The Synthesis and Transformations of some 3-Thiocarbamoylthiazolidines

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

In connection with our studies on potential bioactive compounds some new polysubstituted 3-thiocarbamoylthiazolidines **5, 6, 7, 9** and **10** were prepared in the reaction between 2-(2-methoxyphenyl)iminothiazolidine (**2**) and sulfamoylphenyl isothiocyanates **3** and **4a-c**. The structures for compounds **2** and **5** were established by X-ray analyses, showing that the reaction is taking place at the endocyclic nitrogen atom of thiazolidine ring.

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The thiazolidine moiety occurs in different bioactive substances as an important pharmacophoric group [1]. Since the elucidation of the structure of the penicillins, thiazolidines have been the subject of numerous chemical and pharmaceutical studies [2,3]. They are associated with a broad spectrum of pharmacological properties including antibacterial [4], immunomodulatory [5], antiinflammatory [6], antidiabetic [7,8], anti-platelet activating factor [9] and antiviral [10] activities. Recently they were tested against immune deficiencies such as AIDS [3]. The heterocyclic ring could be polysubstituted or a part of bicyclic system as in the case of the potent immunomodulating agent (-)-2,3,5,6-tetrahydro-6-phenylimidazo-[2,1-*b*]thiazole (levamisole) [11].

Some active sulfanilamides as antibacterials are also known for their immunomodifying effects [12]. These observations encouraged the synthesis of some new polysubstituted 3-thiocarbamoylthiazolidines with potential bioactivity.

In the reaction between primary amines and thiophosgene [13], sulfanilamide and some of its derivatives have been converted into isothiocyanates **3, 4a-c** and than coupled to 2-(2-methoxyphenyl)iminothiazolidine hydrochloride (**1**), prepared by the reaction between 2-chloroethyl isothiocyanate and the corresponding primary amine [14].

The reaction of primary anilines with 2-haloisothiocyanates has been reported to give 2-arylaminothiazolines [17], but no clear evidence for these structures has been made. Furthermore, the literature about the reaction of 2-amino-2-thiazoline and substituted 2-amino-2-thiazolines or their tautomeric forms 2-iminothiazolines with alkyl and arylisothiocyanates is highly controversial about the structure of the products, since two products, either *N,N'*-disubstituted thioureas and/or corresponding substituted 2-iminothiazolidinecarbothioamides can be formed [14,15,16,17,18]. Recently, X-ray structure for 2-imino-*N*-phenyl-3-thiazolidinecarboxamide [16] has been determined [19]. Similarly, the structure of 2-imino-*N,N'*-bis(phenyl)-*N*-thiazolidinecarbothioamide was confirmed [14].

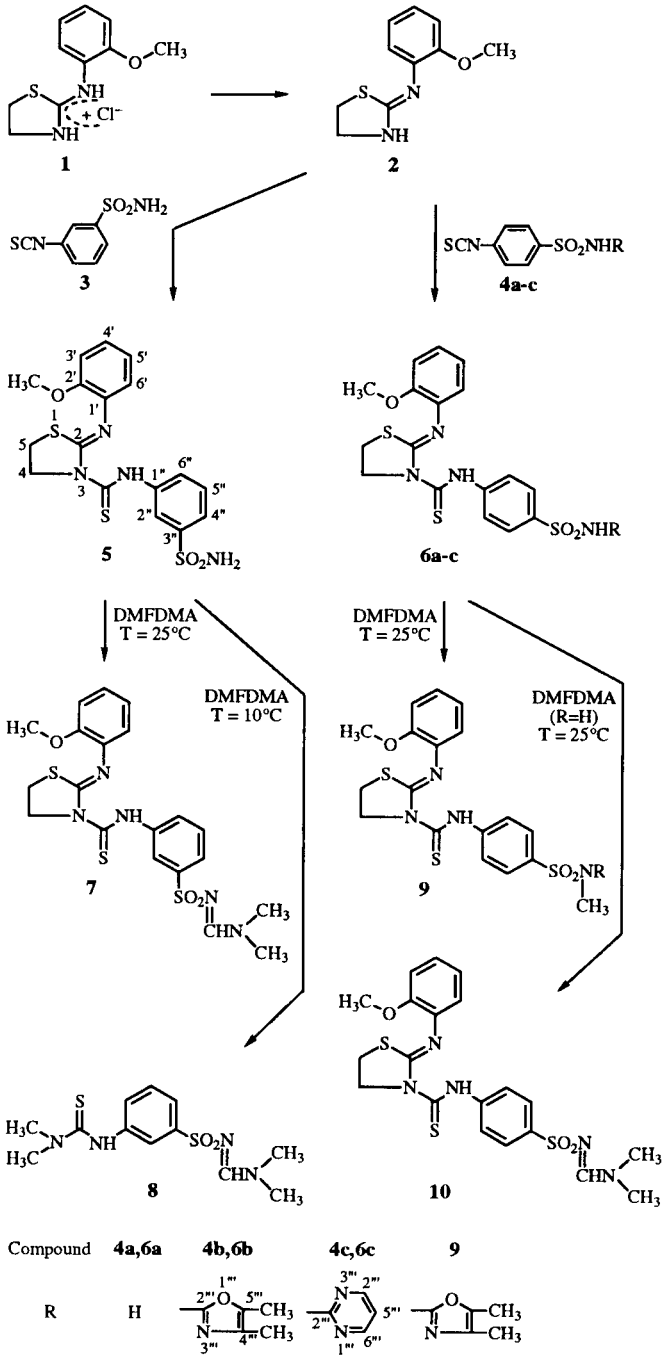
Due to interesting activity of 2-arylamino-2-thiazoline or its tautomeric form 2-aryliminothiazolidine we prepared some new substituted 2-(2-methoxyphenyl)imino-3-thiocarbamoylthiazolidines. The structures of the compounds were established by elemental analyses, ir, ms and nmr spectra and in some instances by X-ray analyses.

We started our research with the reaction between 2-chloroethyl isothiocyanate and 2-methoxyaniline, which gives 2-(2-methoxyphenyl)iminothiazolidine hydrochloride (**1**). Compound **1** was treated with *m*-sulfamoylphenyl isothiocyanate (**3**) to give 2-(2-methoxyphenyl)-imino-3-[*N*-(3-sulfamoylphenyl)]thiocarbamoylthiazolidine (**5**) and with *p*-substituted sulfamoylphenyl isothiocyanates **4a-c** to give substituted 2-(2-methoxyphenyl)imino-3-[*N*-(4-sulfamoylphenyl)]thiocarbamoylthiazolidines **6a-c** (Scheme 1).

The reaction of **5** with *N,N*-dimethylformamide dimethylacetal takes two different courses, dependent on the reaction temperature. The unsubstituted sulfonamido group reacts with *N,N*-dimethylformamide dimethylacetal to give the corresponding *N,N*-dimethylmethylenaminosulfonamide **7**, while at higher temperature (under reflux) the compound **5** or **7** as intermediates react further by substitution of thiazolidineimino part of the molecule with dimethylamine, (formed from *N,N*-dimethylformamide dimethylacetal), to give *N,N*-dimethyl-*N'*-(3-dimethylaminomethyleniminosulfonylphenyl)thiourea (**8**) (Scheme 1).

Compounds **6a-c** react with *N,N*-dimethylformamide dimethylacetal at room temperature, dependent on the substituents of sulfonamido group. The unsubstituted compound **6a** gives with *N,N*-dimethylformamide dimethylacetal at room temperature the corresponding 2-(2-methoxyphenyl)-imino-3-[*N*-(4-dimethylaminomethyleniminosulfonylphenyl)]thiocarbamoylthiazolidine (**10**), while the substituted sulfonamide **6b** is methylated with *N,N*-dimethylformamide dimethylacetal at 60° to give the 2-(2-methoxyphenyl)imino-3-{*N*-[4-(4,5-dimethyloxazolyl-2)-*N*-methylsulfamoylphenyl]}thiocarbamoylthiazolidine **9** (Scheme 1).

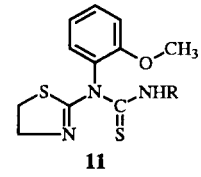
Scheme 1



Elemental analyses, ms and nmr spectra of compounds **5**, **6a-c**, **7**, **9** and **10** are formally in agreement with the proposed structures. However, on the basis of this information one can not exclude the alternative structures of the type **11** that could be formed in the reaction of isothiocyanates with **1** at the exocyclic nitrogen atom. For this purpose, X-ray analyses for the compounds **2** and **5** were carried out confirming the imino structure **2** for the neutral starting compound and for the product **5**, which is formed with isothiocyanates showing that the reaction takes place at endocyclic nitrogen atom. (Scheme 2).

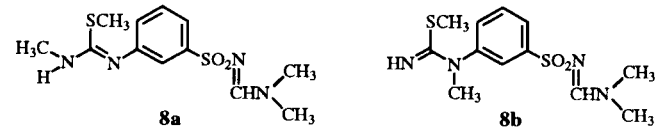
The compound **8** shows in ^{1}H-nmr spectrum a multiplet

Scheme 2

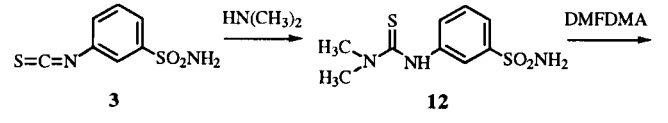


at δ 7.40-7.74 ppm for four aromatic protons and two singlets at δ 2.91 ppm and δ 3.14 ppm, each integrating for three protons. The chemical shifts suggest that these methyl groups could be attached either both to the same nitrogen atom or one to either of nitrogen atoms and one to sulfur atom. The singlet at δ 3.29 ppm, integrating for six protons, corresponds to two equivalent methyl groups attached to nitrogen. On the basis of this information together with other analytical data one can draw three different structures **8, 8a** and **8b** (Scheme 3).

Scheme 3



Scheme 4



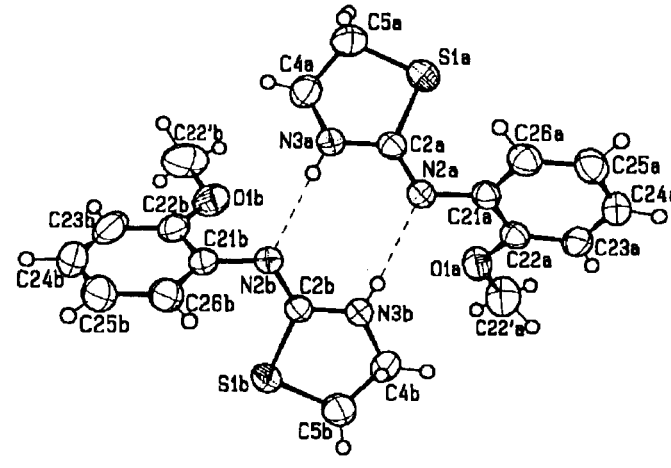


Figure 1. CORTEP view of the asymetric unit of **2**, showing the labeling of the non-hydrogen atoms.

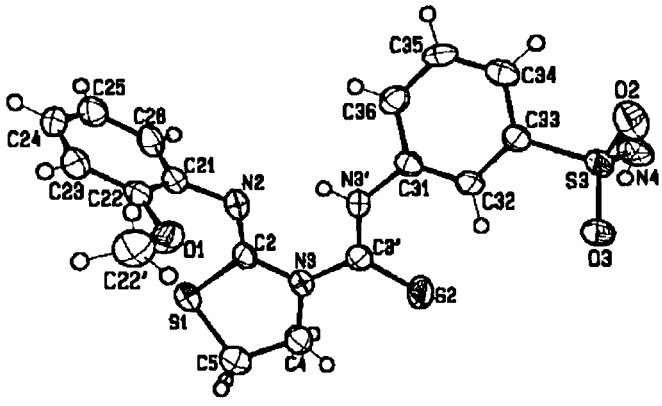


Figure 2. ORTEP view of the asymetric unit of **5**, showing the labeling of the non-hydrogen atoms.

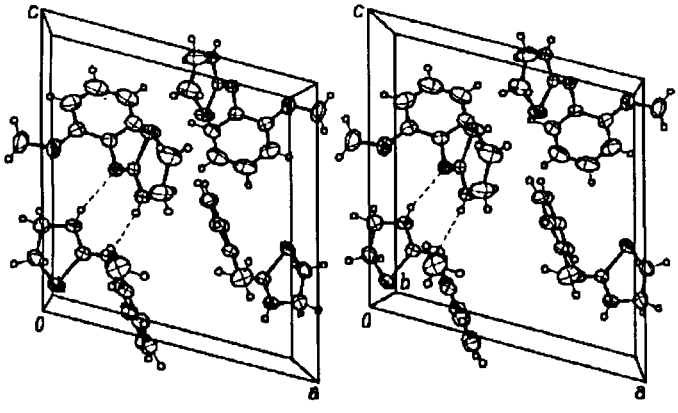


Figure 3. Stereoscopic view of the unit cell of **2**.

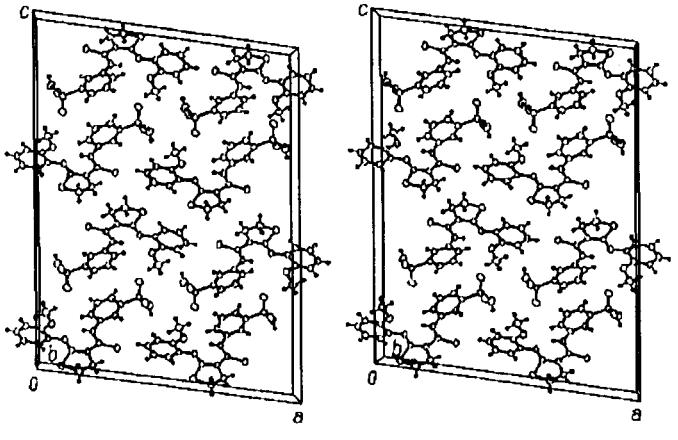


Figure 4. Steroscopic view of the unit cell of **5**.

In order to assign the signals in ^{1}H-nmr spectrum, the isothiocyanate **3** was first transformed with dimethylamine into the corresponding thiourea derivative **12**, which shows in ^{1}H-nmr spectrum a singlet for dimethylamino group at δ 3.29 ppm. This compound **12** was then

Table 1

Fractional Coordinates and Equivalent Temperature Factors (Å^2). U_{eq} is defined as one third of the trace of the orthogonalized Uy tensor

2

	x/a	y/b	z/c	Ueq
S(1a)	0.96106(8)	0.75600	0.41741(6)	0.0551(3)
O(1a)	0.7355(3)	0.2763(3)	0.2751(2)	0.0551(8)
N(2a)	0.7618(3)	0.6108(4)	0.2645(2)	0.0451(8)
N(3a)	0.8950(2)	0.7810(4)	0.1973(2)	0.0454(8)
C(2a)	0.8574(3)	0.7038(4)	0.2824(2)	0.0387(8)
C(4a)	1.0179(3)	0.8504(5)	0.2269(3)	0.055(1)
C(5a)	1.0445(4)	0.9054(7)	0.3508(3)	0.064(1)
C(21a)	0.7196(3)	0.5441(4)	0.3551(2)	0.0394(8)
C(22a)	0.7007(3)	0.3665(4)	0.3571(2)	0.0403(8)
C(23a)	0.6499(3)	0.2966(5)	0.4386(3)	0.048(1)
C(24a)	0.6189(3)	0.3982(5)	0.5194(3)	0.052(1)
C(25a)	0.6375(3)	0.5714(5)	0.5194(3)	0.053(1)
C(26a)	0.6865(3)	0.6436(5)	0.4371(3)	0.048(1)
C(22'a)	0.7279(5)	0.0972(5)	0.2797(5)	0.070(2)
S(1b)	0.6110(1)	0.4555(2)	-0.18423(6)	0.0612(3)
O(1b)	0.9642(2)	0.7221(4)	-0.0510(2)	0.0632(9)
N(2b)	0.7343(2)	0.6979(4)	-0.0359(2)	0.0421(7)
N(3b)	0.6403(2)	0.4758(4)	0.0328(2)	0.0449(8)
C(2b)	0.6696(2)	0.5617(4)	-0.0513(2)	0.0362(7)
C(4b)	0.5748(5)	0.3187(8)	0.0050(5)	0.085(2)
C(5b)	0.5452(6)	0.2898(6)	-0.1178(4)	0.075(2)
C(21b)	0.7573(3)	0.7826(4)	-0.1308(2)	0.0431(8)
C(22b)	0.8781(3)	0.7999(5)	-0.1375(3)	0.055(1)
C(23b)	0.9020(5)	0.8855(6)	-0.2301(4)	0.075(2)
C(24b)	0.8060(6)	0.9610(7)	-0.3119(4)	0.086(2)
C(25b)	0.6886(5)	0.9488(6)	-0.3039(3)	0.076(2)
C(26b)	0.6629(4)	0.8612(5)	-0.2146(3)	0.056(1)
C(22'b)	1.0897(4)	0.762(1)	-0.0424(6)	0.091(2)

5

	x/a	y/b	z/c	Ueq
S(1)	0.09410(4)	-0.0345(2)	0.01982(4)	0.0435(3)
S(2)	0.30411(4)	0.2691(3)	0.08436(4)	0.0523(4)
S(3)	0.39204(4)	0.7143(2)	0.23125(3)	0.0354(3)
O(1)	0.0590(1)	-0.0767(5)	0.1348(1)	0.0443(9)
O(2)	0.3925(1)	0.7856(7)	0.2753(1)	0.054(1)
O(3)	0.4122(1)	0.4666(5)	0.2208(1)	0.049(1)
N(2)	0.1054(1)	0.2802(7)	0.0892(1)	0.038(1)
N(3)	0.1917(1)	0.1333(6)	0.0652(1)	0.034(1)
N(3')	0.2113(2)	0.4296(6)	0.1200(1)	0.038(1)
N(4)	0.4320(2)	0.9117(8)	0.2098(2)	0.049(1)
C(2)	0.1305(2)	0.1462(7)	0.0633(1)	0.031(1)
C(4)	0.2113(2)	-0.0394(9)	0.0330(2)	0.041(1)
C(5)	0.1607(2)	-0.203(1)	0.0146(2)	0.052(2)
C(21)	0.0434(2)	0.2693(7)	0.0875(1)	0.032(1)
C(22)	0.0195(2)	0.0896(7)	0.1138(1)	0.032(1)
C(23)	0.0402(2)	0.0936(8)	0.1155(1)	0.037(1)
C(24)	-0.0763(2)	0.2751(8)	0.0930(1)	0.041(1)
C(25)	-0.0534(2)	0.4516(8)	0.0676(2)	0.043(1)
C(26)	0.0064(2)	0.4465(8)	0.0646(1)	0.040(1)
C(22')	0.0390(3)	-0.238(1)	0.1665(2)	0.053(2)
C(3')	0.2334(2)	0.2822(7)	0.0915(1)	0.032(1)
C(31)	0.2397(2)	0.6020(7)	0.1512(1)	0.032(1)
C(32)	0.2971(2)	0.5740(7)	0.1724(1)	0.033(1)
C(33)	0.3187(2)	0.7477(7)	0.2043(1)	0.032(1)
C(34)	0.2846(2)	0.9462(8)	0.2159(1)	0.040(1)
C(35)	0.2278(2)	0.9703(8)	0.1950(1)	0.042(1)
C(36)	0.2050(2)	0.8008(8)	0.163011)	0.039(1)

Table 2

Bond Distances (Å) and Bond Angles (°) with e.s.d.'s in parentheses

2

S(1a)-C(2a)	1.785(2)	S(1b)-C(2b)	1.777(3)
S(1a)-C(5a)	1.825(5)	S(1b)-C(5b)	1.795(6)
O(1a)-C(22a)	1.362(4)	O(1b)-C(22b)	1.367(4)
O(1a)-C(22'a)	1.414(5)	O(1b)-C(22'b)	1.426(5)
N(2a)-C(2a)	1.274(4)	N(2b)-C(2b)	1.282(4)
N(2a)-C(21a)	1.410(4)	N(2b)-C(21b)	1.412(4)
N(3a)-C(2a)	1.359(4)	N(3b)-C(2b)	1.337(4)
N(3a)-C(4a)	1.444(5)	N(3b)-C(4b)	1.433(7)
C(4a)-C(5a)	1.513(6)	C(4b)-C(5b)	1.453(7)
C(21a)-C(22a)	1.415(5)	C(21b)-C(22b)	1.395(5)
C(21a)-C(26a)	1.392(5)	C(21b)-C(26b)	1.403(4)
C(22a)-C(23a)	1.382(5)	C(22b)-C(23b)	1.396(7)
C(23a)-C(24a)	1.380(5)	C(23b)-C(24b)	1.391(7)
C(24a)-C(25a)	1.379(6)	C(24b)-C(25b)	1.358(9)
C(25a)-C(26a)	1.386(6)	C(25b)-C(26b)	1.378(6)
C(2a)-S(1a)-C(5a)	91.8(2)	C(2b)-S(1b)-C(5b)	91.9(2)
C(22a)-O(1a)-C(22'a)	117.3(4)	C(22b)-O(1b)-C(22'b)	116.5(4)
C(2a)-N(2a)-C(21a)	121.9(2)	C(2b)-N(2b)-C(21b)	119.9(2)
C(2a)-N(3a)-C(4a)	117.1(3)	C(2b)-N(3b)-C(4b)	118.3(3)
S(1a)-C(2a)-N(2a)	127.2(2)	S(1b)-C(2b)-N(2b)	125.7(2)
S(1a)-C(2a)-N(3a)	109.3(2)	S(1b)-C(2b)-N(3b)	110.2(2)
N(2a)-C(2a)-N(3a)	123.4(2)	N(2b)-C(2b)-N(3b)	124.0(2)
N(3a)-C(4a)-C(5a)	106.0(3)	N(3b)-C(4b)-C(5b)	109.8(5)
S(1a)-C(5a)-C(4a)	105.4(3)	S(1b)-C(5b)-C(4b)	109.6(4)
N(2a)-C(21a)-C(22a)	117.7(3)	N(2b)-C(21b)-C(22b)	119.3(2)
N(2a)-C(21a)-C(26a)	123.9(3)	N(2b)-C(21b)-C(26b)	121.8(3)
C(22a)-C(21a)-C(26a)	118.2(3)	C(22b)-C(21b)-C(26b)	118.7(3)
O(1a)-C(22a)-C(21a)	115.3(3)	O(1b)-C(22b)-C(21b)	114.6(3)
O(1a)-C(22a)-C(23a)	124.8(3)	O(1b)-C(22b)-C(23b)	125.6(4)
C(21a)-C(22a)-C(23a)	119.9(3)	C(21b)-C(22b)-C(23b)	119.8(3)
C(22a)-C(23a)-C(24a)	120.6(3)	C(22b)-C(23b)-C(24b)	119.8(5)
C(23a)-C(24a)-C(25a)	120.3(4)	C(23b)-C(24b)-C(25b)	120.6(5)
C(24a)-C(25a)-C(26a)	119.7(4)	C(24b)-C(25b)-C(26b)	120.4(4)
C(21a)-C(26a)-C(25a)	121.3(3)	C(21b)-C(26b)-C(25b)	120.7(4)

Table 2 (continued)

5

S(1)-C(2)	1.757(4)	N(3')-C(31)	1.414(5)
S(1)-C(5)	1.796(5)	C(4)-C(5)	1.488(7)
S(2)-C(3')	1.672(4)	C(21)-C(26)	1.385(5)
S(3)-O(2)	1.413(3)	C(21)-C(22)	1.414(5)
S(3)-O(3)	1.439(3)	C(22)-C(23)	1.378(6)
S(3)-N(4)	1.596(5)	C(23)-C(24)	1.385(6)
S(3)-C(33)	1.772(4)	C(24)-C(25)	1.375(6)
O(1)-C(22)	1.355(5)	C(25)-C(26)	1.388(6)
O(1)-C(22')	1.427(7)	C(31)-C(32)	1.388(5)
N(2)-C(2)	1.270(5)	C(31)-C(36)	1.398(6)
N(2)-C(21)	1.416(5)	C(32)-C(33)	1.383(5)
N(3)-C(2)	1.398(5)	C(33)-C(34)	1.386(6)
N(3)-C(3')	1.401(5)	C(34)-C(35)	1.372(6)
N(3)-C(4)	1.470(6)	C(35)-C(36)	1.378(6)
N(3')-C(3')	1.331(5)		
C(2)-S(1)-C(5)	91.4(2)	O(1)-C(22)-C(23)	126.1(4)
O(2)-S(3)-O(3)	120.1(2)	O(1)-C(22)-C(21)	114.9(3)
O(2)-S(3)-N(4)	107.8(2)	C(23)-C(22)-C(21)	119.0(3)
O(2)-S(3)-C(33)	107.3(2)	C(22)-C(23)-C(24)	121.0(4)
O(3)-S(3)-N(4)	106.0(2)	C(25)-C(24)-C(23)	120.3(4)
O(3)-S(3)-C(33)	107.4(2)	C(24)-C(25)-C(26)	119.5(4)
N(4)-S(3)-C(33)	107.7(2)	C(21)-C(26)-C(25)	121.0(4)
C(22)-O(1)-C(22')	117.0(4)	N(3')-C(3')-N(3)	114.8(3)
C(2)-N(2)-C(21)	120.2(3)	N(3')-C(3')-S(2)	125.8(3)
C(2)-N(3)-C(3)	126.2(3)	N(3)-C(3')-S(2)	119.4(3)
C(2)-N(3)-C(4)	114.2(3)	C(32)-C(31)-C(36)	119.6(3)
C(3')-N(3)-C(4)	119.4(3)	C(32)-C(31)-N(3')	124.2(3)
C(3')-N(3')-C(31)	130.3(3)	C(36)-C(31)-N(3')	116.0(3)
N(2)-C(2)-N(3)	123.3(3)	C(33)-C(32)-C(31)	118.6(3)
N(2)-C(2)-S(1)	125.2(3)	C(32)-C(33)-C(34)	122.1(3)
N(3)-C(2)-S(1)	111.4(3)	C(32)-C(33)-S(3)	118.9(3)
N(3)-C(4)-C(5)	108.6(4)	C(34)-C(33)-S(3)	119.0(3)
C(4)-C(5)-S(1)	107.8(4)	C(35)-C(34)-C(33)	118.7(4)
C(26)-C(21)-C(22)	119.1(3)	C(34)-C(35)-C(36)	120.7(4)
C(26)-C(21)-N(2)	121.8(4)	C(35)-C(36)-C(31)	120.3(4)
C(22)-C(21)-N(2)	118.7(3)		

transformed with *N,N*-dimethylformamide dimethylacetal into the compound identical with the compound **8**, obtained from **5** by treatment with *N,N*-dimethylformamide dimethylacetal at reflux temperature (Scheme 4).

Compound **5** has been tested in an *in vivo* preliminary immunorestoration test, which shows immunorestoration activity of the applied compound [20].

EXPERIMENTAL

Melting points were taken on a Leica hot stage microscope. The ^{1}H-nmr spectra were obtained on a Bruker Avance DPX 300 and on a Varian VXR 300 spectrometer. 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.

The following compounds were prepared according to the procedures described in the literature: 2-(2-methoxyphenyl)-iminothiazolidine hydrochloride (**1**) [14], *m*- (**3**) and *p*-substituted sulfamoylphenyl isothiocyanates **4a-c** [13].

The reaction between 2-(2-methoxyphenyl)iminothiazolidine hydrochloride (**1**) and *m*- (**3**) or *p*-substituted sulfamoylphenyl isothiocyanates (**3**), **4a-c**. The synthesis of 2-(2-methoxyphenyl)imino-3-[*N*-(3-sulphamoylphenyl)]thiocarbamoylthiazolidine (**5**) and 2-(2-methoxyphenyl)imino-3-[*N*-(4-heteroarylsulfamoylphenyl)]thiocarbamoylthiazolidines **6a-c.**

General Procedure.

To a stirred suspension of 2-(2-methoxyphenyl)iminothiazolidine hydrochloride (**1**) (0.12 g, 0.5 mmole) and *m*- (**3**) or *p*-substituted sulfamoylphenyl isothiocyanates **4a-c** (0.5 mmole) in an appropriate solvent (3 ml) triethylamine (0.10 g, 1 mmole) was added. The mixture was stirred at room temperature for several hours. After the reaction was completed, the mixture was poured into ice-water and few drops of 2*M* hydrochloric acid were added. The solid residue was collected by filtration, washed with ice-cold water and recrystallized from an appropriate solvent to give **5** and **6a-c**.

The following compounds were prepared in this manner:

2-(2-Methoxyphenyl)imino-3-[*N*-(3-sulfamoylphenyl)]thiocarbamoylthiazolidine (**5**).

This compound was prepared from **3**, by stirring for 1 hour in anhydrous ethanol, in 90% yield, mp 159-161° (from toluene); ms: m/z 423 (MH^+); ^{1}H nmr (DMSO-d_6): δ 3.31 (t, SCH_2), 3.79 (s, OCH_3), 4.74 (t, NCH_2), 6.90-7.24 (m, 3'-*H*, 4'-*H*, 5'-*H*, 6'-*H*), 7.41 (s, NH_2), 7.60-8.04 (m, 2"-*H*, 4"-*H*, 5"-*H*, 6"-*H*), 14.75 (s, CSN*H*), $J_{SCH_2CH_2N}$ = 7.0 Hz.

Anal. Calcd. for $C_{17}H_{18}N_4O_3S_3$: C, 48.32; H, 4.29; N, 13.26. Found: C, 48.14; H, 4.27; N, 12.98.

2-(2-Methoxyphenyl)imino-3-[*N*-(4-sulfamoylphenyl)]thiocarbamoylthiazolidine (**6a**).

This compound was prepared from **4a**, by stirring for 1 hour in dry dioxane, in 81% yield, mp 168-170° (washed with water); ms: m/z 423 (MH^+); ^1H nmr (DMSO-d_6): δ 3.31 (t, SCH_2), 3.57 (s, CSN*H*), 3.79 (s, OCH_3), 4.71 (t, NCH_2), 6.90-7.25 (m, 3'-*H*, 4'-*H*, 5'-*H*, 6'-*H*), 7.37 (s, NH_2), 7.81-7.86 (m, 2"-*H*, 3"-*H*, 5"-*H*, 6"-*H*), (CSN*H*, exchanged), $J_{SCH_2CH_2N}$ = 7 0 Hz.

Anal. Calcd. for $C_{17}H_{18}N_4O_3S_3$: C, 48.32; H, 4.29; N, 13.26. Found: C, 48.47; H, 4.03; N, 12.88.

2-(2-Methoxyphenyl)imino-3-{*N*-[4-(4,5-dimethyloxazolyl-2)-sulfamoylphenyl]}thiocarbamoylthiazolidine (**6b**).

This compound was prepared from **4b**, by stirring for 2 hours in pyridine, in 85% yield, mp 130-132° (washed with water); ms: m/z 518 (MH^+); ^1H nmr (DMSO-d_6): δ 1.81 (s, 4"'-CH_3), 2.13 (s, 5"'-CH_3), 3.17 (t, SCH_2), 3.81 (s, OCH_3), 4.87 (t, NCH_2), 6.93-7.28 (m, 3'-*H*, 4'-*H*, 5'-*H*, 6'-*H*), 7.11 (s, SO_2NH), 7.79 (d, 2"-*H*, 6"-*H*), 7.90 (d, 3"-*H*, 5"-*H*), 14.93 (s, CSN*H*), $J_{SCH_2CH_2N}$ = 7.0 Hz, $J_{2",3"} = J_{5",6"}$ = 8 77 Hz.

Anal. Calcd. for $C_{22}H_{23}N_5O_4S_3$: C, 51.05; H, 4.48; N, 13.53. Found: C, 51.13; H, 4.25; N, 13.43.

2-(2-Methoxyphenyl)imino-3-{*N*-[4-(pyrimidinyl-2)sulfamoylphenyl]}thiocarbamoylthiazolidine (**6c**).

This compound was prepared from **4c**, by stirring for 3 hours in pyridine, in 72% yield, mp 179-181° (washed with water); ms: m/z 501 (MH^+); ^1H nmr (DMSO-d_6): δ 3.27 (t, SCH_2), 3.75 (s, OCH_3), 4.69 (t, NCH_2), 6.87-7.21 (m, 3'-*H*, 4'-*H*, 5'-*H*, 6'-*H*, 5"'-*H*), 7.86 (d, 2"-*H*, 6"-*H*), 8.00 (d, 3"-H, 5"-*H*), 8.48 (d, 4"'-*H*, 6"'-*H*), (SO_2NH, exchanged), (CSN*H*, exchanged), $J_{SCH2CH2N}$= 7.0 Hz, J2", 3" = J5",6'1 = 8.65 Hz.

Anal. Calcd. for $C_{21}H_{20}N_6O_3S_3$: C, 50.38; H, 4.02; N, 16~75. Found: C, 50.03; H, 3.70; N, 16.75.

2-(2-Methoxyphenyl)imino-3-[*N*-(3-dimethylaminoiminosulfonylphenyl)]thiocarbamoylthiazolidine (**7**).

A suspension of **5** (846 mg, 2 mmoles) in *N,N*-dimethylformamide dimethylacetal (3 ml) was slightly heated until the clear solution was obtained. The reaction mixture was then cooled to room temperature. The separated product was collected by filtration and washed with cold water to give **7** in 30% yield, mp 147-149°; ms: m/z 478 (MH^+); ^1H nmr (deuteriochloroform): δ 3.04 (s, NCH_3), 3.11 (s, NCH_3), 3.19 (t, SCH_2), 3.86 (s, OCH_3), 4.90 (t, NCH_2), 6.94-7.01 (m, 3'-*H*, 4'-*H*, 5'-*H*, 6'-*H*), 8.10 (s, C*H*), 7.45-8.09 (m, 2"-*H*, 4"-*H*, 5"-*H*, 6"-*H*), 14.75 (s, CSN*H*) $J_{SCH_2CH_2N}$= 7.0 Hz

Anal. Calcd for $C_{20}H_{23}N_5O_3S_3$: C, 50.31; H, 4.85; N, 14.67. Found C, 50.04; H, 4.58; N, 14.48.

N,N-Dimethyl-*N'*-(3-dimethylaminomethyleniminosulfonylphenyl)thiourea (**8**).

A suspension of **5** (0.21 g, 0.5 mmole) in dry toluene (5 ml) was heated at reflux temperature until the clear solution was obtained. *N,N*-dimethylformamide dimethylacetal (0.12 g, 1 mmole) was added and upon cooling the reaction mixture was stirred at room temperature for 12 hours. The separated product was collected by filtration and washed with cold water to give **8** in 30% yield, mp 178-179°; ms: m/z 315 (MH^+); ^1H nmr (DMSO-d_6): δ 2.91, 3.14 (s, $(CH_3)_2NCH{=}NSO_2$), 3.29 ($(CH_3)_2NCS$), 7.40-7.74 (m, 3'-*H*, 4'-*H*, 5'-*H*, 6'-*H*), 8.19 (s, CH), 9.19 (s, N*H*).

Anal. Calcd. for $C_{12}H_{18}N_4O_2S_2$: C, 45.79; H, 5.77; N, 17.80. Found: C, 45.46; H, 5.43; N, 17.44.

2-(2-Methoxyphenyl)imino-3-{*N*-[4-(4,5-dimethyloxazolyl-2)-*N*-methylsulfamoylphenyl]}thiocarbamoylthiazolidine (**9**).

To a stirred suspension of **6b** (0.15 g, 0.3 mmole) in dry toluene (3 ml), *N,N*-dimethylformamide dimethylacetal (0.072 g, 0.6 mmole) was added. The mixture was heated at 60° for 3 hours. After the reaction was completed, the mixture was poured into ice-water. The solid residue was collected by filtration and washed with ice-cool water to give **9** in 36% yield, mp 124-126°; ms: m/z 532 (MH^+); ^1H nmr (deuteriochloroform): δ 1.99 (s, 4"'-CH_3), 2.22 (s, 5"'-CH_3), 3.12 (s, NCH_3), 3.84 (s, OCH_3), 3.19 (t, SCH_2), 4.99 (t, NCH_2) 6.91-7.40 (m, 3'-*H*, 4'-*H*, 5'-*H*, 6'-*H*), 7.71 (d, 2"-*H*, 6"-*H*), 7.99 (d, 3"-*H*, 5"-*H*), (CSN*H*, exchanged), $J_{SCH_2CH_2N}$ = 7.0 Hz, $J_{2",3"} = J_{5",6"}$ = 8.30 Hz.

Anal. Calcd. for $C_{23}H_{25}N_5O_4S_3$: C, 51.95; H, 4.72; N, 13.17. Found: C, 51.56; H, 4.72; N, 12.89.

2-(2-Methoxyphenyl)imino-3-[*N*-(4-dimethylaminomethylenimino sulfonylphenyl)] thiocarbamoylthiazolidine (**10**).

A suspension of **6a** (846 mg, 0.2 mmole) in *N,N*-dimethylformamide dimethylacetal (3 ml) was stirred at room temperature for 2 hours. The solid residue was collected by filtration and washed with diethyl ether to give **10** in 94% yield, mp 150-152°; ms: m/z 478 (MH^+); ^1H nmr (deuteriochloroform): δ 3.02 (s, NCH_3), 3.12 (s, NCH_3), 3.19 (t, SCH_2), 3.82 (s, OCH_3), 4.90 (t,. NCH_2), 6.85-7.08 (m, 3'-*H*, 4'-*H*, 5'-*H*, 6'-*H*), 7.81 (d, 2"-*H*, 6"*H*), 7.87 (d, 3"-*H*, 5"-*H*), (CSN*H*, exchanged), (C*H*, exchanged), $J_{SCH_2CH_2N}$ = 7.0 Hz, $J_{2",3"} = J_{5",6"}$ = 8.14 Hz.

Anal. Calcd. for $C_{20}H_{23}N_5O_3S_3$: C, 50.30; H, 4.85; N, 14.67. Found: C, 49.92; H, 4.83; N, 14.44.

N,N-Dimethyl-*N'*-(3-sulfamoylphenyl)thiourea (**12**).

A solution of **3** in 33% dimethylamine in ethanol (2.5 ml) was stirred at room temperature for 15 minutes. The solid residue was collected by filtration and washed with ethanol to give **12** in 44% yield, mp 173-175°; ^1H nmr (DMSO-d_6): δ 3.29 (s, $(CH_3)_2NCS$), 7.43-7.77 (m, 3'-*H*, 4'-*H*, 5'-*H*, 6'-*H*), (SO_2NH_2, exchanged), (CSN*H*, exchanged).

The compound **12** was further transformed with *N,N*-dimethylformamide dimethylacetal into the compound identical with the compound **8**.

X-ray Structure Determination.

2: $C_{10}H_{12}N_2OS$, M_r = 208.3, monoclinic, $P2_1$, No.:4 a = 11.288(1), b = 7.869(1), c = 12.119(1) Å, β = 105.57(1)°, V = 1037.0(2) Å^3, Z = 4, D_x = 1.334 Mg/m^3, MoKα radiation, λ = 0.71069 Å, μ = 0.268 mm^{-1}, T = 293(2) K.

5: $C_{17}H_{18}N_4O_3S_3$, M_r = 422.6, monoclinic, C2/c, No.:15, a = 22.945(6), b = 5.275(1), c = 30.98(1) Å, β = 98.64(3)°, V = 3707(2) Å^3, Z = 8, D_x = 1.514 Mg/m^3, MoKα radiation, λ = 0.71069 Å, μ = 0.409 mm^{-1}, T = 293(2) K.

Diffraction data for both compounds were collected on Enraf Nonius CAD-4 diffractometer with graphite monochromatized MoKα radiation at room temperature (293(2) K). Lattice parameters were determined by a least-square treatment of 100 (**2**) and 50 (**5**) carefully centered θ values in the range 8.2° < θ < 17.5° (**2**) and 8.0° < θ < 14.9° (**5**). For **2** an entire sphere to θ max 30° of data

was measured with an index range $-15 \le h \le 15$, $-11 \le k \le 11$ and $-16 \le 1 \le 16$ with ω-2θ scans. Maximal θ of measured reflections for **5** was 28° and the index range $-30 \le h \le 29$, $-6 \le k \le 6$ and $-40 \le 1 \le 40$. For **5** we used pure ω scans. Scan width was in both cases 0.9 + 0.3 x tgθ, aperture 2.4 + 0.9 x tgθ, and maximum scan time 60 seconds. Background was measured at 1/4 of the scan at each limit. Crystal stability was monitored by periodic measuring of three standard reflections (1,3,-4; 2,-2,-4; 1,3,-1 for **2** and 4,2,-2; 10,0,0; 0,2,-6 for **5**) every 20000 seconds of scanning time. Orientation control was every 600 reflections. A change of -0.64% intensities of standard reflections for **2** was observed and correction applied. In the case of **5** there was no intensity decay. Due to the low value of the linear absorption coefficient (0.268 mm^{-1} (**2**) and 0.409 mm^{-1} (**5**)) no absorption correction was done. 12042 for **2** and 15497 for **5** reflections were collected, averaging gave 3201 for **2** and 4456 for **5** unique reflections with R_{int} 0.048 (**2**) and 0.030 (**5**). 2573 (**2**) and 2561 (**5**) reflections were observed using ($I > 2.5\sigma(I)$) criterion in the former and ($I > 3.0\sigma(I)$) in the latter case.

Structures were solved by direct methods using MULTAN88 [21] system of computer programs. The positions of hydrogen atoms were obtained from difference Fourier maps. We employed full-matrix least-squares refinement on F magnitudes with anisotropic temperature factors for all non-hydrogen atoms, using the weighting function: $w = 6.0 x W_f x W_s$ where $W_f(|F_o|<2.7) = (|F_o|/2.7)$, $W_f(|F_o|>17.1) = (17.1/|F_o|)^3$, $W_f(2.7 \le |F_o| \le 17.1) = 1.0$ and $W_s(\sin\theta<0.37) = (\sin\theta/0.37)^2$, $W_s(\sin\theta>0.63) = (0.63/\sin\theta)$ and $W_s(0.37 \le \sin\theta \le 0.63) = 1$ for (**2**) and $W_f(|F_o|<22)=(|F_o|/22)$, $W_f(|F_o|>44) = (44/|F_o|)^{1.2}$, $W_f(22 \le |F_o| \le 44) = 1.0$ and $W_s(\sin\theta<0.44) = (\sin\theta/0.44)^2$, $W_s(\sin\theta>0.48) = (0.48/\sin\theta)^5$ and $W_s(0.44 \le \sin\theta \le 0.48) = 1$ for **5**. Only the positions of hydrogen atoms were refined. In the final least-square cycle for **2** were 2954 contributing reflections (included were those unobserved reflections for which F_c was greater than F_o) and 324 parameters and for **5** 2561 contributing reflections and 298 parameters. The final R and R_w values were 0.045 and 0.049 for **2** and 0.057 and 0.061 for **5**, respectively. Goodness of fit was 0.925 in the first and 0.975 in the second case. Average and maximal shift/error were 0.0268 and 0.8513 for **2** and 0.0038 and 0.0627 for **5**. The maximal residual density in final difference map was 0.328 e/Å^3 for **2** and 0.789 e/Å^3 for **5** and the minimal -0.317 e/Å^3 for **2** and -0.639 e/Å^3 for **5**.

The Xtal3.2 [22] system of crystallographic programs was used for the correlation and reduction of data, structure refinement and interpretation. ORTEPII [23] was used to produce molecular graphics. All calculations were performed on VAX 8550 computers at the University Computer Center, Ljubljana.

The asymmetric units of **2** and **5** with atom-numbering scheme are shown in the Figures 1 and 2. The stereoviews of the unit cell of both compounds are presented in Figures 3 and 4. Final atomic coordinates and equivalent isotropic thermal parameters with their e.s.d.'s are listed in Table 1. Bond lengths and bond angles are presented in Table 2.

The asymmetric unit of **2** consists of two molecules with the same formula and similar geometry. Such two molecules are joined *via* two weak intermolecular N(3)-H..N(2) hydrogen bonds forming a dimmer. The lengths of these two hydrogen bonds are 2.993(3) Å (N(3a)..N(2b)) and 2.970(3) Å (N(3b)..N(2a)). The asymmetric unit of **5** includes one molecule whose conformation is stabilized with intramolecular hydrogen bond between N(3')-H group and N(2) atom with a distance of 2.597(5) Å. In structure **5** exists also intermolecular N(4)-H..O(3) hydrogen bond of length 2.990(5) Å. Both compounds contain thiazolidine ring and (2-methoxyphenyl)imino group being bonded to C(2) atom of the ring. Molecules of **2** and **5** differ in the group which is substituted to N(3) of thiazolidine ring. In **5** is this substituent (3-sulphamoylphenyl) thiocarbamoyl group. Only hydrogen atom is bonded to N(3) in **2**. The orientation of methoxyphenyl group relative to iminothiazolidine moiety in **5** differs from that in **2**; dihedral angle between the best plane through methoxyphenyl group and the plane through N(2), C(2) and N(3) atoms is 60.0(3)° in **a** molecules of **2**, 64.2(3)° in **b** molecules of **2** and 90.5(4)° in molecules of **5**.

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