Synthesis of New Functionalized Imidazo[2,1-*b*]thiazoles and Thiazolo[3,2-*a*]pyrimidines

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5-Oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid (**4**), and 6-methylimidazo[2,1-*b*]thiazole-5-carboxylic acid (**17**) were reacted with amines **6a-i** by the reaction with oxalyl chloride and *N,N*-dimethylformamide as a catalyst into primary and secondary amide derivatives **7-14** and **19-22**. From compound **24** *N,N'*-disubstituted ureas **26, 27** and perhydroimidazo[1,5-*c*]thiazole **29** derivatives of imidazo[2,1-*b*]thiazole were prepared. By nmr analysis of compound **29**, the existence of two stereoisomers resulting from both optical, due to centre of chirality at C7'a, and conformational isomerism, due to restricted C5-N6' bond rotation were proved.

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Due to considerable interest in their bioactivity the syntheses of heterocycles and their derivatives with a bicycle fused (5,5) and (5,6) ring systems with bridgehead nitrogen atom formed from α-amino nitrogen heterocycles such as 2-aminothiazole, have been explored with significant success [1]. The thiazolidine moiety occurs in different bioactive substances as an important pharmacophoric group. For instance the imidazo[2,1-*b*]thiazole system is the main moiety of the well known antihelmintic and immunomodulatory agent levamisole ((−)-(*S*)-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole) [2,3]. Thiazolo[3,2-*a*]-pyrimidines bear a structural analogy to levamisole and have been well studied as immunomodulators, anticancer, analgesic and psychotropic agents [2,4] (Figure 1).

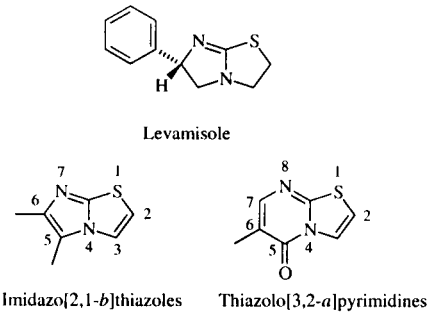
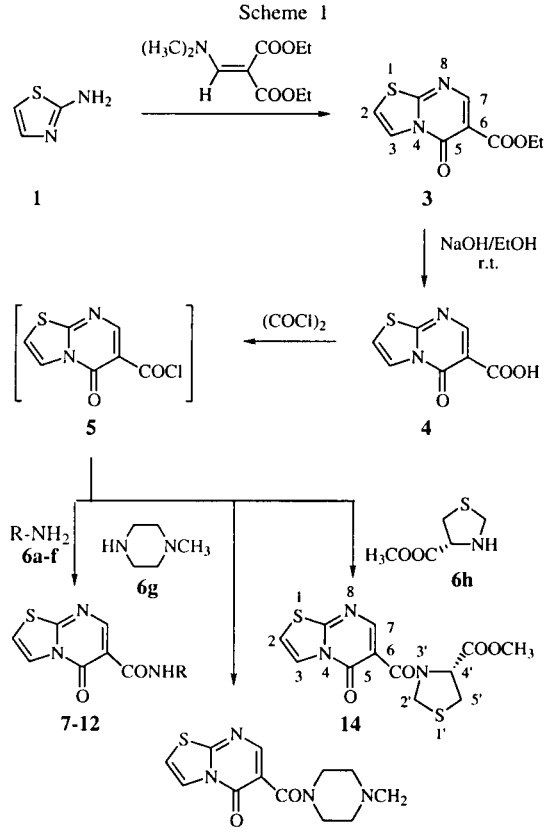


Figure 1

In connection with our studies of potential immunomodulators the synthesis of some new primary and secondary amide and *N,N'*-disubstituted urea derivatives at position 5 of imidazo[2,1-*b*]thiazole and various amide derivatives at position 6 of structurally related thiazolo[3,2-*a*]pyrimidine were prepared [5-7].

5-Oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid (**4**) was prepared from 2-aminothiazole (**1**) and diethyl *N,N*-dimethylaminomethylenemalonate (**2**) [8] by heating in acetic acid under reflux for several hours to afford **3** [9], followed by alkaline hydrolysis at room temperature. The reaction of 2-aminothiazole with Meldrum acid derivatives has been reported [10] to give **4**. As the best method for the activation of the free carboxylic group of compound **4** into acid chloride **5**, the reaction of two equivalents of oxalyl chloride in dichloromethane under mild conditions at 0° in the presence of *N,N*-dimethylformamide as a catalyst has been reported [11]. The same procedure was then used to prepare all compounds listed in the Scheme 1 from **4** with selected amines. Ethyl glycinate (**6a**), methyl ester of *L*-alanine (**6b**), *L*-phenylalanine (**6c**), *S*-trityl-*L*-cysteine (**6d**),

Scheme 1



Compound	R	Compound	R
6a, 7	CH_2COOEt	**6d, 10**	$CH(CH_2SCPh_3)COOH$
6b, 8	$CH(CH_3)COOCH_3$	**6e, 11**	phenyl
6c, 9	$CH(CH_2Ph)COOH$	**6f, 12**	thiazolyl

2-aminothiazole (**6f**), aniline (**6e**), *N*-methylpiperazine (**6g**), and methyl *L*-thiazolidine-4-carboxylate (**6h**) were used to yield **7-14** in 17% to 61% yields, respectively.

The second reaction pathway shown in Scheme 2, represents transformation of 2-aminothiazole (**1**) with 2-bromoacetoacetate (**15**) into ethyl 6-methylimidazo[2,1-*b*][1,3]-thiazole-5-carboxylate (**16**) [12] and further to the corresponding carboxylic acid **17** according to the modified procedure [13]. The carboxylic acid **17** was reacted with ethyl glycinate (**6a**) using three different activation procedures. In the reaction with diphenylphosphoryl azide and triethylamine [14a-c,15] the ^{1}H-nmr spectra, mass spectra and elemental analysis show, that the product of this reaction is not the expected compound ethyl 2{[(6-methylimidazo[2,1-*b*][1,3]thiazol-5-yl)carbonyl]amino}acetate (**19**), instead, *N*-diphenylphosphoryl glycinate was formed. In an attempt to prepare **19** we found out that the activation of carboxylic acid **17** with ethylchloroformate and triethylamine [16] was less effective than activation of **17** with oxalyl chloride in the presence of dimethylformamide as a catalyst. The activation with oxalyl chloride gave better yield, shorter reaction time and a smaller number of side products as judged by tlc chromatography. For these reasons this method was chosen for further reactions with selected amines: ethyl glycinate (**6a**), methyl ester of *L*-alanine (**6b**), 2-aminothiazole (**6f**) and methyl *L*-thiazolidine-4-carboxylate (**6h**) to yield **19-22** (Scheme 2).

Another reaction pathway includes the transformation of compound **23** [12] into the corresponding azide **24** according to the procedure described in the literature [5]. Compound **24** transformed by a Curtius rearrangement of acid azide to isocyanate **25** reacts further with ethyl glycinate (**6a**) and methyl ester of *L*-alanine (**6b**) by heating in ethanol-free chloroform to give *N,N'*-disubstituted ureas **26** and **27** [5,17].

6-(6-Methylimidazo[2,1-*b*][1,3]thiazol-5-yl)-1*H*-imidazo[1,5-*c*][1,3]thiazole-5,7(6*H*,7a*H*)-dione (**29**) was obtained in one step from 5-azidocarbonyl-6-methylimidazo[2,1-*b*][1,3]thiazole (**24**) as shown in the Scheme 2. The Curtius rearrangement of azide **24** to isocyanate **25** at elevated temperature in ethanol-free chloroform was followed by condensation with *L*-(−)-thiazolidine-4-carboxylic acid (**6i**) to give the bicycle derivative **29** [18] (Scheme 2).

Two sets of signals were observed for compound **29** in the ^{1}H-nmr spectrum recorded at 302 K in DMSO-d_6 (c=60 mg/ml), respectively. The ^{1}H-nmr spectrum exhibits two sets of signals for the methyl group at position 6, the proton at position 3 of the imidazo[2,1-*b*]-thiazole part and for all protons of the perhydroimidazo[1,5-*c*]thiazole moiety of **29** (Table 1). The existence of conformational isomers of compound **29** was proven by coalescence of signals at elevated temperature. The coalescence of signals in the ^{1}H-nmr spectrum was

Scheme 2

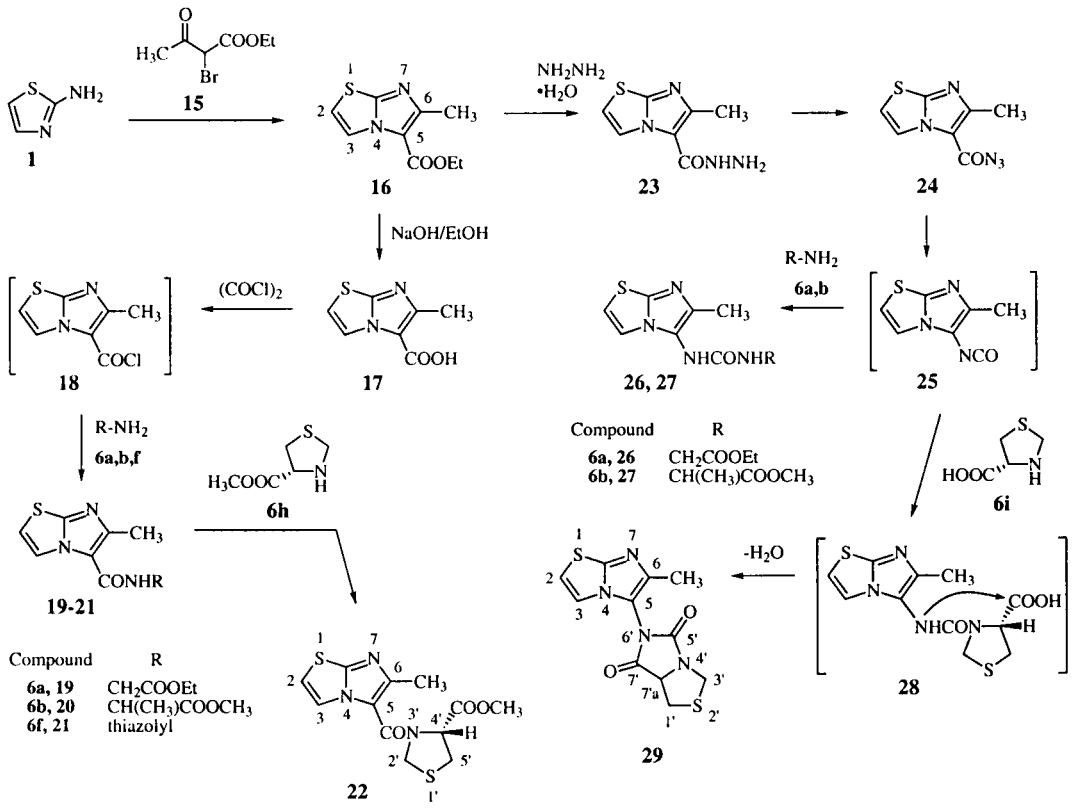


Table 1

^{1}H chemical shifts for compound **29** in DMSO-d_6, measured at 302 K and 342 K [a]

	T=302 K			T=342 K
	isomer 1	both isomers	isomer 2	
2-CH		7.28 (d), J=4.46 Hz		7.24 (d), J=4.46 Hz
3-CH	7.87 (broad s)		7.74 (broad s)	7.72 (broad s)
6-CH_3	2.07 (s)		2.13 (s)	2.11 (s)
1'-CH_2		3.38-3.50 (m)		3.38-3.48 (m)
3'-CH_2	4.84 (d), J=9.03 Hz	4.30-4.34 (m)	4.96 (d), J=9.81 Hz	4.32 (d), J_{AB}=9.52 Hz 4.92 (d), J_{AB}=9.46 Hz
7'a-CH		4.74-4.80 (m)		4.80 (t), J=7.53 Hz

[a] Chemical shifts were confirmed by COSY and HMQC spectra.

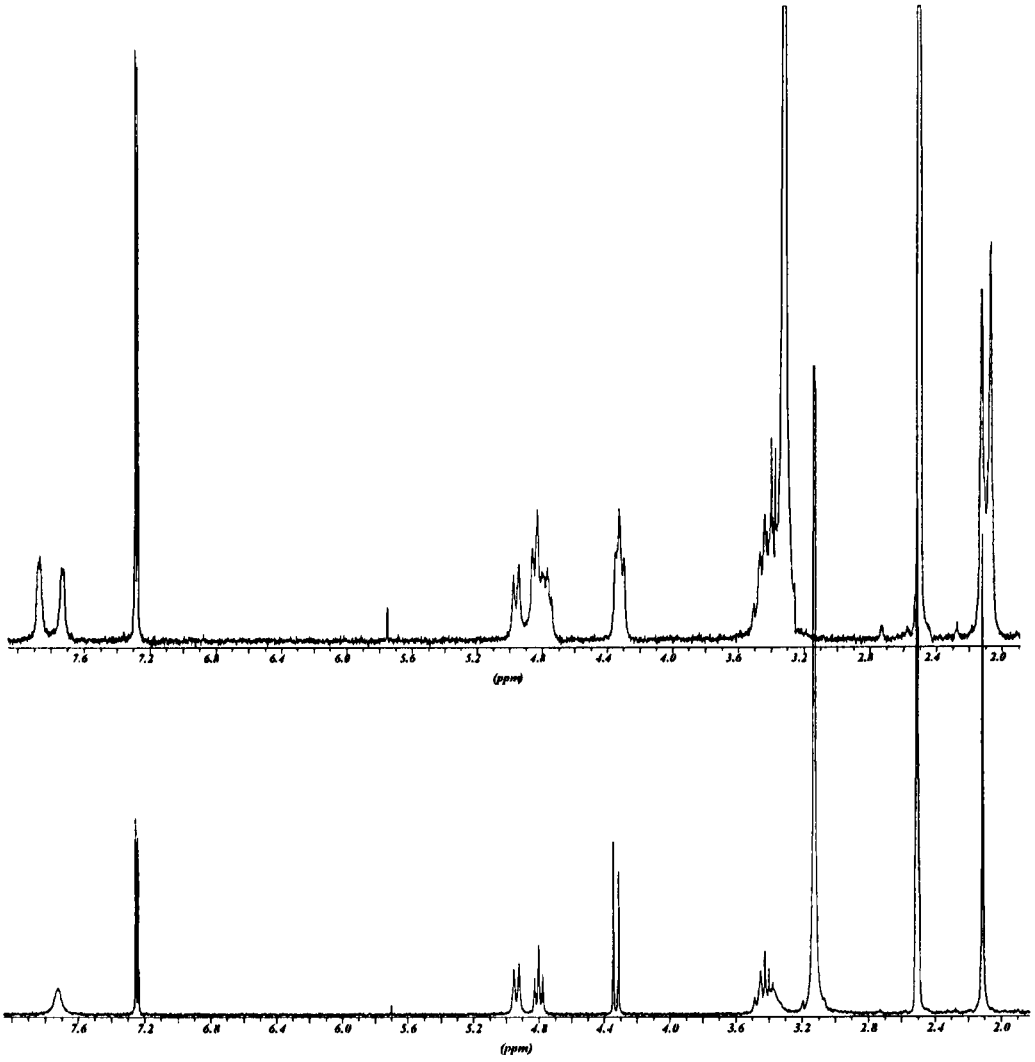


Figure 2. Coalescence of signals of compound **29** in ^{1}H-NMR spectra in DMSO-d_6 at 302 K and 342 K.

observed at 342 K and confirmed by COSY and HMQC spectra (Figure 2). We predicted that the conformational isomers are the result of restricted rotation around the C5-N6' bond. From the data obtained from the nmr analysis of compound **29**, the existence of two stereoisomers resulting from both optical, due to center of chirality at C7'a, and conformational isomerism, due to restricted bond rotation may be postulated.

EXPERIMENTAL

Melting points were taken on a Leica hot stage microscope and are uncorrected. Infrared spectra were obtained from a Perkin Elmer FTIR 1600 instrument as potassium bromide discs. Optical rotations were measured on a Perkin Elmer 240 MC polarimeter. The reported values for specific rotation are average values of ten successive measurements using an integration time of 10 seconds. Elemental analyses were performed on a Perkin Elmer 2400, C, H, N analyser. Mass spectra were obtained on an Autospec Q, VG-Analytical mass spectrometer using EI or FAB ionisation. The ^{1}H-nmr spectra were recorded on a Bruker Advance DPX 300 instrument operating at 300.13 MHz for protons with tetramethylsilane as an internal standard.

6-Ethoxycarbonyl-5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine (**3**) [9], ethyl 6-methylimidazo[2,1-*b*][1,3]thiazole-5-carboxylate (**16**) [12], 6-methylimidazo[2,1-*b*][1,3]thiazole-5-carbohydrazide (**23**) [12], and 5-azidocarbonyl-6-methylimidazo[2,1-*b*]-[1,3]thiazole (**24**) [5] were prepared as described in the literature.

5-Oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylic Acid (**4**).

To a suspension of 6-ethoxycarbonyl-5-oxo-5*H*-[1,3]thiazolo-[3,2-*a*]pyrimidine (**3**) (1.00 g, 4.46 mmoles) in 15 ml of ethanol, aqueous 2 *M* sodium hydroxide (2.68 ml, 5.36 mmoles) was added and the mixture was stirred at room temperature for 3 hours. The separated residue was collected by filtration, dissolved in 15 ml of water, acidified to *p*H 1 with aqueous 1 *M* hydrochloric acid. The solid residue was collected by filtration to give 0.80 g (92%) of **5**, mp 279-281°; ms: *m/z* (%) 179 (MH^+, 66), 154 (100); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.76 (d, 1H, $J_{2,3}$ = 4.50 Hz, 2-C*H*), 8.25 (d, 1H, $J_{2,3}$ = 4.50 Hz, 3-C*H*), 8.71 (s, 1H, 7-C*H*), 12.65 (broad s, 1H, COO*H*).

Anal. Calcd. for $C_7H_4N_2O_3S_1$: C, 42.86; H, 2.04; N, 14.29. Found: C, 42.59; H, 2.07; N, 14.03.

Synthesis of Amide Derivatives of Thiazolo[3,2-*a*]pyrimidine **7-14**.

All primary and secondary amides were prepared following the general procedure illustrated by the preparation of ethyl-2-{[(5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-6-yl)carbonyl]-amino}acetate (**7**), using 5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]-pyrimidine-6-carboxylic acid (**4**) and the appropriate amine (**6a-h**). Analogues are listed after this representative procedure with their physical characteristics, and variations are noted under the individual products.

Ethyl-2-{[(5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-6-yl)-carbonyl]amino}acetate (**7**).

Method A (Acid Chloride Method).

To a stirred suspension of 5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid (**4**) (130 mg, 0.66 mmole) in 10 ml of anhydrous dichloromethane at 0°, catalytic amount of dry *N,N*-dimethylformamide (0.10 equivalent) was added, followed by oxalyl chloride (0.11 ml, 1.32 mmoles). Stirring was continued for 20 minutes at 0° and then for 1.5 hours at room temperature. After evaporation of the solvent under reduced pressure the residue was taken up in 10 ml of anhydrous dichloromethane and reevaporated to give the acid chloride **5**. The uncharacterised acid chloride **5** was suspended in 10 ml of anhydrous dichloromethane, cooled to 0° and added dropwise to a precooled mixture of ethyl glycinate hydrochloride (**6a**) (92 mg, 0.66 mmole) and triethylamine (0.23 ml, 1.65 mmoles) in 10 ml of anhydrous dichloromethane. After 20 hours of stirring at room temperature the mixture was washed successively with 10% citric acid solution (3×4 ml). The combined citric acid phases were reextracted with dichloromethane (5×10 ml). The combined dichloromethane phases were successively washed with water (5×10 ml), saturated sodium hydrogencarbonate solution (5×10 ml), water (5×10 ml) and saturated sodium chloride solution (5×10 ml). The organic layer was dried using magnesium sulphate. After filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatograph (Kieselgel 60, 0.40-0.063 mm, E. Merck, and dichloromethane: methanol = 20:1, as eluent) and precipitated from dichloromethane with hexane to give 60 mg (32%) of **7**, mp 176-177°; ms: *m/z* (%) 282 (MH^+, 34), 154 (100); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.22 (t, 3H, J = 7.16 Hz, $COOCH_2CH_3$), 4.14 (q, 2H, J = 7.16 Hz, $COOCH_2CH_3$), 4.14 (d, 2H, J = 5.65 Hz, $NHCH_2CO$), 7.77 (d, 1H, $J_{2,3}$ = 4.90 Hz, 2-C*H*), 8.28 (d, 1H, $J_{2,3}$ = 4.90 Hz, 3-C*H*), 8.79 (s, 1H, 7-C*H*), 9.16 (t, 1H, J = 5.65 Hz, N*H*CH_2).

Anal. Calcd. for $C_{11}H_{11}N_3O_4S_1$: C, 46.98; H, 3.91; N, 14.95. Found: C, 46.94; H, 3.72; N, 14.61.

Method B (Mixed Anhydride Method).

A suspension of 5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid (**4**) (150 mg, 0.77 mmoles) and triethylamine (0.11 ml, 0.77 mmoles) in 10 ml of chloroform without ethanol was cooled to -15°. After 5 minutes stirring, ethylchloroformate (0.11 ml, 1.20 mmoles) was added dropwise and stirring was continued for 30 minutes at -5° to -15° to give the mixed anhydride. At that time a solution of ethyl glycinate hydrochloride (**6a**) (107 mg, 0.77 mmole) and triethylamine (0.11 ml, 0.77 mmole) in 5 ml of chloroform without ethanol, cooled to -5°, was added dropwise. The reaction mixture was stirred for 20 hours at room temperature and then washed successively with aqueous 1 *M* hydrochloric acid (3×5 ml), water (5×10 ml), saturated sodium hydrogencarbonate solution (5×10 ml) and water (5×10 ml). The organic layer was dried using magnesium sulphate. After filtration, the solvent was removed under reduced pressure and the residue was purified by precipitation from dichloromethane with hexane to give 49 mg, (23%) of **7** with the same characteristics as described above.

Methyl 2-{[(5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-6-yl)-carbonyl]amino}propanoate (**8**).

This compound was prepared in the same way as described in the method A from **4** (150 mg, 0.77 mmole) and the methyl ester of *L*-alanine hydrochloride (**6b**) (117 mg, 0.77 mmole), precipitated from dichloromethane with hexane to give 108 mg (50%) of **8**, mp 132-134°; ms: *m/z* (%) 281 (M^+, 66), 179 (100); $[\alpha]_D$ + 69.3° (c = 0.39, methanol); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.42 (d, 3H, J = 7.16 Hz, CH_3-Ala), 3.68 (s, 3H, $COOCH_3$), 4.53-4.63 (m, 1H, C*H*-Ala), 7.78 (d, 1H, $J_{2,3}$ = 4.90 Hz, 2-C*H*), 8.27 (d, 1H, $J_{2,3}$ = 4.90 Hz, 3-C*H*), 8.78 (s, 1H, 7-C*H*), 9.23 (d, 1H, J = 7.16 Hz, CON*H*CH).

Anal. Calcd. for $C_{11}H_{11}N_3O_4S_1$: C, 46.98; H, 3.91; N, 14.95. Found: C, 46.86; H, 3.84; N, 14.87.

N-[(5-Oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-6-yl)carbonyl]-*L*-phenylalanine (**9**).

This compound was prepared according to the method A from **4** (250 mg, 1.28 mmoles) and *L*-phenylalanine (**5c**) (211 mg, 1.28 mmoles) in ethanol-free chloroform. After the reaction was completed the mixture was washed with water (5×10 ml). The combined water phases were acidified with aqueous 1 *M* hydrochloric acid and the separated residue was collected by filtration to give 53 mg (17%)

of **9**, mp 104-106°; ms: *m/z* (%) 344 (MH^+, 100); $[\alpha]_D$ −43.2° (c = 0.39, methanol); ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.08 (dd, 1H, ABX system, J_{AX} = 7.16 Hz, J_{AB} = 13.92 Hz, CH_2-Phe), 3.19 (dd, 1H, ABX system, J_{BX} = 5.27 Hz, J_{AB} = 13.92 Hz, CH_2-Phe), 4.77 (ddd, 1H, ABX system, J_{AX} = 7.16 Hz, J_{BX} = 5.27 Hz, $J_{NH\text{-}CH}$ = 7.56 Hz, NHC*H*-Phe), 7.20-7.28 (m, 5H, CH_{Ar}-Phe), 7.76 (d, 1H, $J_{2,3}$ = 4.90 Hz, 2-C*H*), 8.24 (d, 1H, $J_{2,3}$ = 4.90 Hz, 3-C*H*), 8.77 (s, 1H, 7-C*H*), 9.18 (d, 1H, $J_{NH\text{-}CH}$ = 7.56 Hz, CON*H*CH).

Anal. Calcd. for $C_{16}H_{13}N_3O_4S_1$: C, 55.98; H, 3.79; N, 12.25. Found: C, 56.31; H, 3.70; N, 11.86.

N-[(5-Oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-6-yl)carbonyl]-*S*-(+)-trityl-*L*-cysteine (**10**).

This compound was prepared according to the method A from **4** (0.60 g, 3.06 mmoles) and *S*-(+)-trityl-*L*-cysteine (**5d**) (1.11 g, 3.06 mmoles) in ethanol-free chloroform. After the reaction was completed the mixture was washed successively with 10% citric acid solution (3×5 ml) and water (3×10 ml). The precipitated product in organic layer was filtered to give 65 mg (40%) of **10**, mp 210-213°; ms: *m/z* (%) 542 (MH^+, 33), 243 (100); $[\alpha]_D$ + 13.4° (c = 0.36, *N,N*-dimethylformamide); ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.56 (dd, 1H, ABX system, J_{AX} = 4.53 Hz, J_{AB} = 12.06 Hz, CH_2-Cys), 2.68 (dd, 1H, ABX system, J_{BX} = 6.40 Hz, J_{AB} = 12.06 Hz, CH_2-Cys), 4.55-4.63 (m, 1H, C*H*-Cys), 7.23-7.32 (m, 15H, 3×Ph), 7.79 (d, 1H, $J_{2,3}$ = 4.90 Hz, 2-C*H*), 8.32 (d, 1H, $J_{2,3}$ = 4.90 Hz, 3-C*H*), 8.77 (s, 1H, 7-C*H*), 9.38 (d, 1H, J = 7.54 Hz, CON*H*CH), 13.11 (broad s, 1H, COO*H*).

Anal. Calcd. for $C_{29}H_{23}N_3O_4S_2$: C, 64.33; H, 4.25; N, 7.76. Found: C, 64.31; H, 4.35; N, 7.78.

5-Oxo-*N*-phenyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide (**11**).

This compound was prepared according to the method A from **4** (225 mg, 1.15 mmoles) and aniline (**6e**) (0.11 ml, 1.15 mmoles). The precipitate was filtered, washed with dichloromethane and purified by precipitation from *N,N*-dimethylformamide with diethyl ether to give 190 mg (61%) of **11**, mp 234-236°; ms: *m/z* (%) 271 (M^+, 52), 179 (100); ^1H nmr (dimethyl-d_6 sulfoxide): δ 7.09-7.16 (m, 1H, 4'-C*H*), 7.34-7.41 (m, 2H, 3',5'-C*H*), 7.68-7.73 (m, 2H, 2',6'-C*H*), 7.82 (d, 1H, $J_{2,3}$ = 4.52 Hz, 2-C*H*), 8.33 (d, 1H, $J_{2,3}$ = 4.52 Hz, 3-C*H*), 8.89 (s, 1H, 7-C*H*), 10.99 (s, 1H, CON*H*).

Anal. Calcd. for $C_{13}H_9N_3O_2S_1$: C, 57.56; H, 3.32; N, 15.50. Found: C, 57.31; H, 3.41; N, 15.38.

5-Oxo-*N*-(1,3-thiazol-2-yl)-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxamide (**12**).

This compound was prepared according to the method A from **4** (200 mg, 1.02 mmoles) and 2-aminothiazole (**6f**) (102 mg, 1.02 mmoles) to give, after precipitation from dichloromethane with diethyl ether, 82 mg (29%) of **12**, mp 238-240°; ms: *m/z* (%) 279 (MH^+, 69), 154 (100); ^1H nmr (dimethyl-d_6 sulfoxide): δ 7.33 (d, 1H, $J_{4',5'}$ = 3.57 Hz, 5'-C*H*), 7.54 (d, 1H, $J_{4',5'}$ = 3.57 Hz, 4'-C*H*), 7.87 (d, 1H, $J_{2,3}$ = 4.52 Hz, 2-C*H*), 8.39 (d, 1H, $J_{2,3}$ = 4.52 Hz, 3-C*H*), 8.94 (s, 1H, CON*H*).

Anal. Calcd. for $C_{10}H_6N_4O_2S_2$: C, 43.17; H, 2.16; N, 20.14. Found: C, 42.82; H, 2.13; N, 20.10.

6-[(4-Methyl-1-piperazinyl)carbonyl]-5*H*-[1,3]thiazolo[3,2-*a*]-pyrimidin-5-one (**13**).

This compound was prepared as described in method A from **4** (115 mg, 0.59 mmole) and *N*-methylpiperazine (**6g**) (0.065 ml, 0.59 mmole). After the reaction was completed the mixture was washed with water (5×10 ml), the combined water phases were reextracted with dichloromethane (5×10 ml) and the combined dichloromethane phases were successively washed with saturated sodium hydrogenecarbonate solution (5×10 ml) and water (5×10 ml). The organic layer was dried using magnesium sulphate. After filtration, the solvent was removed under reduced pressure and the oily residue triturated several times with a mixture of dichloromethane and diethyl ether. The precipitate was collected by filtration to give 35 mg (21%) of **13**, mp 133-135°; ms: *m/z* (%) 278 (M^+, 15), 179 (100); ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.20 (s, 3H, CH_3), 2.30 (s, 2H, 3'-CH_2), 2.35 (s, 2H, 5'-CH_2), 3.32 (s, 2H, 2'-CH_2), 3.60 (s, 2H, 6'-CH_2), 7.66 (d, 1H, $J_{2,3}$ = 4.90 Hz, 2-C*H*), 8.13 (d, 1H, $J_{2,3}$ = 4.90 Hz, 3-C*H*), 8.13 (s, 1H, 7-C*H*).

Anal. Calcd. for $C_{12}H_{14}N_4O_2S_1$: C, 51.80; H, 5.04; N, 20.14. Found: C, 51.64; H, 5.33; N, 19.89.

Methyl (4*S*)-3-[(5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-6-yl)carbonyl]-1,3-thiazolidine-4-carboxylate (**14**).

This compound was prepared in the same way as described in the method A from **4** (200 mg, 1.02 mmoles) and methyl *L*-(−)-thiazolidine-4-carboxylate hydrochloride (**6h**) (187 mg, 1.02 mmoles), precipitated from dichloromethane with diethyl ether to give 70 mg (21%) of **14**, mp 81-83°; ms: *m/z* (%) 326 (MH^+, 57), 154 (100); $[\alpha]_D$ − 254° (c = 0.13, methanol); ^1H nmr (dimethyl-d_6 sulfoxide, T = 332 K): δ 3.15-3.25 (m, 1H, 5'-CH_2), 3.37-3.48 (m, 1H, 5'-CH_2), 3.68 (s, 3H, $COOCH_3$), 4.44-4.55 (m, 1H, 2'-CH_2), 4.73-4.84 (m, 1H, 2'-CH_2), 5.08 (dd, 1H, ABX system, J_{AX} = 4.92 Hz, J_{BX} = 6.39 Hz, 4'-C*H*), 7.69 (d, 1H, $J_{2,3}$ = 4.90 Hz, 2-C*H*), 8.16 (d, 1H, $J_{2,3}$ = 4.90 Hz, 3-C*H*), 8.19 (s, 1H, 7-C*H*).

Anal. Calcd. for $C_{12}H_{11}N_4O_3S_2$: C, 44.31; H, 3.38; N, 12.92. Found: C, 44.12; H, 3.44; N, 12.75.

6-Methylimidazo[2,1-*b*]thiazole-5-carboxylic Acid (**17**).

Ethyl 6-methylimidazo[2,1-*b*][1,3]thiazole-5-carboxylate (**16**) (2.50 g, 1.19 mmoles) was dissolved in 15 ml of ethanol, aqueous 2 *M* sodium hydroxide (12 ml, 2.38 mmoles) was added and stirred at reflux temperature for 2 hours. After evaporation of the solvent under reduced pressure the residue was dissolved in 15 ml of water, acidified to *p*H 1 with aqueous 1 *M* hydrochloric acid and the precipitated product was collected by filtration to give 1.8 g (83%) of **17**, mp 203-205°; ms: *m/z* (%) 182 (M^+, 100); ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.50 (s, 3H, 6-CH_3), 7.80 (d, 1H, $J_{2,3}$ = 4.52 Hz, 2-C*H*), 8.09 (d, 1H, $J_{2,3}$ = 4.52 Hz, 3-C*H*).

Synthesis of Amide Derivatives of Imidazo[2,1-*b*]thiazole **19-22**.

All primary and secondary amides were prepared following the general procedure illustrated by the preparation of ethyl-2-{[(5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-6-yl)carbonyl]amino}acetate (**7**), using 6-methylimidazo[2,1-*b*][1,3]thiazole-5-carboxylic acid (**17**) and the appropriate amine (**6a,b,f,g**). Analogues are listed after this representative procedure with their physical characteristics, and variations are noted under the individual products.

Ethyl 2{[(6-methylimidazo[2,1-*b*][1,3]thiazol-5-yl)carbonyl]-amino}acetate (**19**).

This compound was prepared in a similar manner as described in method A from **17** (130 mg, 0.71 mmole) and ethyl glycinate hydrochloride (**6a**) (100 mg, 0.71 mmole), precipitated from dichloromethane with diethyl ether to give 51 mg (27%) of **19**, mp 107-109°; ms: *m/z* (%) 267 (M^+, 32), 165 (100); ^1H nmr

(dimethyl-d_6 sulfoxide): δ 1.21 (t, 3H, J = 7.16 Hz, $COOCH_2CH_3$), 2.50 (s, 3H, 6-CH_3), 4.02 (d, 2H, J = 5.84 Hz, $CONHCH_2$), 4.13 (q, 2H, J = 7.16 Hz, $COOCH_2CH_3$), 7.34 (d, 1H, $J_{2,3}$ = 4.52 Hz, 2-CH), 7.93 (t, 1H, J = 5.84 Hz, $CONHCH_2$), 8.07 (d, 1H, $J_{2,3}$ = 4.52 Hz, 3-CH).

Anal. Calcd. for $C_{11}H_{13}N_3O_3S_1$: C, 49.44; H, 4.87; N, 15.73. Found: C, 49.14; H, 4.97; N, 15.67.

Compound **19** was also prepared following the general procedure illustrated by method B from **17** (150 mg, 0.82 mmole) and ethyl glycinate hydrochloride (**6a**) (112 mg, 0.82 mmole), precipitated from dichloromethane with hexane to give 48 mg, (22%) of **19** with the same characteristics as described above.

Preparation of Compound **19** was also Attempted by Method C (Acid Azide Method).

To a solution of 6-methylimidazo[2,1-*b*][1,3]thiazole-5-carboxylic acid (**17**) (370 mg, 2.00 mmoles) and ethyl glycinate hydrochloride (**6a**) (280 mg, 2.00 mmoles) in 6 ml of *N,N*-dimethylformamide, diphenyl phosphorazidate (DPPA) (0.43 ml, 2.00 mmoles) and triethylamine (0.40 ml, 4.00 mmoles) were added during stirring at 0°C. Stirring was continued for 1 hour at 0°C and then for 48 hours at room temperature. After addition of 20 ml of ethyl acetate the mixture was washed successively with 10% citric acid solution (3×4 ml). The combined citric acid phases were reextracted with ethyl acetate (5×10 ml). The combined ethyl acetate phases were successively washed with water (5×10 ml), saturated sodium hydrogencarbonate solution (5×10 ml), water (5×10 ml) and saturated sodium chloride solution (5×10 ml). The organic layer was dried using magnesium sulphate. After filtration, the solvent was removed under reduced pressure and the product was purified by column chromatography (Kieselgel 60, 0.40-0.063 mm, E. Merck, and dichloromethane:methanol = 20:1, as eluent) and precipitated from hexane with diethyl ether to give 208 mg (31%) of ethyl *N*-diphenylphosphoryl glycinate and not the expected compound **19**. Analyses for ethyl *N*-diphenyl phosphoryl glycinate: mp 73-74°; ms: *m/z* (%) 336 (MH^+, 100); ^1H nmr (deuteriochloroform): δ 1.28 (t, 3H, J = 7.16 Hz, $COOCH_2CH_3$), 3.61-3.70 (m, 1H, $(PhO)_2PONHCH_2$), 3.88 (dd, 2H, J = 5.65 Hz, J = 9.05 Hz, $NHCH_2CO$), 4.21 (q, 2H, J = 7.16 Hz, $COOCH_2CH_3$), 7.19-7.33 (m, 10H, 2×Ph).

Anal. Calcd. for $C_{16}H_{18}N_1O_5P_1$: C, 57.31; H, 5.37; N, 4.18. Found: C, 57.01; H, 5.26; N, 4.17.

Methyl 2-{[(6-methylimidazo[2,1-*b*][1,3]thiazol-5-yl)carbonyl]-amino}propanoate (**20**).

This compound was prepared in the same way as described in method A from **17** (150 mg, 0.82 mmole) and the methyl ester of *L*-alanine hydrochloride (**6b**) (126 mg, 0.82 mmole), precipitated from dichloromethane with hexane to give 66 mg (30%) of **20**, mp 131-133°; ms: *m/z* (%) 267 (M^+, 66), 179 (100); $[\alpha]_D$ – 14° (c = 0.25, methanol); ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.42 (d, 3H, J = 7.16 Hz, CH_3-Ala), 2.50 (s, 3H, 6-CH_3), 3.67 (s, 3H, $COOCH_3$), 4.45-4.55 (m, 1H, CH-Ala), 7.33 (d, 1H, $J_{2,3}$ = 4.52 Hz, 2-CH), 7.97 (d, 1H, J = 7.91 Hz, CONHCH), 8.01 (d, 1H, $J_{2,3}$ = 4.52 Hz, 3-CH).

Anal. Calcd. for $C_{11}H_{13}N_3O_3S_1$: C, 49.44; H, 4.87; N, 15.73. Found: C, 49.56; H, 4.89; N, 15.63.

6-Methyl-*N*-(1,3-thiazol-2-yl)imidazo[2,1-*b*][1,3]thiazole-5-carboxamide (**21**).

This compound was prepared in a similar manner as described in method A from **17** (150 mg, 0.82 mmole) and 2-aminothiazole (**6f**) (82 mg, 0.82 mmole), to give, after column chromatography (Kieselgel 60, 0.40-0.063 mm, E. Merck, and dichloromethane: methanol = 20:1, as eluent) and precipitated from dichloromethane with diethyl ether, 41 mg (19%) of **21**, mp 242-244°; ms: *m/z* (%) 264 (M^+, 22), 165 (100); ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.62 (s, 3H, 6-CH_3), 5.75 (s, 1H, CONH), 7.10 (d, 1H, $J_{4',5'}$ = 4.15 Hz, 5'-CH), 7.38 (d, 1H, $J_{2,3}$ = 4.52 Hz, 2-CH), 7.48 (d, 1H, $J_{4',5'}$ = 4.15 Hz, 4'-CH), 8.37 (d, 1H, $J_{2,3}$ = 4.52 Hz, 3-CH).

Anal. Calcd. for $C_{10}H_8N_4O_1S_2$: C, 45.45; H, 3.03; N, 20.85. Found: C, 44.83; H, 3.01; N, 21.15.

Methyl (4*S*)-3-[(6-methylimidazo[2,1-*b*][1,3]thiazol-5-yl)carbonyl]-1,3-thiazolidine-4-carboxylate (**22**).

This compound was prepared in a similar manner as described in method A from **17** (130 mg, 0.71 mmole) and methyl *L*-(–)-thiazolidine-4-carboxylate hydrochloride (**6h**) (131 mg, 0.71 mmole). The oily residue was purified by column chromatography (Kieselgel 60, 0.40-0.063 mm, E. Merck, and dichloromethane:methanol = 20:1, as eluent) to give 65 mg (30%) of oily residue **22**, ms: *m/z* (%) 311 (M^+, 67), 165 (100); $[\alpha]_D$ – 281° (c = 0.35, methanol); ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.38 (s, 3H, 6-CH_3), 3.26 (dd, 1H, ABX system, J_{AX} = 5.28 Hz, J_{AB} = 11.30 Hz, 5'-CH_2), 3.47 (dd, 1H, ABX system, J_{BX} = 7.53 Hz, J_{AB} = 11.68 Hz, 5'-CH_2), 3.70 (s, 3H, $COOCH_3$), 4.63 (d, 1H, AB system, J_{AB} = 9.79 Hz, 2'-CH_2), 4.82 (d, 1H, AB system, J_{AB} = 9.42 Hz, 2'-CH_2), 5.26 (dd, 1H, ABX system, J_{AX} = 5.28 Hz, J_{BX} = 7.53 Hz, 4'-CH), 7.34 (d, 1H, $J_{2,3}$ = 4.52 Hz, 2-CH), 7.77 (d, 1H, $J_{2,3}$ = 4.52 Hz, 3-CH).

Anal. Calcd. for $C_{12}H_{13}N_3O_3S_2$: C, 46.30; H, 4.18; N, 13.51. Found: C, 46.37; H, 4.39; N, 13.29.

Synthesis of *N,N'*-disubstituted urea derivatives of imidazo[2,1-*b*]-thiazole **26, 27**.

The urea derivatives were prepared following the general procedure illustrated by the preparation of ethyl 2-({[(6-methylimidazo[2,1-*b*][1,3]thiazol-5-yl)amino]carbonyl}amino)acetate (**26**), using 5-azidocarbonyl-6-methylimidazo[2,1-*b*][1,3]thiazole (**24**) and appropriate amine (**6a,b**). Analogues are listed after this representative procedure with their physical characteristics, and variations are noted under the individual products.

Ethyl 2-({[(6-methylimidazo[2,1-*b*][1,3]thiazol-5-yl)amino]carbonyl}amino)acetate (**26**).

A mixture of 5-azidocarbonyl-6-methylimidazo[2,1-*b*]-[1,3]thiazole (**24**) (72 mg, 0.35 mmole) and ethyl glycinate (**6a**) (42 mg, 0.41 mmole) in 10 ml of anhydrous dichloromethane was stirred at reflux temperature for 24 hours. The mixture was washed successively with 10% citric acid solution (3×5 ml). The combined citric acid phases were reextracted with dichloromethane (5×10 ml) and the combined organic phases were successively washed with water (5×10 ml). The organic layer was dried using magnesium sulphate. After filtration, the solvent was removed under reduced pressure and the residue was purified by precipitation from ethanol with diethyl ether to give 25 mg (26%) of **26**, mp 177-180°; ms: *m/z* (%) 282 (M^+, 29), 179 (100); ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.22 (t, 3H, J = 7.16 Hz, $COOCH_2CH_3$), 2.10 (s, 3H, 6-CH_3), 3.78 (d, 2H, J = 5.84 Hz, $CONHCH_2$), 4.11 (q, 2H, J = 7.16 Hz, $COOCH_2CH_3$), 6.68 (t, 1H, J = 5.84 Hz, $CONHCH_2$), 7.14 (d, 1H, $J_{2,3}$ = 4.52 Hz, 2-CH), 7.41 (d, 1H, $J_{2,3}$ = 4.52 Hz, 3-CH), 8.18 (s, 1H, NHCO).

Anal. Calcd. for $C_{11}H_{14}N_4O_3S_1$: C, 45.36; H, 5.15; N, 19.24. Found: C, 45.17; H, 4.98; N, 19.20.

Methyl 2-({[(6-methylimidazo[2,1-*b*][1,3]thiazol-yl)amino]-carbonyl}amino)propanoate (**27**).

This compound was prepared in the same way from **24** (100 mg, 0.48 mmoles), methyl ester of *L*-alanine hydrochloride (**6b**) (67 mg, 0.48 mmole) and triethylamine (0.084 ml, 0.60 mmole) to give, after precipitation from dichloromethane with diethyl ether, 30 mg (22%) of **27**, mp 128-130°; ms: *m/z* (%) 282 (M^+, 39), 179 (100); ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.41 (d, 3H, J = 7.16 Hz, CH_3-Ala), 2.55 (s, 3H, 6-CH_3), 3.67 (s, 3H, $COOCH_3$), 4.45-4.55 (m, 1H, $NHCHCH_3$), 7.33 (d, 1H, $J_{2,3}$ = 4.14 Hz, 2-C*H*), 7.97 (d, 1H, J = 7.16 Hz, N*H*CH), 8.01 (d, 1H, $J_{2,3}$ = 4.14 Hz, 3-C*H*).

Anal. Calcd. for $C_{11}H_{14}N_4O_3S_1$: C, 46.81; H, 4.96; N, 19.86. Found: C, 46.96; H, 5.22; N, 19.99.

6-(6-Methylimidazo[2,1-*b*][1,3]thiazol-5-yl)-1*H*-imidazo-[1,5*c*][1,3]thiazole-5,7(6*H*,7a*H*)-dione (**29**).

A mixture of 5-azidocarbonyl-6-methylimidazo[2,1-*b*]-[1,3]thiazole (**24**) (200 mg, 0.97 mmole) and *L*-(−)-thiazolidine-4-carboxylic acid (**6i**) (160 mg, 1.20 mmoles) in 15 ml of ethanol-free chloroform was stirred at reflux for 20 hours. After filtration, the solvent was evaporated under reduced pressure and the product was purified by column chromatography (Kieselgel 60, 0.40-0.063 mm, E. Merck, and dichloromethane:methanol = 20:1, as eluent) to give 60 mg (21%) of white crystals, mp 97-99°; ms: *m/z* (%) 294 (M^+, 61), 179 (100); hrms: *m/z* 294.024519 (M^+); $[\alpha]_D$ − 52° (c = 0.084, methanol).

Anal. Calcd. for $C_{11}H_{10}N_4O_2S_2$: C, 44.90; H, 3.40; N, 19.05. Found: C, 44.66; H, 3.43; N, 18.70.

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