Transformations of Methyl *L*-(–)-Thiazolidine-4-carboxylate, 2-Amino-2-thiazoline and 2-Aminothiazole into Thiazoloazines and Azolothiazoles

Mateja Malešič [a], Aleš Krbavčič [a] and Branko Stanovnik* [b]

[a] Faculty of Pharmacy, [b] Faculty of Chemistry and Chemical Technology, University of Ljubljana, 1000 Ljubljana, Slovenia

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Dedicated to Professor Dr. Miha Tišler, University of Ljubljana, on the occasion of his 70th birthday

In the search for potential immunomodulators methyl *L*-(–)-thiazolidine-4-carboxylate (**2**), 2-amino-2-thiazoline (**12**), and 2-aminothiazole (**19**) were transformed into derivatives of various bicyclic systems. Thus, from compound **2** derivatives of perhydrothiazolo[3,4-*a*]pyrazine **4** and **5**, perhydrothiazolo[4,3-*c*]-[1,4]oxazine **7**, and perhydroimidazo[1,5-*c*]thiazole **9a,b**, from compound **12** derivatives of 2,3-dihydrothiazolo[2,3-*b*]pyrimidine **13a,b**, and from compound **19** derivatives of imidazo[2,1-*b*]thiazole **21**, **22**, **24**, and **25** were prepared. 6-(*p*-Sulfamoylphenyl)-7-oxoperhydroimidazo[1,5-*c*]thiazole-5-thione (**9a**) was found to exhibit immunorestoration activity.

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The thiazolidinecarboxylic acid, aminothiazoline and aminothiazole are important pharmacophoric structures found in different bioactive substances, especially in some immunomodulating agents [1,2,3,4,5,6]. (–)-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-*b*]thiazole (levamisole) is a well-known immunomodulatory agent with the imidazo[2,1-*b*]-thiazole structure [1]. These observations encourage the synthesis of some new imidazo[2,1-*b*]thiazoles incorporating sulfamoylphenyl group, as the main part of some antibacterially active sulfanilamides, which are also known for their immunomodifying effects [7,8]. 2-Amino-2-thiazoline has been selected as the starting compound for the synthesis of thiazolo[3,2-*a*]pyrimidines, which bear a structural analogy to the levamisole and some other bioactive substances [9]. Various synthetic compounds, structurally unrelated to levamisole also stimulate the immune system, including some amides of *L*-(–)-thiazolidine-4-carboxylic acid [3,4,5,10].

In connection with our studies on potential immunomodulators some new compounds, which are structurally more or less related to levamisole were prepared.

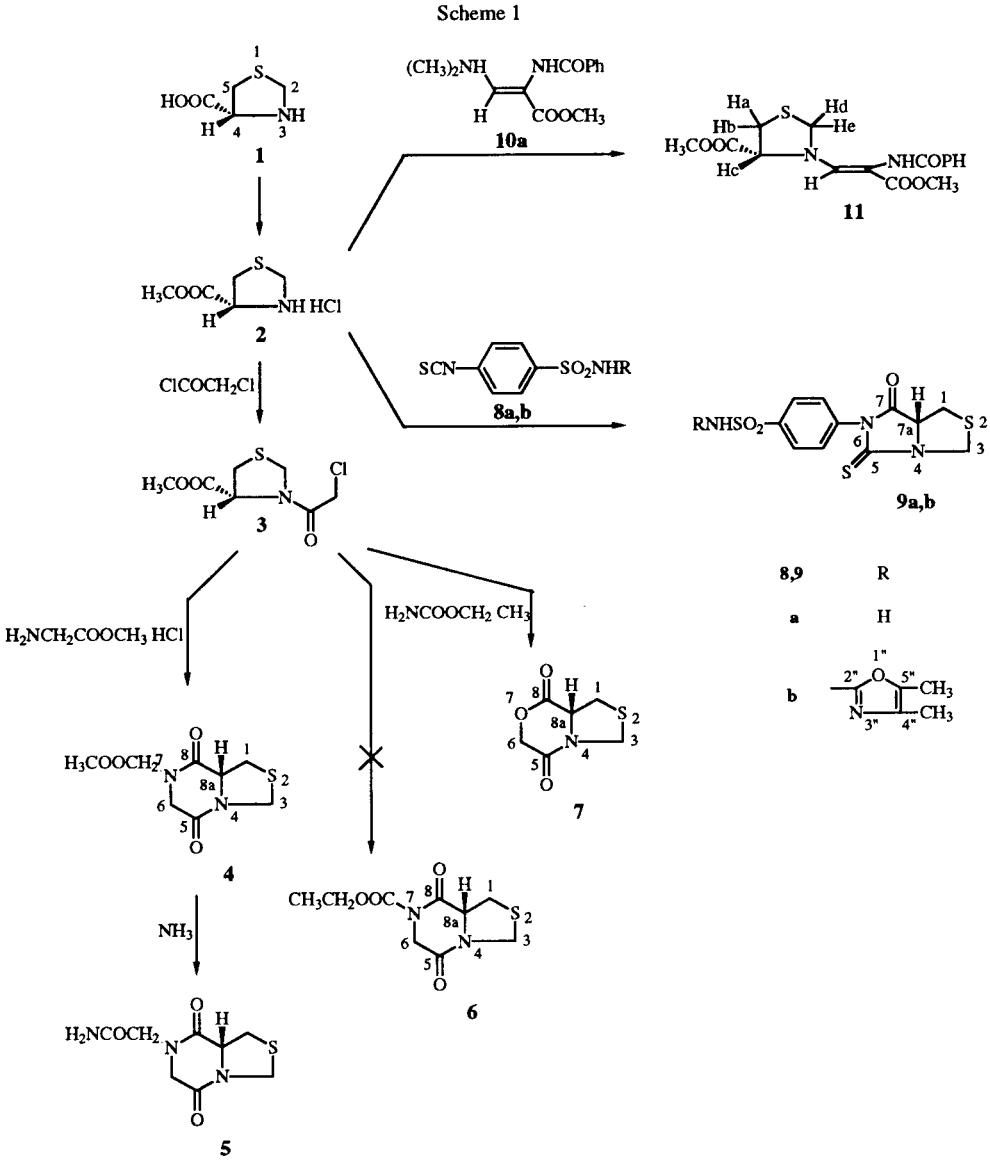
We started our research with the synthesis of some bicyclic amides derived from *L*-(–)-thiazolidine-4-carboxylic acid (**1**). *L*-(–)-thiazolidine-4-carboxylic acid (**1**) was first transformed into the methyl *L*-(–)-thiazolidine-4-carboxylate hydrochloride (**2**) and further into methyl *L*-(–)-3-chloroacetylthiazolidine-4-carboxylate (**3**), according to known procedures [3]. In the reaction between **3** and methyl glycinate hydrochloride, 7-methoxycarbonylmethyl-5,8-dioxo-8a(*L*)-perhydrothiazolo[3,4-*a*]pyrazine (**4**) was prepared. The compound **4** is a viscous oil with high boiling point. Attempts to purify the compound **4** by column chromatography, as described in the literature for the ethyl ester analog [3], were unsuccessful. Therefore, we used fractional distillation under high *vacuo* (215°, 10^{-2} Pa), which gave the analytically pure sample. After one month, the compound **4** decomposes by standing at room temperature (Scheme 1).

In order to prepare more stable and crystalline derivatives of this bicyclic system, we tried to transform the ester **4** into the corresponding amide **5** by treatment with 25% aqueous ammonia solution at room temperature. The product, which was isolated from the reaction mixture, shows in the mass spectrum a peak at m/z 229 (M^+), which corresponds to the molecular formula $C_8H_{11}N_3O_3S$, the structure of which was confirmed by ^{1}H-nmr spectrum (Scheme 1).

The reaction between **3** and ethyl carbamate takes two different courses, dependent on the reaction temperature. When the mixture was heated under reflux in cellosolve for 20 hours, 7-ethoxycarbonyl-5,8-dioxo-8a(*L*)-perhydrothiazolo[3,4-*a*]pyrazine (**6**) was presumably formed, since in the mass spectrum m/z 244 (M^+), corresponding to the molecular formula $C_9H_{12}N_2O_4S$, was observed. However, the purification by column chromatography was not successful. When the reaction was preformed in ethanol in an autoclave by heating at 100° for 15 hours, the oily residue, obtained after evaporation of the solvent, was distilled under reduced pressure (150°, 10^{-1} Pa), to give the product **7** in the form of white crystals (Scheme 1).

The compound **7** exhibits in the mass spectrum a peak at m/z 173 (M^+), which together with elemental analysis and nmr spectrum gives molecular formula $C_6H_7NO_3S$, suggesting that the nitrogen from ethyl carbamate has not been incorporated into the molecule. The ir spectrum shows two signals at ν = 1676.0 cm^{-1} and ν = 1757.9 cm^{-1}, which could correspond either to amidocarbonyl or carbonyl group. In ^{1}H-nmr spectrum two multiplets at δ 3.40-3.52 ppm and δ 4.28-5.05 ppm, which are integrated in ratio 2:5, are present. One could infer from this data, that

Scheme 1



there are three partially overlapped non-equivalent methylene groups and one methyne group in the molecule.

According to all the above mentioned analytical data we could conclude, that the ascribed compound has the following structure - 5,8-dioxo-8a(*L*)-perhydrothiazolo[4,3-*c*][1,4]oxazine (**7**) (Scheme 1).

The second reaction pathway, shown in the Scheme 1, represents transformation of *L*-(–)-thiazolidine-4-carboxylic acid (**1**) or its ester **2** with 4-sulfamoylphenyl isothiocyanates **8a,b** into 6-(*p*-sulfamoylphenyl)-7-oxoperhydroimidazo-[1,5-*c*]thiazole-5-thiones **9a,b**. The reactions occur in a few minutes of stirring in an appropriate solvent at room temperature to give 6-(*p*-sulfamoylphenyl)-7-oxoperhydroimidazo[1,5-*c*]thiazole-5-thione (**9a**) and 6-[*p*-(4,5-dimethyloxazolyl-2)sulfamoylphenyl]-7-oxoperhydroimidazo[1,5-*c*]thiazole-5-thione (**9b**) in a 45% and 97% yields, respectively.

Compound **2** reacts with methyl 2-benzoylamino-3-dimethylaminopropenoate (**10a**) at endocyclic nitrogen atom at position **3** of the thiazolidine ring to give methyl 2-benzoylamino-3-(4-methoxycarbonylthiazolidinyl-3)propenoate (**11**) (Scheme 1).

2-Amino-2-thiazoline (**12**) reacts with 2-acylamino-3-dimethylaminopropenoates **10a,b** by heating in acetic acid under reflux for several hours to yield 6-acylamino-5-oxo-2,3-dihydro-5*H*-thiazolo[2,3-*b*]pyrimidines **13a,b** in a 73% and 12% yields, respectively (Scheme 2).

Compound **12** was transformed by the reaction with *N,N*-dimethylformamide dimethylacetal into *N'*-(2-thiazolinyl-2)-*N,N*-dimethylformamidine (**14**). The dimethylamino group in compound **14** could be substituted with different nucleophiles to give intermediates, which could serve in the formation of various heterocyclic systems. In this connec-

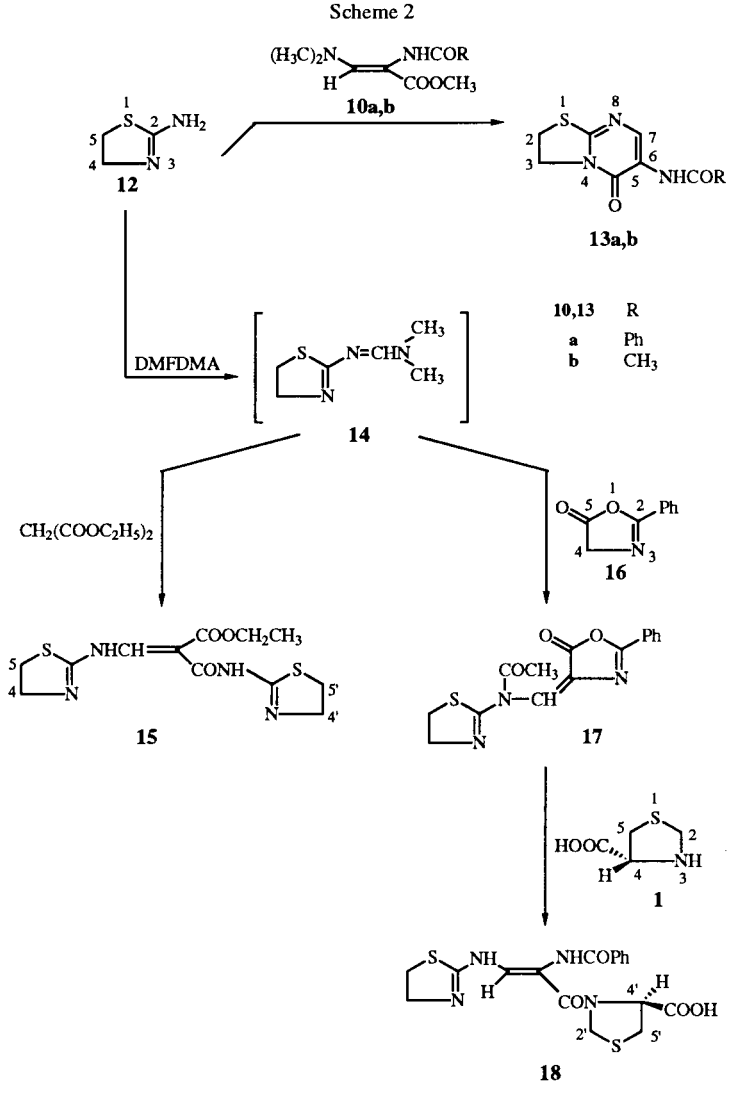
tion, compound **14** was further transformed by the reaction with 5-oxo-4,5-dihydro-2-phenyl-1,3-oxazole (**16**), prepared *in situ* from hippuric acid in acetic anhydride, into the corresponding heteroarylaminomethyleneoxazole **17**. Mass spectrum of this compound shows the peak at m/z 315 (M^+), that corresponds to the *N*-acylated product **17**. The ^{1}H-nmr spectrum and elemental analysis also support this structure. Compound **17** was further transformed with *L*-(–)-thiazolidine-4-carboxylic acid (**1**) into *L*-(–)-{[2-benzoylamino-3-(2-thiazolinyl-2)amino]propenoyl}thiazolidine-4-carboxylic acid (**18**) (Scheme 2).

In an attempt to prepare fused thiazolo[3,2-*a*]pyrimidines, compound **14** was allowed to react with dimethylaminomalonate in acetic acid. However, the ^{1}H-nmr, mass spectrum and elemental analysis show, that the product of this reaction is not a fused bicyclic system, instead, ethyl 2-[(2-thiazolinyl-2)carboxamido]-3-(2-amino-2-thiazolinyl-2)propenoate (**15**) was formed (Scheme 2).

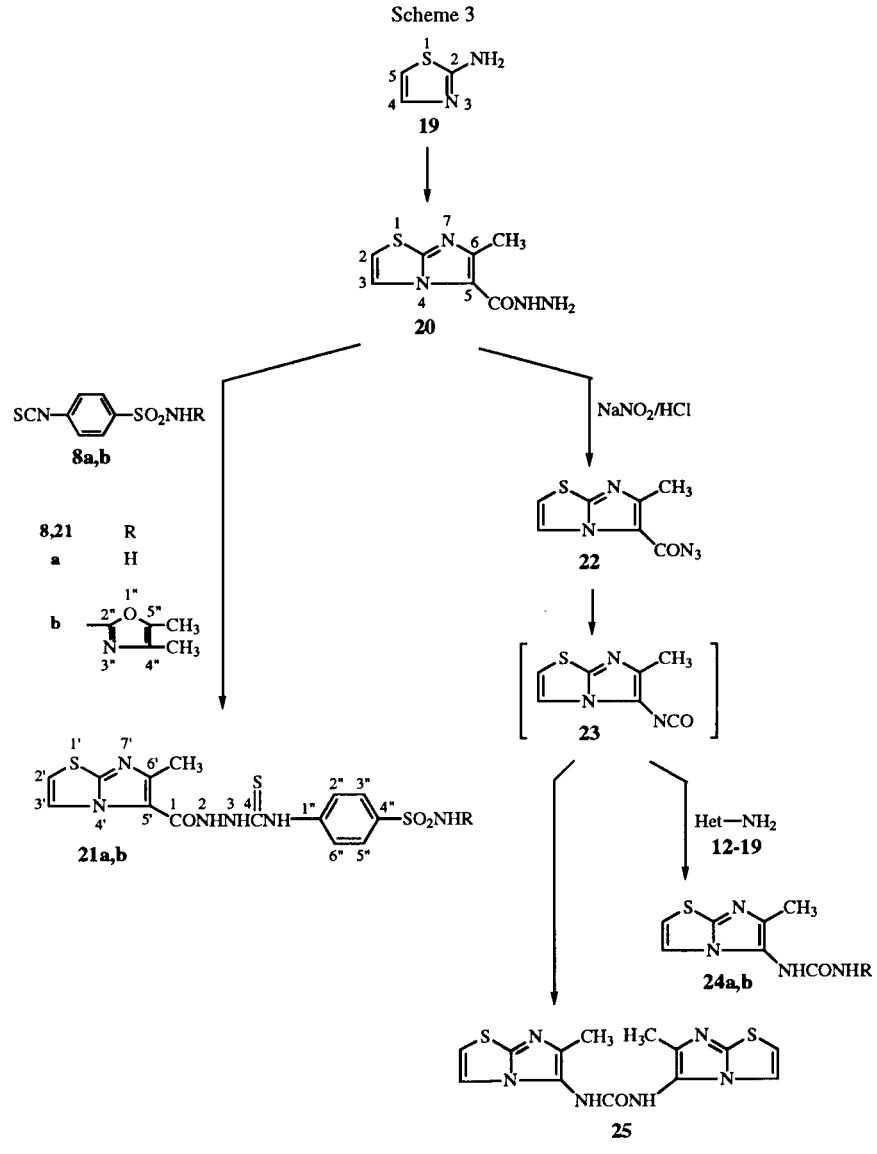
2-Aminothiazole (**19**) was transformed into 6-methylimidazo[2,1-*b*]thiazole-5-carbohydrazide (**20**) according to the literature [7]. The carbohydrazide group of compound **20** reacts with isothiocyanate group of compounds **8a,b** to give 1,4-disubstituted thiosemicarbazides **21a,b** (Scheme 3).

Another reaction pathway includes the transformation of compound **20** into the corresponding azide **22** according to the procedures described for other carbonyl azides [14,15]. Compound **22** reacts further with heterocyclic amines **12**, **19** to give *N,N'*-disubstituted ureas **24a,b** [15]. By heating compound **22** in the presence of toluene, symmetric *N,N'*-di(6-methylimidazo[2,1-*b*]thiazolyl-5)urea (**25**) was presumably formed. The structure is supported by mass spectrum which shows the molecular peak at m/z 332 (M^+) and the base peak at m/z 179 (M^+), which corresponds to 6-methylimidazo[2,1-*b*]thiazolyl-5 isocyanate. The ^{1}H nmr spectrum shows a singlet at δ 2.14

Scheme 2



Scheme 3



ppm integrating for six protons, corresponding to two equivalent methyl groups at positions 6 and 6', a doublet at δ 7.15 ppm, integrating for two protons at positions 2 and 2', a doublet at δ 7.64 ppm, integrating for two protons at positions 3 and 3', with the coupling constant $J_{2,3}$ = 4.40 Hz, and a singlet at δ 8.40 ppm, integrating for two N*H* protons (Scheme 3).

Compound **9a** has been tested in an *in vivo* preliminary immunorestoration test, which shows immunorestoration activity of this compound [17].

EXPERIMENTAL

Melting points were taken on a Leica hot stage microscope. The ^{1}H-nmr spectra were obtained on a Bruker Avance DPX 300 a Varian VXR 300 spectrometers. The ir spectra were recorded on a Perkin-Elmer FTIR 1600. Microanalyses for C, H and N were done on a Perkin-Elmer Analyser 2400. Mass spectra (FAB spectra: MH^+) were recorded on a Varian-MAT 311 A mass spectrometer. Fractional distillation under high vacuum was done on Büchi Kugelrohr.

The following compounds were prepared according to the procedures described in the literature: methyl *L*-(–)-thiazolidine-4-carboxylate (**1**) [3], methyl *L*-(–)-3-chlorothiazolidine-4-carboxylate (**3**) [3], *p*-substituted sulfamoylphenyl isothiocyanates **8a,b** [16], and 6-methylimidazo[2,1-*b*]thiazole-5-carbohydrazide (**20**) [7].

7-Methoxycarbonylmethyl-5,8-dioxo-8a(*L*)-perhydrothiazolo[3,4-*a*]pyrazine (**4**).

To a stirred suspension of methyl 3-chloroacetylthiazolidine-4(*L*)-carboxylate (**3**) (6.26 g, 0.028 mole) and methyl glycinate hydrochloride (4.52 g, 0.0036 mole) in cellosolve (100 ml), triethylamine (6.07 g, 0.06 mole) was added dropwise at room

temperature. The mixture was then heated under reflux for 20 hours. After the solvent was evaporated under reduced pressure, the residue was dissolved in a mixture of benzene and dichloromethane (1:1) and filtered. The filtrate was washed with 5% hydrochloric acid and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The oily residue was purified by column chromatography (with chloroform:methanol 9:1 as the eluent) and by fractional distillation under high vacuo (10^{-2} Pa, 215°) to give **4** in 60% yield; ms: m/z 244 (M^+); ^1H nmr (deuteriochloroform): δ 3.26 (dd, 1H, 1-CH_2, J = 9.30 Hz), 3.44 (dd, 1H, 1-CH_2, J = 5.88 Hz), 3.77 (s, 3H, OCH_3), 3.93 (dd, 2H, COCH_2N, J = 4.88 Hz), 4.34-4.48 (m, 4H, 3-C*H*, 6-CH_2, 8a-C*H*), 4.90 (d, 1H, 3-CH_2, J = 9.76 Hz).

Anal. Calcd. for $C_9H_{12}N_2O_4S$: C, 44.27; H, 4.95; N, 11.47. Found: C, 44.27; H, 4.83; N, 11.40.

7-Carbamoylmethyl-5,8-dioxo-7,8a(*L*)-perhydrothiazolo-[3,4-*a*]pyrazine (**5**).

A mixture of 7-methoxycarbonyl-5,8-dioxo-8a(*L*)-perhydrothiazolo[3,4-*a*]pyrazine (**4**) (0.98 g, 0.004 mole) and aqueous ammonia (25%, 10 ml) was stirred at room temperature for 15 minutes. The precipitate was collected by filtration and recrystallized from diethyl ether to give **5** in 55% yield, mp 187-190°; ms: m/z 229 (M^+); ^1H nmr (DMSO-d_6): δ 3.16 (dd, 1H, 1-CH_2, J = 9.19 Hz), 3.35 (dd, 1H, 1-CH_2, J = 6.57 Hz), 3.93 (dd, 2H, COCH_2N, J = 16.70), 4.25 (d, 2H, 6-CH_2), 4.35 (d, 1H, 3-CH_2, J = 6.62 Hz), 4.49 (deg dd, 1H, 8a-C*H*), 4.79 (d, 1H, 3-CH_2, J = 6.62 Hz).

Anal. Calcd. for $C_8H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33. Found: C, 42.12; H, 4.93; N, 18.43.

5,8-Dioxo-8a(*L*)-perhydrothiazolo[4,3-*c*][1,4]oxazine (**7**).

To a suspension of methyl 3-chloroacetylthiazolidine-4(*L*)-carboxylate (**3**) (2 g, 0.009 mole) and ethyl carbamate (1.03 g, 0.011 mole) in ethanol (35 ml), triethylamine (1.09 g, 0.011 mole) was added. The mixture was heated in an autoclave at 100° for 15 hours. After filtration, the filtrate was evaporated under reduced pressure. The oily residue was purified by fractional destillation under high *vacuo* (10^{-1} Pa, 150°). After addition of anhydrous ethanol, white crystals were separated and collected by filtration to give **7** in 17% yield, mp 87-88°; ms: m/z 173 (M^+); ^1H nmr (deuteriochloroform): δ 3.16 (dd, 1H, 1-CH_2, J = 8.63 Hz), 3.38 (dd, 1H, 1-CH_2, J = 6.36 Hz), 3.95 (d, 1H, 6-CH_2, J = 16.67 Hz), 4.30 (d, 1H, 6-CH_2, J = 16.67 Hz), 4.36 (d, 1H, 3-CH_2, J = 9.64 Hz), 4.54 (deg dd, 1H, 8a-C*H*, J = 7.67 Hz), 4.778 (d, 1H, 3-CH_2, J = 9.64 Hz).

Anal. Calcd. for $C_6H_7NO_3S$: C, 41.62; H, 4.08; N, 8.09. Found: C, 41.29; H, 3.98; N, 7.72.

6-(*p*-Sulfamoylphenyl)-7-oxoperhydroimidazo[1,5-*c*]thiazole-5-thione (**9a**).

A mixture of methyl *L*-(–)-thiazolidine-4-carboxylate (0.34 g, 2.31 mmoles) and *p*-sulfamoylphenyl isothiocyanate (0.49 g, 2.31 mmoles) (**8a**) in anhydrous methanol was stirred at room temperature for a few minutes. The separated solid material was collected by filtration and washed with methanol to give **9a** in 45% yield, mp 200-202°; ms: m/z 330 (MH^+), $[\alpha]_D^{20}$ = -21.0° (c = 0.5, DMF); ^1H nmr (DMSO-d_6): 3.39 (d, 2H, 1-CH_2), 4.60 (d, 1H, 3-CH_2, J = 9.44 Hz), 4.98 (deg dd, 1H, 7a-C*H*), 5.17 (d, 1H, 3-CH_2, J = 9.44 Hz), 7.47 (s, 2H, NH_2), 7.59 (d, 2H, 2'-*H*, 6'-*H*), 7.94 (d, 2H, 3'-*H*, 5'-*H*), (SO_2N*H*, exchanged), $J_{1,7a}$ = 8.34 Hz, $J_{2',3'} = J_{5',6'}$ = 8.58 Hz.

Anal. Calcd. for $C_{11}H_{11}N_3O_3S_3$: C, 40.10; H, 3.36; N, 12.75. Found: C, 39.75; H, 3.03; N, 12.36.

6-[*p*-(4,5-Dimethyloxazolyl-2)sulfamoylphenyl]-7-oxoperhydroimidazo[1,5-*c*]thiazole-5-thione (**9b**).

To a stirred mixture of methyl *L*-(–)-thiazolidine-4-carboxylate hydrochloride (**2**) (0.25 g, 1.35 mmoles) and *p*-(4,5-dimethyloxazolyl-2)sulfamoyl isothiocyanate (0.49 g, 1.35 mmoles) (**8b**) in methanol (4 ml), triethylamine (1.35 mmoles) was added. The mixture was stirred at room temperature for 19 hours. After the reaction was completed, the mixture was poured into ice-cold water and few drops of 2*M* hydrochloric acid were added. The solid material was collected by filtration and washed with water to give **9b** in 97% yield, mp 105-115°; ms: m/z 424 (MH^+); ^1H nmr (DMSO-d_6): 1.60 (s, 3H, 4''-CH_3), 2.08 (s, 3H, 5''-CH_3), 3.40 (d, 2H, 1-CH_2), 4.60 (d, 1H, 3-CH_2, J = 9.52 Hz), 4.97 (deg dd, 1H, 7a-C*H*), 5.15 (d, 1H, 3-CH_2, J = 9.52 Hz), 7.72 (d, 2H, 2'-*H*, 6'-*H*), 7.92 (d, 2H, 3'-*H*, 5'-*H*), 11.20 (bs, 1H, SO_2N*H*), $J_{1,7a}$ = 8.34 Hz, $J_{2',3'} = J_{5',6'}$ = 8.79 Hz.

Anal. Calcd. for $C_{16}H_{17}N_4O_4S_3$: C, 45.28; H, 4.00; N, 13.19. Found: C, 45.16; H, 3.80; N, 12.74.

Methyl 2-Benzoylamino-3-(4-methoxycarbonylthiazolidinyl-3)-propenoate (**11**).

A mixture of L-(–)-thiazolidine-4-carboxylic acid (**1**) (0.18 g, 1 mmole) and methyl 2-benzoylamino-3-dimethylamino-propenoate (**10a**) (0.25 g, 1 mmole) in acetic acid (1.4 ml) was heated under reflux for 3 hours. After the reaction was completed, acetic acid was evaporated under reduced pressure and the solid material was washed with cold water to give **11** in 62% yield, mp 119-121°; ms: m/z 350 (M^+), $[\alpha]_D^{20}$ = -153.5° (c = 0.5, acetic acid); ^1H nmr (deuteriochloroform): 3.20 (dd, 1H, CH_b), 3.28 (dd, 1H, CH_a), 3.65 (s, 3H, CH_3), 3.70 (s, 3H, COOCH_3), 4.63 (d, 1H, CH_d), 4.64 (d, 1H, CH_e), 4.73 (dd, 1H, CH_c), 7.14 (s, 1H, N*H*), 7.40-7.58 (m, 2H, Ph), 7.83-7.85 (m, 3H, Ph), 7.65 (s, N*H*), (N*H*CO, exchange) $J_{Ha,Hc}$ = 6.60 Hz, $J_{Hb,Hc}$ = 2.69 Hz, $J_{Ha,Hb}$ = 11.70 Hz, $J_{Hd,He}$ = 8.55 Hz.

Anal. Calcd. for $C_{16}H_{18}N_2O_5S$: C, 54.84; H, 5.18; N, 7.99. Found: C, 54.64; H, 4.74; N, 7.62.

The Reaction Between 2-Amino-2-thiazoline (**12**) and Methyl 2-Benzoylamino- (**10a**) or Methyl 2-Acetylamino-3-dimethylaminopropenoate (**10b**). The Synthesis of 6-Benzoylamino-5-oxo-2,3-dihydro-5*H*-thiazolo[2,3-*b*]pyrimidine (**13a**) and 6-Acetylamino-5-oxo-2,3-dihydro-5*H*-thiazolo[2,3-*b*]pyrimidine (**13b**).

General Procedure [12].

To a solution of 2-amino-2-thiazoline (**12**) (0.2 g, 2 mmoles) in acetic acid (2.4 ml) of **10a** (0.45 g, 2 mmoles) or **10b** (0.46 g, 2 mmoles) was added. The mixture was heated under reflux for several hours. After the reaction was completed, acetic acid was evaporated under reduced pressure. The solid material was washed with cold water and recrystallized from an appropriate solvent to give **13a** and **13b**.

The following compounds were prepared in this manner:

6-Benzoylamino-5-oxo-2,3-dihydro-5*H*-thiazolo[2,3-*b*]pyrimidine (**13a**).

This compound was prepared from **12** and **10a**, by heating at reflux temperature for 6 hours, in 73% yield, mp 171-173° (from a mixture of ethanol and DMF); ms: m/z 273 (M^+); ^1H nmr (deuteriochloroform): δ 3.53 (t, 2H, 2-CH_2), 4.53 (t, 2H, 3-CH_2), 7.45-7.60 (m, 5H, PhCO), 8.58 (s, 1H, 7-C*H*), 9.06 (s, 1H, NHCO), $J_{SCH_2CH_2N}$ = 7.57 Hz.

Anal. Calcd. for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06; N, 15.37. Found: C, 57.04; H, 3.93; N, 14.97

6-Acetylamino-5-oxo-2,3-dihydro-5*H*-thiazolo[2,3-*b*]pyrimidine (**13b**).

This compound was prepared from **12** and **10b**, by heating at reflux temperature for 4 hours, in 12% yield, mp 236-238° (from acetonitrile); ms: m/z 211 (M^+); ^{1}H nmr (DMSO-d_6): δ 2.09 (s, 3H, COCH_3), 3.56 (t, 2H, 2-CH_2), 4.42 (t, 2H, 3-CH_2), 8.52 (s, 1H, 7-C*H*), 9.31 (s, 1H, N*H*CO), $J_{SCH_2CH_2N}$ = 7.62 Hz.

Anal. Calcd. for $C_8H_9N_3O_2S$: C, 45.49; H, 4.29; N, 19.89. Found: C, 45.25; H, 4.10; N, 19.72.

Ethyl 2-[(2-Thiazolinyl-2)carboxamido]-3-(2-amino-2-thiazolinyl-2)propenoate (**15**).

A mixture of 2-amino-2-thiazoline (**12**) (650 mg, 6.4 mmoles) and *N,N*-dimethyformamide dimethylacetal (1 ml, 6.4 mmoles) in dry toluene (5 ml) was heated under reflux for 2 hours. After the solvent was evaporated, diethyl malonate (6.56 mg, 6.4 mmoles) and acetic acid (2 ml) were added. The mixture was heated at 75° for 10 hours. Acetic acid was evaporated under reduced pressure and the oily residue was left at room temperature for 4 days. The separated crystals were recrystallized from diethyl ether to give **15** in 36% yield, mp 130-135°; ms: m/z 329 (MH^+); ^{1}H nmr (deuteriochloroform): δ 1.25 (t, 3H, CH_3CH$_2$), 3.24 (t, 2H, 5-CH_2), 3.58 (t, 2H, 5'-CH_2), 3.78 (t, 2H, 4-CH_2), 4.20 (q, 2H, CH$_3$CH_2), 4.41 (t, 2H, 4'-CH_2), (CH, N*H*, CON*H*, exchange), $J_{CH_3CH_2}$ = 7.09 Hz, $J_{4,5}$ = 7.40 Hz, $J_{4',5'}$ = 7.97 Hz. The ^{1}H nmr spectrum shows, that crystalline material contains also acetic acid and water (δ 1.88 (s, CH_3), 6.20 (br, H_2O, COO*H*)). After drying *in vacuo* (1.87 x 10^3 Pa), solid sodium hydroxide and phosphorus pentoxide at 70° for 3 days, the crystalline material still contains water and acetic acid.

Anal. Calcd. for $C_{12}H_{16}N_4O_3S_2$:xH_2Ox0.5CH$_3$COOH: C, 41.49; H, 5.32; N, 14.89. Found: C, 41.87; H, 5.37; N, 14.95.

4-{[*N*-Acetyl-*N*-(2-thiazolinyl-2)]aminomethylene}-2-phenyl-5-oxo-4,5-dihydro-1,3-oxazole (**17**).

To a stirred suspension of 2-methyl-2-thiazoline (**12**) (1.02 g, 10 mmoles) in dry toluene (10 ml), *N,N*-dimethylformamide dimethylacetal (1.5 ml, 11.3 mmoles) was added and the mixture was heated under reflux for 2 hours. After the solvent was evaporated, hippuric acid (2 g, 11 mmoles) and acetic anhydride (2 ml) were added to the residue. The mixture was heated at 70° for 3 hours. The solid material was, after cooling to room temperature, collected by filtration to give **17** in 69% yield, mp 200-202° (from ethanol); ms: m/z 315 (M^+); ^{1}H nmr (deuteriochloroform): δ 2.85 (s, 3H, COCH_3), 3.31 (t, 2H, 5'-CH_2), 4.32 (t, 2H, 4'-CH_2), 7.28-7.55 and 8.05-8.13 (m, 5H, PhCO), 7.60 (s, 1H, C*H*), $J_{SCH_2CH_2N}$ = 7.15 Hz.

Anal. Calcd. for $C_{15}H_{13}N_3O_3S$: C, 57.13; H, 4.14; N, 13.33. Found: C, 56.90; H, 4.08; N, 12.96.

L-(−)-3-{[2-Benzoylamino-3-(2-thiazolinyl-2)amino]-propenoyl}thiazolidine-4-carboxylic Acid (**18**).

A mixture of **17** (0.5 g, 1.59 mmoles), *L*-(−)-thiazolidine-4(*L*)-carboxylic acid (**1**) (0.24 g, 1.82 mmoles) and sodium carbonate (92 mg, 0.87 mmole) in acetonitrile (7.5 ml) was heated under reflux for 3 hours. The solid material was, after cooling to room temperature, collected by filtration to give **18** in 20% yield, mp 224-226° (from acetonitrile); ms: m/z 407 (MH^+), $[\alpha]_D^{20}$ = -240.46° (c = 0.5, acetic acid); ^{1}H nmr (DMSO-d_6): δ 3.23 (dd, 1H, 5'-CH_2, J = 6.76 Hz), 3.36 (dd, 1H, 5'-CH_2, J = 2.22 Hz), 3.44 (t, 2H, 5-CH_2), 3.83 (t, 2H, 4-CH_2), 4.84 (d, 1H, 2'-CH_2), 4.86 (dd, 1H, 4'-C*H*, J = 2.22 Hz), 4.87 (d, 1H, NHC*H*), 4.89 (d, 1H, 2'-CH_2), 5.27 (d, 1H, N*H*CH), 7.49-7.67 (m, 5H, PhCO), (N*H*CO, COO*H*, exchange), $J_{5',5'}$ = 10.86 Hz, $J_{5',4'}$ = 2.22 Hz, $J_{5,4}$ = 7.49 Hz, $J_{CH,NH}$ = 11.07 Hz.

Anal. Calcd. for $C_{17}H_{18}N_4O_4S_2$: C, 50.23; H, 4.46; N, 13.78. Found: C, 49.87; H, 4.39; N, 13.73.

The Reaction Between 6-Methylimidazo[2,1-*b*]thiazole-5-carbohydrazide (**20**) and *p*-Sulfamoylphenyl Isothiocyanate **8a,b**. The Synthesis of 1-[(6-Methylimidazo[2,1-*b*]thiazolyl-5)carbonyl]-4-(*p*-sulfamoylphenyl)thiosemicarbazides **21a,b**.

General Procedure.

The suspension of 6-methylimidazo[2,1-*b*]thiazole-5-carbohydrazide (**20**) (0.15 g, 0.76 mmole) and corresponding sulfamoylphenyl isothiocyanate **8a** (0.16 g, 0.76 mmole), **8b** (0.23 g, 0.76 mmole) in anhydrous ethanol (2 ml) was stirred at room temperature or slightly heated for 10-30 minutes. The solid residue was collected by filtration and recrystallized from an appropriate solvent.

The following compounds were prepared in this manner:

1-[(6-Methylimidazo[2,1-*b*]thiazolyl-5)carbonyl]-4-(*p*-sulfamoylphenyl)thiosemicarbazide (**21a**).

This compound was prepared from **8a**, by stirring at room temperature for 10 minutes, in 64% yield, mp 213-215° (washed with hot ethanol); ms: m/z 411 (MH^+); ^{1}H nmr (DMSO-d_6): δ 2.58 (s, 3H, 6'-CH$_3$), 7.31 (s, 2H, NH_2), 7.38 (d, 2H, 2'-C*H*), 7.72-7.80 (m, 4H, 2"-*H*, 3"-*H*, 5"-*H*, 6"-*H*), 8.12 (d, 1H, 3'-C*H*), (1-N*H*, 2-N*H*, 4-N*H*, exchanged), $J_{2',3'}$ = 4.28 Hz.

Anal. Calcd. for $C_{14}H_{14}N_6O_3S_3$: C, 40.96; H, 3.44; N, 20.47. Found: C, 40.66; H, 3.10; N, 20.25.

1-[(6-Methylimidazo[2,1-*b*]thiazolyl-5)carbonyl]-4-[*p*-(4,5-dimethyloxazolyl-2)sulfamoylphenyl]thiosemicarbazides (**21b**).

This compound was prepared from **8b** by gently heating for 30 minutes in 79% yield, mp 221-223° (washed with hot ethanol); ms: m/z 411 (MH^+); ^{1}H nmr (DMSO-d_6): δ 1.65 (s, 3H, 4"'-CH$_3$), 2.09 (s, 3H, 6'-CH$_3$), 2.58 (s, 3H, 5"'-CH$_3$), 7.38 (d, 1H, 2'-C*H*), 7.72 (d, 2H, 2"-*H*, 6"-*H*), 7.82 (d, 2H, 3"-*H*, 5"-*H*), 8.12 (d, 1H, 3'-C*H*), (1-N*H*, 2-N*H*, 4-N*H*, SO_2NH, exchange), $J_{2',3'}$ = 4.45 Hz, $J_{2'',3''} = J_{5'',6'''}$ = 8.29 Hz.

Anal. Calcd. for $C_{19}H_{19}N_7O_4S_3$: C, 45.14; H, 3.79; N, 19.39. Found: C, 45.40; H, 3.65; N, 19.30.

5-Azidocarbonyl-6-methylimidazo[2,1-*b*]thiazole (**22**).

6-Methylimidazo[2,1-*b*]thiazole-5-carbohydrazide (**20**) (0.3 g, 1.53 mmoles) was suspended in water (8.5 ml) and few drops of concentrated hydrochloric acid were added. The solution was cooled on ice and under stirring treated dropwise with aqueous sodium nitrite (0.15 g in 4 ml of water). After the reaction was completed, the precipitate was collected by filtration and washed with cold water to give **22** in 90% yield; ir: ν = 2148 (CON_3). The product was used for further reaction without purification.

The Reaction Between 5-Azidocarbonyl-6-methylimidazo-[2,1-*b*]thiazole (**22**) and Heterocyclic Amines **12,19**. The Synthesis of *N,N'*-Disubstituted ureas **24a,b** and **25**.

General Procedure.

A mixture of the heterocyclic amines **12**, **19** (0.15 g, 1.5 mmoles) and 5-azidiocarbonyl-6-methylimidazo[2,1-*b*]thiazole-5-carbohydrazide (**22**) (0.24 g, 1.2 mmoles) was heated under reflux for 20 hours. The separated residue was collected by filtration and recrystallized from an appropriate solvent.

N-(6-Methylimidazo[2,1-*b*]thiazolyl-5)-*N'*-(2-thiazolinyl-2)urea (**24a**).

This compound was prepared from **12** in 21% yield, mp 221-223° (from ethanol/water); ms: m/z 281 (M^+); ^1H nmr (DMSO-d_6): δ 2.07 (s, 3H, 6-CH_3), 3.18 (t, 2H, 5'-CH_2), 3.46 (t, 2H, 4'-CH_2), 7.09 (d, 1H, 2-C*H*), 7.39 (d, 1H, 3-C*H*), (2xN*H*, exchanged), $J_{2,3}$ = 4.46 Hz, $J_{4',5'}$ = 7.49 Hz.

Anal. Calcd. for $C_{10}H_{11}N_5OS_2$: C, 42.69; H, 3.94; N, 24.89. Found: C, 41.99; H, 3.60; N, 24.95. (Better analysis could not be obtained, due to slow decomposition by heating).

N-(6-Methylimidazo[2,1-*b*]thiazolyl-5)-*N'*-(thiazolyl-2)urea (**24b**).

This compound was prepared from **19** in 65% yield, mp 225-227° (washed with chloroform); ms: m/z 279 (M^+); ^1H nmr (DMSO-d_6): δ 2.12 (s, 3H, 6-CH_3), 7.09 (d, 1H, 5'-C*H*), 7.15 (d, 1H, 2-C*H*), 7.37 (d, 1H, 4'-C*H*), 7.61 (d, 1H, 3-C*H*), (2xN*H*, exchanged), $J_{2,3}$ = 4.46 Hz, $J_{4',5'}$ = 3.61 Hz.

Anal. Calcd. for $C_{10}H_9N_5OS_2$: C, 42.99; H, 3.25; N, 25.07. Found: C, 42.73; H, 3.04; N, 25.05.

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