Synthesis of novel derivatives of 2-(azolylimino)thiazoline

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Successive alkylation of 5-(3-phenylthioureido)-3*H*-imidazole-4-carboxamides with alkyl halides and chloroacetone gave (*N*-oxopropylimidazolyl)isothioureas, which were easily converted into derivatives of purine and imidazopyrazinone. In the case of ethyl 5-(3-phenylthioureido)-3*H*-imidazole-4-carboxylate, primary alkylation occurs at the N atom of the imidazole ring. Reactions of 5-(3-phenylthioureido)-3*H*-imidazole-4-carboxamides with haloketones afforded a number of 4-hydroxy-2-imidazolyliminothiazolidines and 2-imidazolylimino-Δ^4-thiazolines.

Key words: haloketone, alkylation, 2-imidazolylimino-Δ^4-thiazolines, imidazo[5,1-*c*]pyrazin-7-ones, imidazolylthiourea, purine derivatives, alkyl halides, (*N*-alkylimidazolyl)isothioureas.

At present, a successful search for new biologically active substances among 2-azolylthiazolines is being conducted.[1,2] The goal of this study was to obtain imidazole analogs of antipyriliminothiazolines, which exhibit anti-inflammatory activity.[2]

One of the most rational ways of synthesizing thiazole compounds is condensation of thioureido derivatives with haloketones.[3] We found (Scheme 1) that imidazolylthioureas **2a—c** obtained by reactions of 5-aminoimidazoles **1a—d** with phenyl isothiocyanate react with haloketones **3a—d** to give stable 4-hydroxy-2-imidazolyliminothiazolidines **4a—l**. Their structures were confirmed by data from ^{1}H NMR spectroscopy and mass spectrometry. The ^{1}H NMR spectra show resonance signals at δ 3.7—3.4 (AB system) for the nonequivalent CH_2 protons of the thiazolidine ring and no signals for the NH protons. The mass spectra of these compounds contain molecular ion peaks (Table 1). It should be noted that in the presence of CD_3CO_2D, the ^{1}H NMR spectra of compounds **4a—l** show singlets for the CH protons of the thiazoline ring, the integrated intensity of the signals for the CH_2 protons of the thiazolidine ring being reduced. The discovered process was confirmed preparatively: when heated in acetic acid at 70 °C, compounds **4a—l** rapidly lose a water molecule to form 2-imidazolylimino-Δ^4-thiazolines **5a—l**. In their ^{1}H NMR spectra, a signal for the proton of the thiazole ring appears at δ 6.3—6.5; the molecular ion peaks in the mass spectra correspond to the peaks $[M - 18]^+$ in the spectra of intermediates **4a—l**.

In contrast to imidazolylthioureas **2a—c**, thioureide **2d** reacts with haloalkanes **6a,b** and chloroacetone to give, as noted earlier,[4] *N*-alkylimidazolylthioureas **7a—c**. The reactions of compounds **7a—c** with haloketones **3a—d** afforded the target products **5m—x**; however, in contrast to compounds **2a—c**, intermediate 2-(*N*-alkylimidazolylimino)-4-hydroxythiazolidines of the type **4** could not be isolated.

Analysis of the ^{1}H NMR spectra of compounds **5a—x** and the ^{13}C NMR spectra of compounds **5b,m—o** showed that their heterocyclic systems are identical. For instance, the ^{13}C chemical shifts of the carbon atoms of the thiazoline fragment are very close for compounds **5b** and **5n** (spaced at 0.5 to 1.9 ppm). The ^{1}H and ^{13}C signals for the imidazolyliminothiazoline **5n** were assigned by using 2D ^{1}H—^{1}H and ^{13}C—^{1}H COSY NMR spectroscopy for direct (J = 135, 165, and 195 Hz) and long-range (J = 10 Hz) spin-spin coupling constants. The tentative structure of compound **5n** was fully confirmed by X-ray diffraction data.[4] The proof of the structures of products **5a—x** allows a conclusion about similar structures of intermediates **4a—l**.

Unlike compound **2d**, thioureas **2a—c** react with alkyl halides to give S-alkylation products **8a—f**. In particular, their ^{1}H NMR spectra show the signals for the protons of the alkyl residue (CH_2S) at δ 2.96—3.16. Subsequent reactions of isothioureas **8a—f** with chloroacetone could be expected to yield both (*N*-alkylimidazolyl)isothioureas through the involvement of an N atom of the imidazole

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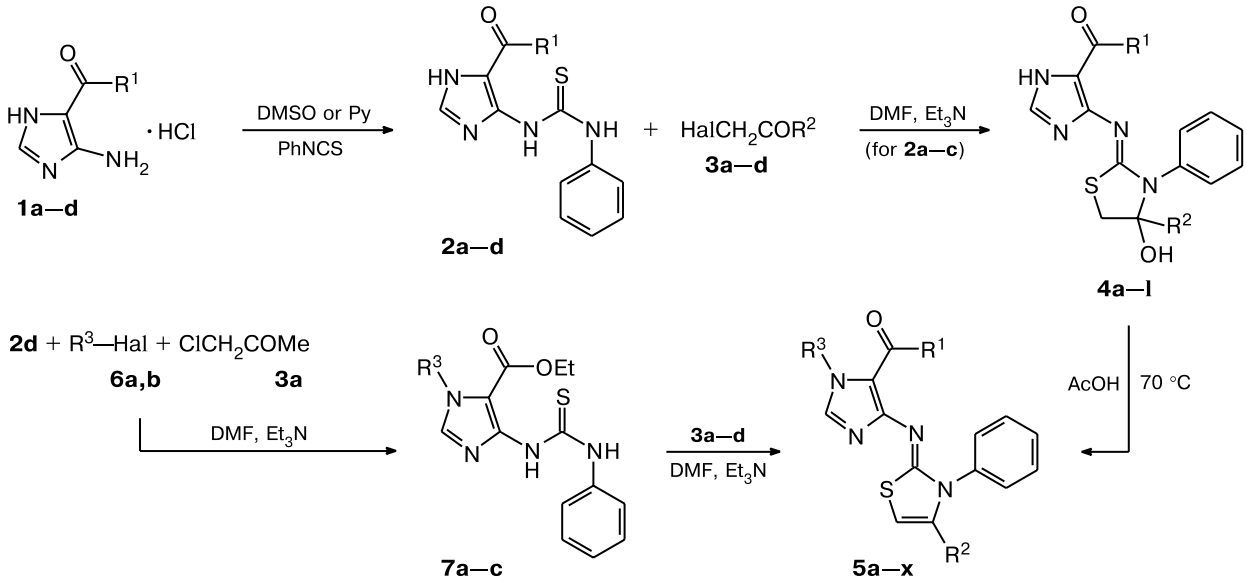
Scheme 1



1, 2: R^1 = NH_2 (**a**), NHMe (**b**), NHC_6H_4-Me-*p* (**c**), OEt (**d**)

3: R^2 = Me (**a**), Ph (**b**), C_6H_4-Me-*p* (**c**), C_6H_4-Cl-*p* (**d**); Hal = Cl (**a**), Br (**b—d**)

4a—l, 5a—l: R^3 = H; **5m—x:** R^1 = OEt

6: R^3 = Et, Hal = I (**a**); Pr, Br (**b**);

7: R^3 = Et (**a**), Pr (**b**), CH_2COMe (**c**)

4, 5	R^1	R^2	**5**	R^2	R^3
a	NH_2	Me	**m**	Me	Et
b	NHMe	Me	**n**	Me	Pr
c	NHC_6H_4Me-*p*	Me	**o**	Me	CH_2COMe
d	NH_2	Ph	**p**	Ph	Et
e	NHMe	Ph	**q**	Ph	Pr
f	NHC_6H_4Me-*p*	Ph	**r**	Ph	CH_2COMe
g	NH_2	C_6H_4Me-*p*	**s**	C_6H_4Me-*p*	Et
h	NHMe	C_6H_4Me-*p*	**t**	C_6H_4Me-*p*	Pr
i	NHC_6H_4Me-*p*	C_6H_4Me-*p*	**u**	C_6H_4Me-*p*	CH_2COMe
j	NH_2	C_6H_4Cl-*p*	**v**	C_6H_4Cl-*p*	Et
k	NHMe	C_6H_4Cl-*p*	**w**	C_6H_4Cl-*p*	Pr
l	NHC_6H_4Me-*p*	C_6H_4Cl-*p*	**x**	C_6H_4Cl-*p*	CH_2COMe

ring and fused bicyclic compounds (imidazopyrazines or imidazotriazepines) as the result of intramolecular cyclization. The ^1H NMR spectra of the compounds obtained contain two signals at δ 11.6—11.8 for the NH fragments and a singlet at δ 5.1 for the CH_2 group, which corresponds to the structure of *N*-substituted

Table 1. Characteristics of the compounds obtained

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)					Molecular formula
			C	H	N	S	Cl	
2a	75	>300	50.80	4.04	27.00	12.20	—	$C_{11}H_{11}N_5OS$
			50.57	4.21	26.82	12.27		
2b	82	>300	52.58	4.90	25.54	11.81	—	$C_{12}H_{13}N_5OS$
			52.36	4.73	25.45	11.64		
2c	87	>300	61.22	4.99	19.78	9.00	—	$C_{18}H_{17}N_5OS$
			61.54	4.84	19.94	9.12		
2d	72	192—193	53.55	4.61	19.50	10.95	—	$C_{13}H_{14}N_4O_2S$
			53.79	4.83	19.31	11.03		
4a	61	144—145	52.90	4.92	22.22	9.91	—	$C_{14}H_{15}N_5O_2S$
			52.98	4.76	22.07	10.10		

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)					Molecular formula
			C	H	N	S	Cl	
4b	82	256—258	54.19	4.99	21.30	9.92	—	$C_{15}H_{17}N_5O_2S$
			54.37	5.17	21.13	9.68		
4c	83	263—264	62.05	5.33	17.43	8.06	—	$C_{21}H_{21}N_5O_2S$
			61.90	5.19	17.19	7.87		
4d	70	141—143	60.29	4.70	18.12	8.59	—	$C_{19}H_{17}N_5O_2S$
			60.14	4.52	18.46	8.45		
4e	95	284—285	61.21	4.69	17.70	7.91	—	$C_{20}H_{19}N_5O_2S$
			61.05	4.87	17.80	8.15		
4f	98	>300	66.70	5.11	14.80	6.62	—	$C_{26}H_{23}N_5O_2S$
			66.51	4.94	14.91	6.83		
4g	84	139—140	61.21	4.99	18.01	8.29	—	$C_{20}H_{19}N_5O_2S$
			61.05	4.87	17.80	8.15		
4h	93	271—272	61.78	5.35	17.05	8.06	—	$C_{21}H_{21}N_5O_2S$
			61.90	5.19	17.19	7.87		
4i	90	>300	67.24	5.39	14.59	6.59	—	$C_{27}H_{25}N_5O_2S$
			67.06	5.21	14.48	6.63		
4j	75	135—136	55.31	4.03	16.70	7.50	8.40	$C_{19}H_{16}ClN_5O_2S$
			55.14	3.90	16.92	7.75	8.57	
4k	96	266—268	55.98	4.10	16.60	7.70	8.51	$C_{20}H_{18}ClN_5O_2S$
			56.14	4.24	16.37	7.49	8.29	
4l	93	>300	61.78	4.49	13.71	6.21	7.24	$C_{26}H_{22}ClN_5O_2S$
			61.90	4.40	13.90	6.35	7.03	
5a	69	290—292	56.27	4.21	23.05	10.98	—	$C_{14}H_{13}N_5OS$
			56.17	4.38	23.39	10.71		
5b	71	>300	57.30	4.99	22.20	9.99	—	$C_{15}H_{15}N_5OS$
			57.49	4.82	22.35	10.23		
5c	78	>300	64.30	5.10	17.75	8.05	—	$C_{21}H_{19}N_5OS$
			64.14	4.92	17.98	8.23		
5d	79	>300	63.22	4.35	19.21	9.05	—	$C_{19}H_{15}N_5OS$
			63.14	4.18	19.38	8.87		
5e	88	>300	64.13	4.70	18.50	8.42	—	$C_{20}H_{17}N_5OS$
			63.98	4.56	18.65	8.54		
5f	80	>300	69.32	4.82	15.77	7.34	—	$C_{26}H_{21}N_5OS$
			69.16	4.69	15.51	7.10		
5g	80	>300	64.05	4.72	18.41	8.39	—	$C_{20}H_{17}N_5OS$
			63.98	4.56	18.65	8.54		
5h	74	>300	64.61	5.08	18.20	8.09	—	$C_{21}H_{19}N_5OS$
			64.76	4.92	17.98	8.23		
5i	85	>300	69.52	4.82	15.31	7.05	—	$C_{27}H_{23}N_5OS$
			69.66	4.98	15.04	6.89		
5j	71	>300	57.49	3.41	17.79	8.00	8.71	$C_{19}H_{14}ClN_5OS$
			57.65	3.56	17.69	8.10	8.96	
5k	74	>300	58.45	4.02	17.00	7.91	8.51	$C_{20}H_{16}ClN_5OS$
			58.61	3.93	17.09	7.82	8.65	
5l	68	>300	64.42	4.22	14.65	6.85	7.02	$C_{26}H_{20}ClN_5OS$
			64.26	4.15	14.41	6.60	7.29	
5p	42	143—145	66.20	5.11	13.21	7.84	—	$C_{23}H_{22}N_4O_2S$
			66.01	5.30	13.39	7.66		
5q	41	164—165	66.50	5.74	12.71	7.64	—	$C_{24}H_{24}N_4O_2S$
			66.64	5.59	12.95	7.41		
5r	40	171—173	66.71	4.91	12.42	7.33	—	$C_{24}H_{22}N_4O_3S$
			64.56	4.97	12.55	7.18		

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)					Molecular formula
			C	H	N	S	Cl	
5s	45	162—163	66.48	5.64	12.69	7.54	—	$C_{24}H_{24}N_4O_2S$
			66.64	5.59	12.95	7.41		
5t	50	152—153	67.12	6.05	12.79	7.38	—	$C_{25}H_{26}N_4O_2S$
			67.24	5.87	12.55	7.18		
5u	34	205—206	65.34	5.15	12.39	7.15	—	$C_{25}H_{24}N_4O_3S$
			65.20	5.25	12.16	6.96		
5v	47	165—167	61.14	4.80	12.64	7.00	7.99	$C_{23}H_{21}ClN_4O_2S$
			60.99	4.67	12.37	7.08	7.83	
5w	53	179—180	61.58	4.90	11.89	7.06	7.78	$C_{24}H_{23}ClN_4O_2S$
			61.73	4.96	12.00	6.87	7.59	
5x	40	209—211	59.81	4.55	11.79	6.33	7.11	$C_{24}H_{21}ClN_4O_3S$
			59.93	4.40	11.65	6.67	7.37	
8a	57	172—173	53.80	5.40	24.42	11.23	—	$C_{13}H_{15}N_5OS$
			53.96	5.23	24.20	11.08		
8b	52	183—185	55.30	5.48	23.19	10.80	—	$C_{14}H_{17}N_5OS$
			55.43	5.65	23.08	10.57		
8c	88	209—210	55.28	5.50	23.28	10.77	—	$C_{14}H_{17}N_5OS$
			55.43	5.65	23.08	10.57		
8d	80	163—165	56.89	5.89	21.95	10.33	—	$C_{15}H_{19}N_5OS$
			56.76	6.03	22.06	10.10		
8e	82	207—208	63.21	5.72	18.28	8.59	—	$C_{20}H_{21}N_5OS$
			63.30	5.58	18.45	8.45		
8f	80	205—206	64.28	6.02	17.98	7.99	—	$C_{21}H_{23}N_5OS$
			64.10	5.89	17.80	8.15		
9a	41	185—186	55.78	5.71	20.20	9.41	—	$C_{16}H_{19}N_5O_2S$
			55.64	5.54	20.27	9.28		
9b	41	218—219	56.74	5.80	19.75	8.61	—	$C_{17}H_{21}N_5O_2S$
			56.81	5.89	19.48	8.92		
9c	89	192—193	56.99	5.69	19.79	8.99	—	$C_{17}H_{21}N_5O_2S$
			56.81	5.89	19.48	8.92		
9d	62	190—191	57.71	6.09	18.92	8.45	—	$C_{18}H_{23}N_5O_2S$
			57.89	6.21	18.75	8.59		
9e	63	183—184	63.60	5.91	16.22	7.55	—	$C_{23}H_{25}N_5O_2S$
			63.43	5.79	16.08	7.36		
9f	71	178—180	64.00	5.89	15.88	7.01	—	$C_{24}H_{27}N_5O_2S$
			64.12	6.05	15.58	7.13		
10a	52	258—260	59.50	4.49	24.49	—	—	$C_{14}H_{13}N_5O_2$
			59.36	4.63	24.72			
10b	50	249—251	60.68	5.18	23.81	—	—	$C_{15}H_{15}N_5O_2$
			60.60	5.09	23.55			
11a	60	229—231	58.79	5.09	21.22	9.64	—	$C_{16}H_{17}N_5OS$
			58.70	5.23	21.39	9.79		
11b	65	205—206	59.65	5.78	20.72	9.11	—	$C_{17}H_{19}N_5OS$
			59.80	5.61	20.51	9.39		
11c	68	165—166	59.95	5.58	20.75	9.24	—	$C_{17}H_{19}N_5OS$
			59.80	5.61	20.51	9.39		
11d	71	173—174	60.69	5.87	19.89	9.00	—	$C_{18}H_{21}N_5OS$
			60.82	5.95	19.70	9.02		

Note. Imidazolylthiazolines **5m**—**o** were described earlier.[4]

Table 2. ^{1}H NMR and mass spectra of the compounds obtained

Compound	δ (*J*/Hz)	*m/z* $[M]^+$
2a	7.13—7.69 (m, 8 H, Ph, $CONH_2$); 7.34 (s, 1 H, CH, Im); 10.10, 12.43 (both br.s, 1 H each, 2 NH)	261
2b	2.83 (d, 3 H, NH<u>Me</u>, *J* = 4.6); 7.12—7.74 (m, 6 H, Ph, NH); 7.76 (s, 1 H, CH, Im); 10.11, 10.41 (both br.s, 1 H each, 2 NH)	275
2c	2.31 (s, 1 H, Me); 7.09—7.56 (AA´BB´, 4 H, Ar, *J* = 8.2); 7.17—7.80 (m, 5 H, Ph); 7.83 (s, 1 H, CH, Im); 9.58, 10.11, 12.46, 12.85 (all br.s, 1 H each, 4 NH)	351
2d	1.35 (t, 3 H, OCH_2<u>Me</u>, *J* = 7.0); 4.37 (q, 2 H, OC<u>H_2</u>Me, *J* = 7.0); 7.20—7.68 (m, 5 H, Ph); 7.95 (s, 1 H, CH, Im); 9.19, 12.43, 13.53 (all br.s, 1 H each, 3 NH)	290
4a	1.40 (s, 3 H, Me); 3.17—3.32 (AB, 2 H, CH_2, *J* = 11.4); 6.30 (s, 1 H, OH); 6.37, 6.93 (both br.s, 1 H each, $CONH_2$); 7.36 (s, 1 H, CH, Im); 7.32—7.44 (m, 5 H, Ph); 12.25 (br.s, 1 H, NH, Im)	317
4b	1.41 (s, 3 H, Me); 2.35 (d, 3 H, NH<u>Me</u>, *J* = 4.9); 3.28—3.49 (AB, 2 H, CH_2, *J* = 11.4); 7.39 (s, 1 H, CH, Im); 7.33—7.50 (m, 7 H, Ph, OH, N<u>H</u>Me); 12.28 (br.s, 1 H, NH, Im)	331
4c	1.35, 2.24 (both s, 3 H each, 2 Me); 3.26—3.45 (AB, 2 H, CH_2, *J* = 11.4); 6.35 (s, 1 H, OH); 6.54—6.89 (AA´BB´, 4 H, Ar, *J* = 8.2); 7.44—7.46 (m, 6 H, Ph, CH, Im); 9.51 (br.s, 1 H, NH); 12.46 (br.s, 1 H, NH, Im)	407
4d	3.45—3.65 (AB, 2 H, CH_2, *J* = 11.9); 6.47, 7.01 (both br.s, 1 H each, $CONH_2$); 7.42 (s, 1 H, CH, Im); 7.04—7.56 (both m, 5 H each, 2 Ph); 7.55 (s, 1 H, OH); 12.31 (br.s, 1 H, NH, Im)	379
4e	2.36 (d, 3 H, NH<u>Me</u>, *J* = 4.9); 3.44—3.70 (AB, 2 H, CH_2, *J* = 11.6); 7.39 (s, 1 H, CH, Im); 7.10—7.56 (m, 11 H, 2 Ph, OH); 7.46 (br.s, 1 H, N<u>H</u>Me); 12.37 (br.s, 1 H, NH, Im)	393
4f	2.21 (s, 3 H, Me); 3.49—3.75 (AB, 2 H, CH_2, *J* = 11.9); 6.53—6.82 (AA´BB´, 4 H, Ar, *J* = 8.2); 7.15—7.56 (m, 11 H, 2 Ph, OH); 7.52 (s, 1 H, CH, Im); 9.52 (br.s, 1 H, NH); 12.55 (br.s, 1 H, NH, Im)	469
4g	2.24 (s, 3 H, Me); 3.40—3.65 (AB, 2 H, CH_2, *J* = 11.9); 6.47 (br.s, 1 H, $CONH_2$); 6.99—7.07 (m, 5 H, Ar, $CONH_2$); 7.23—7.45 (m, 5 H, Ph); 7.50 (s, H, CH, Im); 12.32 (br.s, 1 H, NH, Im)	393
4h	2.24 (s, 3 H, Me); 3.43—3.69 (AB, 2 H, CH_2, *J* = 11.9); 7.03 (d, 2 H, Ar, *J* = 7.9); 7.12—7.48 (m, 10 H, Ar, OH, CH, Im); 12.36 (br.s, 1 H, NH, Im)	407
4i	2.22, 2.24 (both s, 3 H each, 2 Me); 3.44—3.71 (AB, 2 H, CH_2, *J* = 11.9); 6.52—6.85 (AA´BB´, 4 H, Ar, *J* = 8.2); 7.01—7.40 (AA´BB´, 4 H, Ar, *J* = 7.9); 7.12—7.29 (m, 6 H, Ph, OH); 7.51 (s, 1 H, CH, Im); 9.52, 12.55 (both br.s, 1 H each, 2 NH)	483
4j	3.44—3.68 (AB, 2 H, CH_2, *J* = 11.9); 6.49, 6.99 (both br.s, 1 H each, $CONH_2$); 7.04—7.28 (m, 7 H, Ar); 7.34, 7.42 (both s, 1 H each, OH, CH, Im); 7.56 (d, 2 H, Ar, *J* = 8.6); 12.36 (br.s, 1 H, NH, Im)	413
4k	2.38 (d, 3 H, NH<u>Me</u>, *J* = 4.9); 3.45—3.70 (AB, 2 H, CH_2, *J* = 11.9); 7.15—7.31 (m, 9 H, Ar, N<u>H</u>Me); 7.32, 7.39 (both s, 1 H each, OH, CH, Im); 7.56 (d, 2 H, Ar, *J* = 8.8); 12.38 (br.s, 1 H, NH, Im)	427
4l	2.22 (s, 3 H, Me); 3.47—3.74 (AB, 2 H, CH_2, *J* = 11.6); 6.52—6.83 (AA´BB´, 4 H, Ar, *J* = 8.2); 7.51 (s, 1 H, CH, Im); 7.34—7.54 (m, 10 H, Ar, OH); 9.49, 12.57 (both br.s, 1 H each, 2 NH)	503
5a	1.93 (d, 3 H, Me, *J* = 0.9); 6.41, 6.96 (both br.s, 1 H each, $CONH_2$); 6.16 (br.s, 1 H, $CH_{thiazol}$); 7.34—7.58 (m, 5 H, Ph); 7.43 (s, 1 H, CH, Im); 12.31 (br.s, 1 H, NH, Im)	299
5b[a]	1.95 (d, 3 H, Me, *J* = 0.9); 2.39 (d, 3 H, NH<u>Me</u>, *J* = 4.6); 6.16 (br.s, 1 H, $CH_{thiazol}$); 7.57 (s, 1 H, CH, Im); 7.34—7.58 (m, 6 H, Ph, N<u>H</u>Me); 12.32 (br.s, 1 H, NH, Im);	313
5c	1.95, 2.25 (both s, 3 H each, 2 Me); 6.21 (br.s, 1 H, $CH_{thiazol}$); 6.57—6.87 (AA´BB´, 4 H, Ar, *J* = 7.9); 7.38—7.77 (m, 6 H, Ph, CH, Im); 9.54 (br.s, 1 H, NH); 12.52 (br.s, 1 H, NH, Im);	389
5d	6.61, 7.04 (both br.s, 1 H each, $CONH_2$); 7.16—7.40 (both m, 5 H each, 2 Ph); 6.58, 7.42 (both s, 1 H each, $CH_{thiazol}$, CH, Im); 12.40 (br.s, 1 H, NH, Im)	361
5e	2.45 (d, 3 H, NH<u>Me</u>, *J* = 4.9); 7.18—7.50 (m, 11 H, 2 Ph, N<u>H</u>Me); 6.65, 7.52 (both s, 1 H each, $CH_{thiazol}$, CH, Im); 12.46 (br.s, 1 H, NH, Im)	375
5f	2.24 (s, 3 H, Me); 6.60—6.88 (AA´BB´, 4 H, Ar, *J* = 8.2); 7.07—7.43 (both m, 5 H each, 2 Ph); 6.58, 7.57 (both s, 1 H each, CH, Im, $CH_{thiazol}$); 9.47, 12.59 (both br.s, 1 H each, NH)	451
5g	2.24 (s, 3 H, Me); 6.61 (s, 1 H, $CONH_2$); 6.99—7.07 (m, 5 H, Ar, $CONH_2$); 7.22—7.42 (m, 5 H, Ph); 6.53, 7.51 (both s, 1 H each, $CH_{thiazol}$, CH, Im); 12.39 (br.s, 1 H, NH, Im)	375
5h	2.24 (s, 3 H, Me); 2.45 (d, 3 H, NH<u>Me</u>, *J* = 4.9); 6.99—7.09 (AA´BB´, 4 H, Ar, *J* = 8.2); 6.56, 7.50 (both s, 1 H each, $CH_{thiazol}$, CH, Im); 7.27—7.53 (m, 6 H, Ph, N<u>H</u>Me); 12.42 (br.s, 1 H, NH, Im)	389
5i	2.23, 2.24 (both s, 3 H each, 2 Me); 6.61—6.90 (AA´BB´, 4 H, Ar, *J* = 8.2); 6.93—7.01 (m, 4 H, Ar); 7.01—7.43 (m, 5 H, Ph); 6.54, 7.59 (both s, 2 H, $CH_{thiazol}$, CH, Im); 9.47 (br.s, 1 H, NH); 12.59 (br.s, 1 H, NH, Im)	465
5j	6.61, 7.02 (both br.s, 1 H each, $CONH_2$); 7.15—7.53 (m, 9 H, Ar); 6.64, 7.50 (both s, 1 H each, $CH_{thiazol}$, CH, Im); 12.40 (br.s, 1 H, NH, Im)	395

(*to be continued*)

Table 2 (*continued*)

Compound	δ (*J*/Hz)	*m/z* $[M]^+$
5k	2.46 (d, 3 H, NHMe, *J* = 4.9); 6.62, 7.46 (both s, 1 H each, $CH_{thiazol}$, CH, Im); 7.15—7.59 (m, 10 H, Ar, NHMe); 12.43 (br.s, 1 H, NH, Im)	409
5l[b]	2.23 (s, 3 H, Me); 6.60—6.91 (AA´BB´, 4 H, Ar, *J* = 8.2); 6.68, 7.61 (both s, 1 H each, $CH_{thiazol}$, CH, Im); 7.10—7.23 (AA´BB´, 4 H, Ar, *J* = 8.6); 7.35—7.45 (m, 5 H, Ph); 9.45, 12.63 (both br.s, 1 H each, NH)	485
5p	1.04, 1.36 (both t, 3 H each, OCH_2Me, NCH_2Me, *J* = 7.2); 4.11, 4.27 (both q, 2 H each, OCH_2Me, NCH_2Me, *J* = 7.2); 6.25 (s, 1 H, $CH_{thiazol}$); 7.07—7.34 (both m, 5 H each, 2 Ph); 7.48 (s, 1 H, CH, Im)	418
5q	0.87 (t, 3 H, NCH_2CH_2Me, *J* = 7.3); 1.04 (t, 3 H, OCH_2Me, *J* = 7.0); 1.76 (tq, 2 H, NCH_2CH_2Me, *J*´ = 7.0, *J*″ = 7.3); 4.12, 4.19 (both q, 2 H each, NCH_2CH_2Me, OCH_2Me, *J* = 7.0); 6.26 (s, 1 H, $CH_{thiazol}$); 7.10—7.34 (both m, 5 H each, 2 Ph); 7.46 (s, 1 H, CH, Im)	432
5r	1.03 (t, 3 H, OCH_2Me, *J* = 7.3); 2.22 (s, 3 H, NCH_2COMe); 4.08 (q, 2 H, OCH_2Me, *J* = 7.3); 5.07 (s, 2 H, NCH_2COMe); 6.43 (s, 1 H, $CH_{thiazol}$); 7.12—7.44 (both m, 5 H each, 2 Ph); 7.69 (s, 1 H, CH, Im)	446
5s	1.04 (t, 3 H, OCH_2Me, *J* = 7.2); 1.36 (t, 3 H, NCH_2Me, *J* = 7.0); 2.26 (s, 3 H, Me); 4.09 (q, 2 H, OCH_2Me, *J* = 7.2); 4.26 (q, 2 H, NCH_2Me, *J* = 7.0); 6.20 (s, 1 H, $CH_{thiazol}$); 6.90—7.00 (m, 4 H, Ar); 7.25—7.35 (m, 5 H, Ph); 7.47 (s, 1 H, CH, Im)	432
5t	0.87 (t, 3 H, NCH_2CH_2Me, *J* = 7.3); 1.03 (t, 3 H, OCH_2Me, *J* = 7.0); 1.75 (tq, 2 H, NCH_2CH_2Me, *J*´ = 7.0, *J*″ = 7.3); 2.26 (s, 3 H, Me); 4.09 (q, 2 H, OCH_2Me, *J* = 7.0); 4.18 (t, 2 H, NCH_2CH_2Me, *J* = 7.0); 6.21 (s, 1 H, $CH_{thiazol}$); 6.92—7.00 (m, 4 H, Ar); 7.24—7.34 (m, 5 H, Ph); 7.45 (s, 1 H, CH, Im)	446
5u	1.02 (t, 3 H, OCH_2Me, *J* = 7.3); 2.22, 2.27 (both s, 3 H each, Me, NCH_2COMe); 4.08 (q, 2 H, OCH_2Me, *J* = 7.3); 5.07 (s, 2 H, NCH_2COMe); 6.39 (s, 1 H, $CH_{thiazol}$); 6.98—7.19 (m, 4 H, Ar); 7.21—7.26 (m, 5 H, Ph); 7.68 (s, 1 H, CH, Im)	460
5v	1.04, 1.36 (both t, 3 H each, OCH_2Me, NCH_2Me, *J* = 7.0); 4.12, 4.27 (both q, 2 H each, NCH_2CH_2Me, OCH_2Me, *J* = 7.0); 6.26 (s, 1 H, CH); 7.03—7.17 (AA´BB´, 4 H, Ar, *J* = 8.5); 7.23—7.37 (m, 5 H, Ph); 7.48 (s, 1 H, CH, Im)	452
5w	0.87 (t, 3 H, NCH_2CH_2Me, *J* = 7.4); 1.03 (t, 3 H, OCH_2Me, *J* = 7.3); 1.73 (tq, 2 H, NCH_2CH_2Me, *J*´ = 7.0, *J*″ = 7.4); 4.09 (q, 2 H, OCH_2Me, *J* = 7.3); 4.19 (t, 2 H, NCH_2CH_2Me, *J* = 7.0); 6.26 (s, 1 H, $CH_{thiazol}$); 7.00—7.17 (AA´BB´, 4 H, Ar, *J* = 8.5); 7.21—7.33 (m, 5 H, Ph); 7.45 (s, 1 H, CH, Im)	466
5x	1.02 (t, 3 H, OCH_2Me, *J* = 7.0); 2.27 (s, 3 H, NCH_2COMe); 4.08 (q, 2 H, OCH_2Me, *J* = 7.0); 5.04 (s, 2 H, NCH_2COMe); 6.42 (s, 1 H, $CH_{thiazol}$); 7.18—7.03 (AA´BB´, 4 H, Ar, *J* = 8.1); 7.46—7.26 (m, 5 H, Ph); 7.70 (s, 1 H, CH, Im)	480
8a	1.35 (t, 3 H, SCH_2Me, *J* = 7.3); 2.99 (q, 2 H, SCH_2Me, *J* = 7.3); 7.21—7.47 (m, 5 H, Ph); 6.20, 8.70 (both br.s, 1 H each, $CONH_2$); 7.51 (s, 1 H, CH, Im); 11.83, 12.36 (both br.s, 1 H each, 2 NH)	289
8b	0.96 (t, 3 H, SCH_2CH_2Me, *J* = 7.3); 1.70 (tq, 2 H, SCH_2CH_2Me, *J*´ = *J*″ = 7.3); 2.97 (t, 2 H, SCH_2CH_2Me, *J* = 7.3); 6.16, 8.69 (both br.s, 1 H each, $CONH_2$); 7.27—7.40 (m, 5 H, Ph); 7.51 (s, 1 H, CH, Im); 11.83, 12.38 (both br.s, 1 H each, 2 NH)	303
8c	1.36 (t, 3 H, SCH_2Me, *J* = 7.6); 2.96 (q, 2 H, SCH_2Me, *J* = 7.6); 3.03 (d, 3 H, NHMe, *J* = 4.1); 7.26—7.41 (m, 5 H, Ph); 7.49 (s, 1 H, CH, Im); 8.85 (br.s, 1 H, NHMe); 11.76, 12.24 (both br.s, 1 H each, 2 NH)	303
8d	1.05 (t, 3 H, SCH_2CH_2Me, *J* = 7.3); 1.78 (tq, 2 H, SCH_2CH_2Me, *J*´ = *J*″ = 7.3); 3.00 (t, 2 H, SCH_2CH_2Me, *J* = 7.3); 3.03 (d, 3 H, NHMe, *J* = 4.9); 7.28—7.41 (m, 5 H, Ph); 7.49 (s, 1 H, CH, Im); 8.81 (br.s, 1 H, NHMe); 11.79, 12.30 (both br.s, 1 H each, 2 NH)	317
8e	1.32 (t, 3 H, SCH_2Me, *J* = 7.3); 2.30 (s, 3 H, Me); 3.14 (q, 2 H, SCH_2Me, *J* = 7.3); 7.10 (d, 2 H, Ar, *J* = 8.2); 7.20—7.45 (m, 7 H, Ph, Ar); 7.58 (s, 1 H, CH, Im); 10.23, 12.07, 12.93 (all br.s, 1 H each, 3 NH)	379
8f	0.99 (t, 3 H, SCH_2CH_2Me, *J* = 7.3); 1.70 (tq, 2 H, SCH_2CH_2Me, *J*´ = *J*″ = 7.3); 3.16 (t, 2 H, SCH_2CH_2Me, *J* = 7.3); 7.12—7.46 (m, 5 H, Ph); 7.12—7.54 (AA´BB´, 4 H, Ph); 7.35 (s, 1 H, CH, Im); 10.49, 11.97, 12.03 (all br.s, 1 H each, 3 NH)	393
9a	1.33 (t, 3 H, SCH_2Me, *J* = 7.3); 2.12 (s, 3 H, NCH_2COMe); 2.98 (q, 2 H, SCH_2Me, *J* = 7.3); 5.13 (s, 2 H, NCH_2COMe); 5.65, 8.83 (both br.s, 1 H each, $CONH_2$); 7.23—7.40 (m, 6 H, Ph, CH, Im); 11.71 (br.s, 1 H, NH)	345
9b	0.98 (t, 3 H, SCH_2CH_2Me, *J* = 7.3); 1.70 (tq, 2 H, SCH_2CH_2Me, *J*´ = *J*″ = 7.3); 2.29 (s, 3 H, NCH_2COMe); 2.98 (t, 2 H, SCH_2CH_2Me, *J* = 7.3); 5.13 (s, 2 H, NCH_2COMe); 5.39, 8.80 (both br.s, 1 H each, $CONH_2$); 7.31—7.41 (m, 5 H, Ph); 7.34 (s, 1 H, CH, Im); 11.68 (br.s, 1 H, NH)	359
9c	1.38 (t, 3 H, SCH_2Me, *J* = 7.3); 2.30 (s, 3 H, NCH_2COMe); 2.90 (d, 3 H, NHMe, *J* = 5.2); 2.97 (q, 2 H, SCH_2Me, *J* = 7.3); 5.14 (s, 2 H, NCH_2COMe); 7.36 (s, 1 H, CH, Im); 7.24—7.40 (m, 5 H, Ph); 9.09, 11.65 (both br.s, 1 H each, NHMe, NH)	359

(*to be continued*)

Table 2 (*continued*)

Compound	δ (*J*/Hz)	*m/z* $[M]^+$
9d	1.05 (t, 3 H, $SCH_2CH_2\underline{Me}$, $J = 7.3$); 1.75 (tq, 2 H, $SCH_2C\underline{H}_2Me$, $J' = J'' = 7.3$); 2.29 (s, 3 H, $NCH_2CO\underline{Me}$); 2.91 (d, 3 H, $NH\underline{Me}$, $J = 5.1$); 2.99 (t, 2 H, $SC\underline{H}_2CH_2Me$, $J = 7.3$); 5.14 (s, 2 H, $NC\underline{H}_2COMe$); 7.32 (s, 1 H, CH, Im); 7.22—7.40 (m, 5 H, Ph); 9.04, 11.66 (both br.s, 1 H each, NH, $N\underline{H}Me$)	373
9e	1.29 (t, 3 H, $SCH_2\underline{Me}$, $J = 7.2$); 2.30, 2.31 (both s, 3 H each, Me, $NCH_2CO\underline{Me}$); 3.12 (q, 2 H, $SC\underline{H}_2Me$, $J = 7.2$); 5.17 (s, 2 H, $NC\underline{H}_2COMe$); 7.12 (d, 2 H, Ar, $J = 8.3$); 7.31 (s, 1 H, CH, Im); 7.33—7.40 (m, 7 H, Ph, Ar); 10.71, 11.84 (both br.s, 1 H each, 2 NH)	435
9f	0.95 (t, 3 H, $SCH_2CH_2\underline{Me}$, $J = 7.3$); 1.65 (tq, 2 H, $SCH_2C\underline{H}_2Me$, $J' = J'' = 7.3$); 2.30 (s, 6 H, $NCH_2CO\underline{Me}$, Me); 3.10 (t, 2 H, $SC\underline{H}_2CH_2Me$, $J = 7.3$); 5.14 (s, 2 H, $NC\underline{H}_2COMe$); 7.13 (d, 2 H, Ar, $J = 8,2$); 7.35 (s, 1 H, CH, Im); 7.23—7.41 (m, 7 H, Ph, Ar); 11.86, 10.73 (both br.s, 1 H each, 2 NH)	449
10a	2.20 (s, 3 H, $NCH_2CO\underline{Me}$); 5.18 (s, 2 H, $NC\underline{H}_2COMe$); 7.00—7.67 (m, 5 H, Ph); 7.81 (s, 1 H, CH, Im); 8.45, 10.63 (both br.s, 1 H each, 2 NH)	283
10b	2.21, 3.52 (both s, 3 H each, Me, $NCH_2CO\underline{Me}$); 5.19 (s, 2 H, $NC\underline{H}_2COMe$); 7.02—7.58 (m, 5 H, Ph); 7.79 (s, 1 H, CH, Im); 8.40 (br.s, 1 H, NH)	297
11a	1.36 (t, 3 H, $SCH_2\underline{Me}$, $J = 7.3$); 2.11 (s, 3 H, Me); 3.26 (q, 2 H, $SC\underline{H}_2Me$, $J = 7.3$); 7.18—7.43 (m, 6 H, Ph, NH); 6.68, 7.66 (both s, 1 H each, CH, Im, CH); 10.25 (br.s, 1 H, NH)	327
11b	1.01 (t, 3 H, $SCH_2CH_2\underline{Me}$, $J = 6.7$); 1.74 (tq, 2 H, $SCH_2C\underline{H}_2Me$, $J' = J'' = 6.7$); 2.08 (s, 3 H, Me); 3.20 (t, 2 H, $SC\underline{H}_2Me$, $J = 6.7$); 7.17—7.43 (m, 6 H, Ph, NH); 6.69, 7.67 (both s, 1 H each, CH, CH, Im); 10.21 (br.s, 1 H, NH)	341
11c	1.40 (t, 3 H, $SCH_2\underline{Me}$, $J = 7.3$); 3.28 (q, 2 H, $SC\underline{H}_2Me$, $J = 7.3$); 2.19, 3.40 (both s, 3 H each, Me, NMe); 6.67, 7.52 (both s, 1 H each, CH, CH, Im); 7.14—7.40 (m, 5 H, Ph); 11.20 (br.s, 1 H, NH)	341
11d	1.03 (t, 3 H, $SCH_2CH_2\underline{Me}$, $J = 7.4$); 1.75 (tq, 2 H, $SCH_2C\underline{H}_2Me$, $J' = J'' = 7.4$); 2.18, 3.40 (both s, 3 H each, Me, NMe); 3.29 (m, 2 H, $SC\underline{H}_2CH_2Me$); 6.66, 7.50 (both s, 1 H each, CH, CH, Im); 7.17—7.34 (m, 5 H, Ph); 11.21 (br.s, 1 H, NH)	355

[a] ^{13}C NMR (100 MHz, DMSO-d_6), δ: 14.59, 24.62, 98.44, 112.05, 128.61, 128.85, 129.59, 133.44, 133.51, 137.62, 146.16, 159.61, 160.40.

[b] Spectroscopic data for imidazolylthiazolines **5m—o** were reported earlier.[4]

isothioureas **9a—f** (Scheme 2). To confirm the structures of these products, their cyclization reactions were carried out under acidic and basic conditions. It turned out that in the presence of 1% KOH in ethanol, they lose an alkanethiol molecule to give purine derivatives **10a,b**, which were characterized by ^1H NMR spectra. In acetic acid, compounds **9a—f** undergo cyclization into imidazopyrazinones **11a—d**. The structures of the latter were confirmed by their ^1H NMR (δ: 6.66—6.69, s, CH) and mass spectra containing the corresponding molecular ion peaks. In addition, the participation of the carbamoyl group in both cyclizations is evident from the absence of a signal for the NH proton of the amide fragment in the ^1H NMR spectra of compounds **9a—f** and **10a—d**. The Me protons in compounds **10b** and **11c,d** are manifested as a singlet, in contrast to a doublet for the corresponding intermediates (see Table 1). The formation of compounds **11a—d** indicates that chloroacetone alkylates 5-imidazolylisothioureides **8a—f** at position 3 of the imidazole ring.

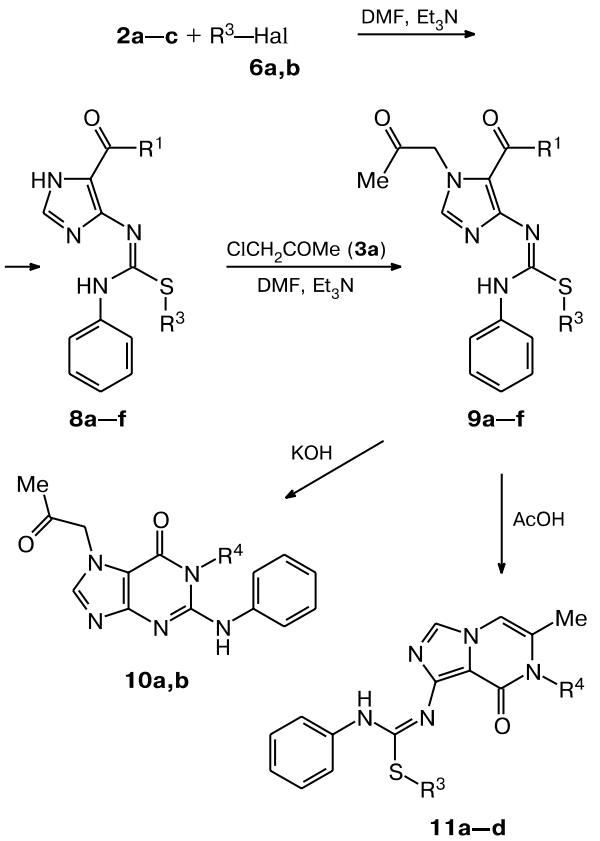
To prove the configuration of the C=N bond in products **8a—f**, **9a—f**, and **11a—d**, a number of IR experiments was performed under the assumption that these compounds can be stabilized in a fixed geometry by intramolecular hydrogen bonding.

No intermolecular associates are known to form in low concentrations in inert solvents, while intramolecular bonds and the corresponding absorption bands in the IR spectra are retained even in the lowest concentrations.[5] In addition, the hydrogen bonding causes a slight shift of the absorption band to the lower frequencies.[5—7]

In the IR spectra of compounds **8c**, **9c**, and **11c**, the NH stretching vibrations are manifested as the absorption bands at 3460, 3260 (**8c**), 3440, 3270 (**9c**), and 3200 cm^{-1} (**11c**). Being somewhat lower than the frequencies characteristic of amines (3500—3300 cm^{-1}),[5—7] such values suggest the presence of hydrogen bonding in these compounds. It was found that the ν(NH) bands in the IR spectra are virtually insensitive to a change in the concentrations of the samples studied in CCl_4 from 10^{-2} to 10^{-5} mol L^{-1}, which allows this hydrogen bond in compounds **8c**, **9**, and **11c** to be regarded as intramolecular. Apparently, all the products **8a—f**, **9a—f**, and **11a—d** are *E*-isomers.

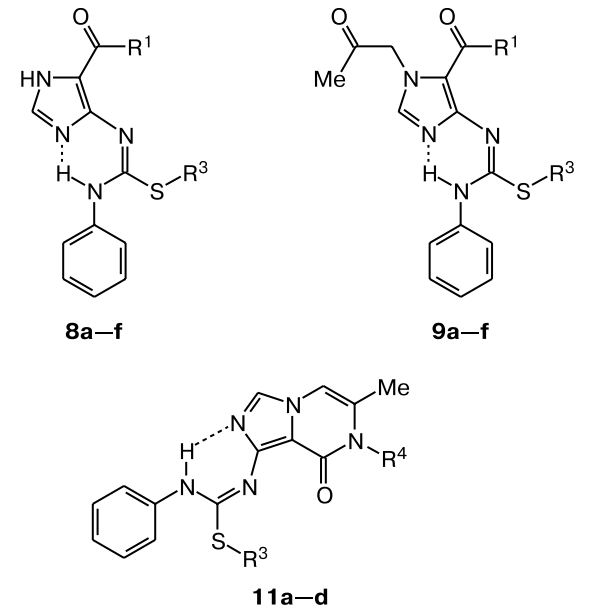
Thus, through the chemiselective blocking of the most reactive site of imidazolylthiourea by alkyl residues, we obtained and isolated 4-hydroxy-2-imidazolylimino-thiazolidines **4a—l** and synthesized a wide range of 2-imidazolylimino-Δ^4-thiazolines **5a—x**, which are struc-

Scheme 2



8, 9, 11	R^1	R^3	R^4	8, 9	R^1	R^3
a	NH_2	Et	H	**e**	NHC_6H_4Me-*p*	Et
b	NH_2	Pr	H	**f**	NHC_6H_4Me-*p*	Pr
c	NHMe	Et	Me			
d	NHMe	Pr	Me			

10: R^4 = H (**a**), Me (**b**)



tural analogs of biologically active antipyryliminothiazolines. The successive reactions of imidazolylthioureas **2a—c** with alkyl halides and chloroacetone give (*N*-oxopropylimidazolyl)isothioureas **8a—f** used in the synthesis of a number of purine and imidazopyrazinone derivatives.

We found that the alkylation of 4-carbamoylimidazolylthioureas **2** involves the sulfur atom, while the corresponding esters yield *N*-derivatives of imidazole. This difference can be due to the stronger electron-withdrawing properties of the ester group.

Experimental

^{1}H NMR spectra were recorded on a Bruker WM-250 instrument (250.13 MHz) in DMSO-d_6 (**1c**, **4a—l**, **5a—l**, and **10a—b**) and $CDCl_3$ (**5p—x**, **8a—f**, **9a—f**, and **11a—d**) with Me_4Si as the internal standard. The 2D ^{1}H—^{1}H COSY ^{13}C—^{1}H HETCOR NMR spectra of compounds **5m—o** were recorded on a Bruker DRX-500 instrument (500.13 (^{1}H) and 125.76 MHz (^{13}C)) in $CDCl_3$. The signals of the solvent (δ_C 76.900, δ_H = 7.26) were used as the internal standards. IR spectra were recorded on a Specord IR75 instrument (KBr pellets and solutions in CCl_4 in NaCl cells (1.01 mm)). The course of the reaction was monitored and the purity of the products was checked by TLC on Sorbfil UV-254 plates in ethyl acetate. Mass spectra (EI, 70 eV) were recorded on a Varian MAT 311A instrument. Melting points are given uncorrected. The starting derivatives of 5-aminoimidazole-4-carboxylic acid (**1a**, [8] **1b**, [9] and **1d** [10]) were prepared according to known procedures.

N-*p*-Tolyl-5-aminoimidazole-4-carboxamide hydrochloride **1c** was synthesized as described below by reduction of the corresponding nitro derivative prepared from 5-nitroimidazole-4-carboxylic acid.[11]

***N*-*p*-Tolyl-5-nitroimidazole-4-carboxamide.** Phosphorus pentachloride (13.28 g, 0.064 mol) was added to a solution of 5-nitroimidazole-4-carboxylic acid (10 g, 0.064 mol) in 100 mL of anhydrous benzene. The reaction mixture was refluxed for 1.5 h in a water bath and cooled to ~20 °C. *p*-Toluidine (0.076 mol) was added and the resulting mixture was kept in a water bath for 2 h and then cooled. The precipitate that formed was filtered off and recrystallized from ethanol. The yield of the target product was 82%, m.p. 293—295 °C. Found (%): C, 53.50; H, 4.11; N, 23.03. $C_{11}H_{10}N_4O_3$. Calculated (%): C, 53.66; H, 4.09; N, 22.75. ^{1}H NMR, δ: 2.32 (s, 3 H, Me); 7.14—7.55 (AA´BB´, 4 H, Ar, J = 8.2 Hz); 7.77 (s, 1 H, CH, Im); 10.58 (s, 1 H, NH); 13.75 (br.s, 1 H, NH). MS, m/z (I_{rel} (%)): 246 $[M]^+$ (100).

***N*-*p*-Tolyl-5-aminoimidazole-4-carboxamide hydrochloride (1c).** *N*-(*p*-Tolyl)-5-nitroimidazole-4-carboxamide (0.04 mol) was added in portions at 0 to 5 °C to a stirred cooled solution of $SnCl_2 \cdot 2H_2O$ (46 g, 0.2 mol) in 200 mL of conc. HCl. The reaction mixture was kept for 24 h with gradual warming to room temperature. The precipitate was filtered off and dissolved in 400 mL of water. Hydrogen sulfide was passed through the resulting solution to complete precipitation of tin sulfide, which was filtered off. The filtrate was lightened with activated carbon and evaporated to dryness *in vacuo*. The residue was recrystallized from ethanol to give compound **1c** in 70% yield, m.p. 193—195 °C. Found (%): C, 52.10; H, 5.11; N, 21.82.

$C_{11}H_{12}N_4O \cdot HCl$. Calculated (%): C, 52.28; H, 5.19; N, 22.17. ^1H NMR, δ: 2.29 (s, 3 H, Me); 6.34 (br.s, 2 H, NH_2); 7.07—7.67 (AA´BB´, 4 H, Ar, J = 8.2 Hz); 8.62 (s, 1 H, CH, Im); 10.53 (s, 1 H, NH); 14.18 (br.s, 1 H, NH). MS, m/z (I_{rel} (%)): 216 $[M]^+$ (85).

5-(3-Phenylthioureido)-3*H*-imidazole-4-carboxamide (2a), *N*-methyl-5-(3-phenylthioureido)-3*H*-imidazole-4-carboxamide (2b), and *N*-*p*-tolyl-5-(3-phenylthioureido)-3*H*-imidazole-4-carboxamide (2c). Triethylamine (1.03 g, 10.2 mmol) and phenyl isothiocyanate (0.46 g, 3.4 mmol) were added to a solution of the corresponding hydrochloride **1a—c** (2.8 mmol) in 5 mL of DMSO. The reaction mixture was kept at ~20 °C for 12 h. Water (50—100 mL) was added and the precipitate of imidazolyl(phenyl)thiourea that formed was filtered off. The precipitate was suspended in ethyl acetate, filtered off, and dried.

Ethyl 5-(3-phenylthioureido)-3*H*-imidazole-4-carboxylate (2d). Phenyl isothiocyanate (3.1 mmol) was added to a solution of ethyl 5-aminoimidazole-4-carboxylate hydrochloride (**1d**) (2.6 mmol) in 6 mL of pyridine. The reaction mixture was kept at 60 °C for 1 h and cooled. Water (50 mL) was added and the precipitate of imidazolyl(phenyl)thiourea that formed was filtered off and recrystallized from ethanol.

5-(4-Hydroxy-4-methyl-3-phenylthiazolidin-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (4a), *N*-methyl-5-(4-hydroxy-4-methyl-3-phenylthiazolidin-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (4b), *N*-*p*-tolyl-5-(4-hydroxy-4-methyl-3-phenylthiazolidin-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (4c), 5-(4-hydroxy-3,4-diphenylthiazolidin-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (4d), *N*-methyl-5-(4-hydroxy-3,4-diphenylthiazolidin-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (4e), *N*-*p*-tolyl-5-(4-hydroxy-3,4-diphenylthiazolidin-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (4f), 5-(4-hydroxy-3-phenyl-4-*p*-tolylthiazolidin-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (4g), *N*-methyl-5-(4-hydroxy-3-phenyl-4-*p*-tolylthiazolidin-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (4h), *N*-*p*-tolyl-5-(4-hydroxy-3-phenyl-4-*p*-tolylthiazolidin-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (4i), 5-[4-(4-chlorophenyl)-4-hydroxy-3-phenylthiazolidin-2*Z*-ylideneamino]-3*H*-imidazole-4-carboxamide (4j), *N*-methyl-5-[4-(4-chlorophenyl)-4-hydroxy-3-phenylthiazolidin-2*Z*-ylideneamino]-3*H*-imidazole-4-carboxamide (4k), and *N*-*p*-tolyl-5-[4-(4-chlorophenyl)-4-hydroxy-3-phenylthiazolidin-2*Z*-ylideneamino]-3*H*-imidazole-4-carboxamide (4l). Triethylamine (0.76 mmol) and the corresponding haloketone (0.76 mmol) were added to a solution of 5-imidazolyl(phenyl)thiourea **2a—c** (0.69 mmol) in 2 mL of DMF. The reaction mixture was kept at ~20 °C for 1 to 2 h. Water (30 mL) was added and the precipitate of hydroxy(imidazolyl)thiazolidines that formed was filtered off, washed with ethanol, and dried.

5-(4-Methyl-3-phenyl-3*H*-thiazol-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (5a), *N*-methyl-5-(4-methyl-3-phenyl-3*H*-thiazol-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (5b), *N*-*p*-tolyl-5-(4-methyl-3-phenyl-3*H*-thiazol-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (5c), 5-(3,4-diphenyl-3*H*-thiazol-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (5d), *N*-methyl-5-(3,4-diphenyl-3*H*-thiazol-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (5e), *N*-*p*-tolyl-5-(3,4-diphenyl-3*H*-thiazol-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (5f), 5-(3-phenyl-4-*p*-tolyl-3*H*-thiazol-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (5g), *N*-methyl-5-(3-phenyl-4-*p*-tolyl-3*H*-thiazol-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (5h), *N*-*p*-tolyl-5-(3-phenyl-4-*p*-tolyl-3*H*-thiazol-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxamide (5i), 5-[4-(4-chlorophenyl)-3-phenyl-3*H*-thiazol-2*Z*-ylideneamino]-3*H*-imidazole-4-carboxamide (5j), *N*-methyl-5-[4-(4-chlorophenyl)-3-phenyl-3*H*-thiazol-2*Z*-ylideneamino]-3*H*-imidazole-4-carboxamide (5k), and *N*-*p*-tolyl-5-[4-(4-chlorophenyl)-3-phenyl-3*H*-thiazol-2*Z*-ylideneamino]-3*H*-imidazole-4-carboxamide (5l). A solution or suspension of compound **4a—l** (0.70 mmol) in 5 mL of AcOH was refluxed for 1 to 4 h. The reaction mixture was diluted with cold water (30 mL) and the precipitates of compounds **5a—l** were filtered off.

Ethyl 3-ethyl-5-(3,4-diphenyl-3*H*-thiazol-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxylate (5p), ethyl 5-(3,4-diphenyl-3*H*-thiazol-2*Z*-ylideneamino)-3-propyl-3*H*-imidazole-4-carboxylate (5q), ethyl 5-(3,4-diphenyl-3*H*-thiazol-2*Z*-ylideneamino)-3-(2-oxopropyl)-3*H*-imidazole-4-carboxylate (5r), ethyl 3-ethyl-5-(3-phenyl-4-*p*-tolyl-3*H*-thiazol-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxylate (5s), ethyl 5-(3-phenyl-4-*p*-tolyl-3*H*-thiazol-2*Z*-ylideneamino)-3-propyl-3*H*-imidazole-4-carboxylate (5t), ethyl 3-(2-oxopropyl)-5-(3-phenyl-4-*p*-tolyl-3*H*-thiazol-2*Z*-ylideneamino)-3*H*-imidazole-4-carboxylate (5u), ethyl 5-[4-(4-chlorophenyl)-3-phenyl-3*H*-thiazol-2*Z*-ylideneamino]-3-ethyl-3*H*-imidazole-4-carboxylate (5v), ethyl 5-[4-(4-chlorophenyl)-3-phenyl-3*H*-thiazol-2*Z*-ylideneamino]-3-propyl-3*H*-imidazole-4-carboxylate (5w), and ethyl 5-[4-(4-chlorophenyl)-3-phenyl-3*H*-thiazol-2*Z*-ylideneamino]-3-(2-oxopropyl)-3*H*-imidazole-4-carboxylate (5x). Triethylamine (0.76 mmol) and the corresponding haloketone (0.76 mmol) were added to solutions of *N*-alkylimidazole derivatives **7a—c** (0.69 mmol) in 2 mL of DMF. The reaction mixture was kept at ~20 °C for 10 h. Water (30 mL) was added and the precipitate that formed was filtered off and dried. The isolated product was dissolved in 5 mL of AcOH, kept at 70 °C for 0.5 h, and concentrated. The residue was crystallized from aqueous ethanol to give compounds **5p—x**.

5-(2-Ethyl-3-phenyl-*E*-isothioureido)-3*H*-imidazole-4-carboxamide (8a), 5-(3-phenyl-2-propyl-*E*-isothioureido)-3*H*-imidazole-4-carboxamide (8b), *N*-methyl-5-(2-ethyl-3-phenyl-*E*-isothioureido)-3*H*-imidazole-4-carboxamide (8c), *N*-methyl-5-(3-phenyl-2-propyl-*E*-isothioureido)-3*H*-imidazole-4-carboxamide (8d), *N*-*p*-tolyl-5-(2-ethyl-3-phenyl-*E*-isothioureido)-3*H*-imidazole-4-carboxamide (8e), and *N*-*p*-tolyl-5-(3-phenyl-2-propyl-*E*-isothioureido)-3*H*-imidazole-4-carboxamide (8f). Triethylamine (0.76 mmol) and alkyl halide (0.76 mmol) were added to a solution of 5-imidazolyl(phenyl)thiourea **2a—c** (0.69 mmol) in 2 mL of DMF. The reaction mixture was kept at ~20 °C for 8 to 12 h and diluted with water. The precipitates of compounds **8** that formed were filtered off and crystallized from ethanol.

5-(2-Ethyl-3-phenyl-*E*-isothioureido)-3-(2-oxopropyl)-3*H*-imidazole-4-carboxamide (9a), 3-(2-oxopropyl)-5-(3-phenyl-2-propyl-*E*-isothioureido)-3*H*-imidazole-4-carboxamide (9b), *N*-methyl-5-(2-ethyl-3-phenyl-*E*-isothioureido)-3-(2-oxopropyl)-3*H*-imidazole-4-carboxamide (9c), *N*-methyl-3-(2-oxopropyl)-5-(3-phenyl-2-propyl-*E*-isothioureido)-3*H*-imidazole-4-carboxamide (9d), *N*-*p*-tolyl-5-(2-ethyl-3-phenyl-*E*-isothioureido)-3-(2-oxopropyl)-3*H*-imidazole-4-carboxamide (9e), and *N*-*p*-tolyl-3-(2-oxopropyl)-5-(3-phenyl-2-propyl-*E*-isothioureido)-3*H*-imidazole-4-carboxamide (9f). Triethylamine (0.07 g, 0.76 mmol) and chloroacetone (0.07 g, 0.76 mmol) were added

to a solution of imidazolylisothiourea **8a—f** (0.69 mmol) in 2 mL of DMF. The reaction mixture was kept at 70 °C for 2 to 4 h and diluted with ice water. The product was filtered off and recrystallized from aqueous ethanol.

7-(2-Oxopropyl)-2-phenylamino-1,7-dihydropurin-6-one (10a) and 1-methyl-7-(2-oxopropyl)-2-phenylamino-1,7-dihydropurin-6-one (10b). A solution of imidazolylisothiourea **9a—b** (0.76 mmol) in 3 mL of 1% KOH in ethanol was refluxed for 30 min. The reaction mixture was neutralized with 1 *N* HCl to pH 5—6 and the precipitate of the purine derivative that formed was filtered off and recrystallized from aqueous ethanol.

2-Ethyl-*E*-1-(6-methyl-8-oxo-7,8-dihydroimidazo[1,5-*a*]pyrazin-1-yl)-3-phenylisothiourea (11a), *E*-1-(6-methyl-8-oxo-7,8-dihydroimidazo[1,5-*a*]pyrazin-1-yl)-3-phenyl-2-propylisothiourea (11b), *E*-1-(6,7-dimethyl-8-oxo-7,8-dihydroimidazo[1,5-*a*]pyrazin-1-yl)-2-ethyl-3-phenylisothiourea (11c), and *E*-1-(6,7-dimethyl-8-oxo-7,8-dihydroimidazo[1,5-*a*]pyrazin-1-yl)-3-phenyl-2-propylisothiourea (11d). A solution of imidazolylisothiourea **9a—d** (0.76 mmol) in 5 mL of acetic acid was refluxed for 30 min and concentrated. The residue was crystallized from aqueous ethanol to give imidazopyrazinones **11a—d**.

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