CHS]^+$, 238 [M - F-C_6H_4-$C_4H_4NS]^+$, 193 [F-C_6H_4-$C_4H_4NS]^+$.

Anal. Calcd. for $C_{20}H_{18}FN_3O_3S_2$ (431.51): C, 55.67; H, 4.20; N, 9.74. Found: C, 55.50; H, 3.65; N, 9.77.

N'-{3-[2-(4-Fluorophenyl)-thiazol-4-yl]-2-mercaptopropanoyl}-*N*''-[(*N*-benzyloxycarbonyl)-glycyl Hydrazine (**17**).

Compound **7b** (2.16 g, 5 mmol) and *N*-carbobenzoxyglycine hydrazide (1.67 g, 7.5 mmol) were reacted in 50 ml of acetonitrile. Yield: 1.83 g (75%) **17**; mp 221 °C, white crystals; ir (KBr): ν 3510-3320, 1700, 1610, 1510, 1455, 1235, 1155 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.09 (dd, J = 14.7 Hz, J = 6.9 Hz, 1H), 3.34 (dd, J = 14.7 Hz, J = 7.5 Hz, 1H), 3.71 (d, J = 6.0 Hz, 2H), 3.93 (t, J = 7.2 Hz, 1H), 5.06 (s, 2H), 7.33 (s, 1H), 7.38 (m, 6H), 7.45 (s, 1H), 7.55 (t, J = 6.0 Hz, 1H), 8.00 (m, 2H), 10.12 (s br., 1H, NH), 10.25 ppm (s br., 1H, NH); ^{13}C nmr (DMSO-d_6): δ 36.9, 38.4, 41.9, 65.5, 116.1, 116.4, 116.5, 127.7, 128.4, 129.8, 137.0, 153.9, 156.5, 161.5, 164.8, 165.2, 167.8, 170.3 ppm; ms (EI): *m/z* = 489 $[M]^+$, 456 $[M - SH]^+$, 379 [456 - C_6H_5], 321 [456 - $C_7H_7CO_2]^+$, 264 [321 - $COCH_2NH]^+$, 206 [264 - $CON_2H_2]^+$, 193 [206 - $CH]^+$.

Anal. Calcd. for $C_{22}H_{21}FN_4O_4S_2$ (488.56): C, 54.09; H, 4.33; N, 11.47. Found: C, 53.80; H, 4.30; N, 11.30.

Acknowledgements.

We are grateful to Volkswagen-Stiftung, Hannover, for financial support.

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