Reactions of monothiooxamides with N-nucleophiles. Synthesis of 4,5-dihydroimidazole-2-carboxanilides

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A convenient procedure was developed for the preparation of 4,5-dihydroimidazole-2-carboxanilides by the reaction of monothiooxamides with ethylenediamine.

Key words: monothiooxamides, 4,5-dihydroimidazole-2-carboxanilides, ethylenediamine, amines.

4,5-Dihydroimidazole derivatives find application as corrosion inhibitors[1,2] and as starting compounds in the synthesis of biologically active compounds, for example, 4,5-dihydroimidazole-2-carboxanilides, possessing antihypertensive properties.[3]

Previously, a procedure has been reported[4] for the preparation of 4,5-dihydroimidazole-2-carboxanilides by reactions of ethylenediamine with monothiooxamides, which were synthesized from the corresponding oxamides under the action of the Lawesson reagent. A limitation of this procedure is that the synthesis of oxamides from low-basicity amines is performed with the use of difficultly accessible oxalyl chlorides. Imidazolines can also be prepared by prolonged boiling of chloroacetamides with ethylenediamine and sulfur in toluene.[3] A substantial drawback of the last-mentioned method is the drastic conditions of the process. Thus we managed to prepare 4,5-dihydroimidazole-2-carboxanilides bearing the thiazole ring or the sulfonamide group in the amide fragment by this method, albeit in low yields.

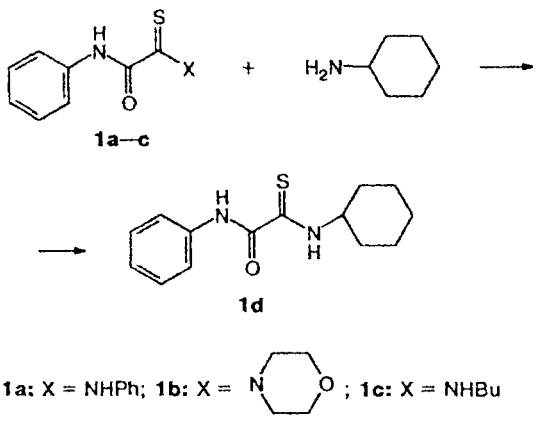
Previously, we have developed a simple approach to the synthesis of monothiooxamides[5] by the reactions of chloroacetamides with a solution of elemental sulfur in amines (prepared in advance) at room temperature.

In this work, we studied the reactions of monothiooxamides with N-nucleophiles and developed a simple convenient procedure for the preparation of 4,5-dihydroimidazole-2-carboxanilides.

Results and Discussion

It is known[6] that the reactions of primary amines with thioamides can either proceed with the formation of an imine fragment or result in transamidation. With the aim of examining general regularities of reactions of monothiooxamides with amines, we first studied the reactions of *N*(*O*)-phenylmonothiooxamides (**1a—c**) with cyclohexylamine (Scheme 1).

Scheme 1



1a: X = NHPh; **1b**: X = ; **1c**: X = NHBu

It was found that transamidation did not affect the C=S group and the amino group of the amide fragment. The replacement proceeded most smoothly in compounds **1b** and **1c**. Their reactions with cyclohexylamine were completed in 3 h at ~20 °C, while the reaction with **1a** under these conditions was completed in 20 h. The highest yield of compound **1d** was obtained in the reaction with compound **1b**. *N*(*S*)-Morpholino derivatives of monothiooxamides, which can be used in the synthesis of imidazolines, can be obtained from chloroacetamides in high yields.[5] The electron-acceptor and electron-donor substituents in the benzene ring of the amide fragment have no noticeable effect on transamidation under the action of cyclohexylamine (Scheme 2).

It was demonstrated that *N*(*S*)-morpholino derivatives of monothiooxamides smoothly react not only with cyclohexylamine but also with other primary and secondary amines (Scheme 3).

The reactions were conducted at ~20 °C in the amine as the solvent or in DMF. Transamidation pro-

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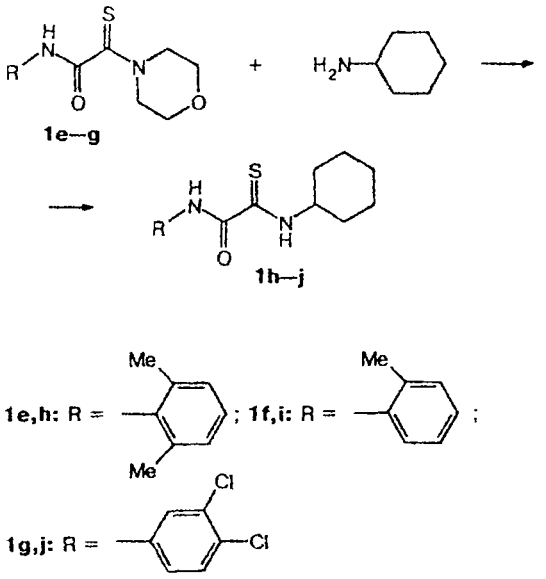
Scheme 2



ceeded more smoothly under the action of primary amines than with secondary amines. It should be noted that these reactions allow one to extend the scope of the procedure which we have developed previously for the synthesis of monothiooxamides, and, in spite of the involvement of an additional stage, in some instances make it possible to prepare monothiooxamides in higher yields.

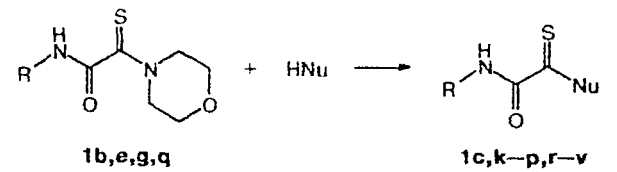
With the aim of synthesizing 4,5-dihydroimidazole-2-carboxanilides, we studied the reactions of *N*(*S*)-morpholino derivatives with ethylenediamine (Scheme 4). The reactions were carried out in ethylenediamine or DMF at ~20 °C. 4,5-Dihydroimidazole-2-carboxanilides were prepared in 60–90% yields.

Based on the results of transamidation of monothiooxamides, it can be concluded that the first stage of the reaction with ethylenediamine involves the replacement of the morpholine fragment to form the corresponding monothiooxamide. We examined the possibility of the synthesis of 4,5-dihydroimidazole-2-carboxanilides in one stage by the reaction of chloroacetanilides with a solution (prepared preliminarily) of elemental sulfur in ethylenediamine. It appeared that the direction of the reaction depended on the order in which the reagents were introduced into the reaction. When a solution of elemental sulfur in ethylenediamine was added to chloroacetanilide, *N*,*N*′-ethylenebis(thiooxamide) **4** was formed (Scheme 5).

When chloroacetanilide was added to a solution of sulfur in ethylenediamine, the corresponding 4,5-dihydroimidazole-2-carboxanilides **2a–i** were obtained in 50–80% yields (Scheme 6).

Thus, we developed a simple procedure for the synthesis of 4,5-dihydroimidazole-2-carboxanilides from readily available reagents.

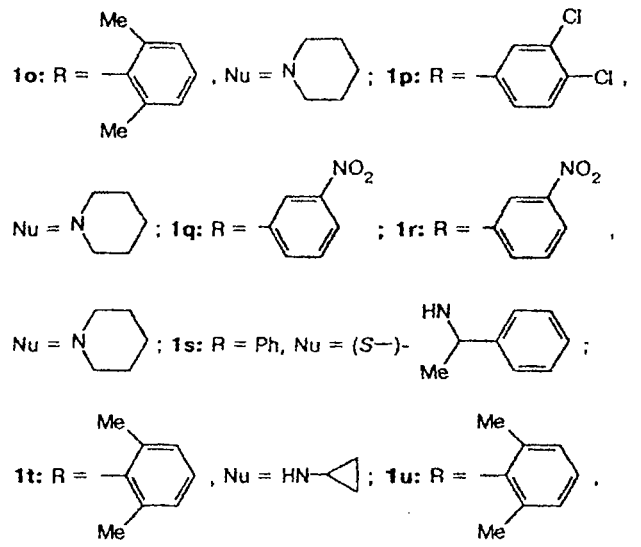
Scheme 3



1k: R = Ph, Nu = $HNCH_2CH{=}CH_2$;

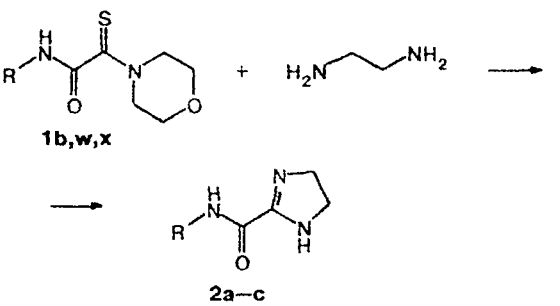
1l: R = Ph, Nu = HN–  ;

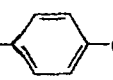
1m: R = Ph, Nu = NEt_2; **1n:** R = Ph, Nu = $HN(CH_2)_6Me$;

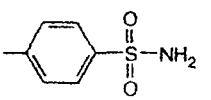


Nu = HNMe; **1v:** R = Ph, Nu = HNMe

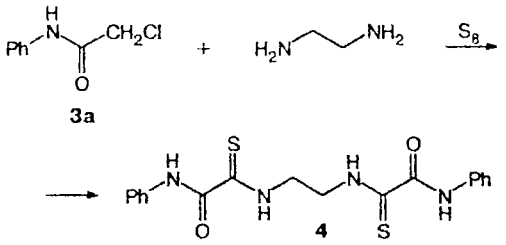
Scheme 4



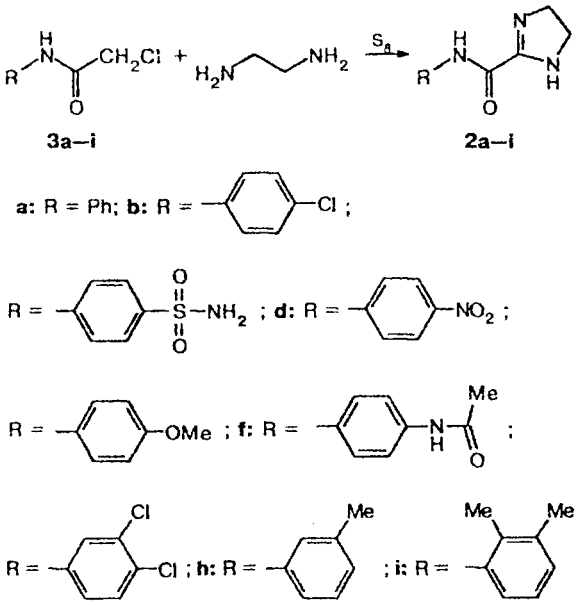
1b, 2a: R = Ph; **1w, 2b:** R =  ;

1x, 2c: R = 

Scheme 5



Scheme 6



Experimental

The IR spectra were recorded on a Specord IR-80 spectrophotometer in KBr pellets. The ^{1}H NMR spectra were obtained on Bruker AC-200 (200 MHz) and Bruker WM-250 (250 MHz) instruments in DMSO-d_6 relative to HMDS. The mass spectra were measured on a Varian MAT CH-6 instrument with direct inlet of the sample into the ion source with a control voltage of 1.75 kV; the energy of ionizing electrons was 70 eV. The melting points were measured on a Boetius table and are uncorrected. The reaction mixtures were analyzed and the purity of the products isolated was monitored by TLC on Silufol UV-254 plates in an EtOAc—hexane system (1 : 1, v/v).

Reactions of *N*(*O*)-arylthiooxamides with primary and secondary amines (general procedure). *N*(*O*)-Arylthiooxamide (0.10 g) was dissolved in the corresponding amine (1 mL). The solution was kept until the initial compound disappeared (TLC control) and then poured into water (20 mL). The precipitate that formed was filtered off, washed with water, dried, and recrystallized from ethanol.

***N*(*S*)-Cyclohexyl-*N*(*O*)-phenylthiooxamide (1d).** *A.* From compound **1a**, the reaction time was 20 h, the yield was 0.08 g (85%), m.p. 136—139 °C.

B. From compound **1b**, the reaction time was 3 h, the yield was 0.10 g (93%), m.p. 136—139 °C.

C. From compound **1c**, the reaction time was 3 h, the yield was 0.06 g (57%), m.p. 136—139 °C.

Found (%): C, 64.25; H, 6.97; N, 10.51. $C_{14}H_{18}N_2OS$. Calculated (%): C, 64.09; H, 6.92; N, 10.68. ^{1}H NMR, δ: 1.10—1.90 (m, 10 H, 5 $-CH_2-$); 4.2 (s, 1 H, —CH—); 7.10 (t, 1 H, H arom.); 7.35 (t, 2 H, 2 H arom.); 7.70 (d, 2 H, 2 H arom.); 10.40 (s, 1 H, NH); 10.95 (s, 1 H, NH). MS, *m*/*z*: 262 $[M]^+$.

Thiooxamides **1c,h—p,r—t** were synthesized as described above. The characteristics of the resulting compounds are given in Table 1.

Reactions of *N*(*O*)-arylthiooxamides with methylamine (general procedure). Dry methylamine was passed through a solution of *N*(*O*)-arylthiooxamide (0.10 g) in DMF (3 mL) for 5 min (the color of the reaction mixture changed from pale-yellow to dark-green). Then the solution was poured into water and the precipitate was filtered off and recrystallized from ethanol.

***N*(*S*)-Methyl-*N*(*O*)-(2,6-dimethylphenyl)thiooxamide (1u).** From compound **1e**, the yield was 0.06 g (75%), m.p. 136—137 °C. Found (%): C, 59.32; H, 6.25; N, 12.75. $C_{11}H_{14}N_2OS$. Calculated (%): C, 59.43; H, 6.35; N, 12.60. ^{1}H NMR, δ: 2.15 (s, 6 H, 2 MeAr); 3.10 (s, 3 H, MeNH); 7.10 (s, 3 H, 3 H arom.); 9.95 (s, 1 H, NH); 10.85 (s, 1 H, NH). MS, *m*/*z*: 222 $[M]^+$.

***N*(*S*)-Methyl-*N*(*O*)-phenylthiooxamide (1v).** From compound **1b**, the yield was 0.065 g (81%), m.p. 152—153 °C. Found (%): C, 55.49; H, 4.98; N, 14.65. $C_9H_{10}N_2OS$. Calculated (%): C, 55.65; H, 5.19; N, 14.42. ^{1}H NMR, δ: 3.10 (s, 3 H, MeNH); 7.15 (t, 1 H, H arom.); 7.35 (t, 2 H, 2 H arom.); 7.75 (d, 2 H, 2 H arom.); 10.35 (s, 1 H, NH); 10.85 (s, 1 H, NH). MS, *m*/*z*: 194 $[M]^+$.

Reactions of *N*(*O*)-arylthiooxamides with ethylenediamine. 4,5-Dihydro-1*H*-imidazole-2-carboxanilide (2a). A solution of *S*-morpholino-*N*(*O*)-phenylthiooxamide **1b** (0.10 g, 0.4 mmol) in ethylenediamine (1 mL, 15 mmol) was kept for 1.5 h. Then the reaction mixture was poured into water and the precipitate that formed was filtered off and dried. After recrystallization from ethanol, the yield of compound **2a** was 0.23 g (60%), m.p. 195—196 °C.

4,5-Dihydro-1*H*-imidazole-2-carbox(4-chloroanilide) (2b). The reaction with thiooxamide **1w** was carried out analogously. The yield of compound **2b** was 0.07 g (90%), m.p. 235—236.5 °C (from ethanol).

4,5-Dihydro-1*H*-imidazole-2-carbox[(4-aminosulfonyl)anilide] (2c). A solution of thiooxamide **1x** (0.10 g, 0.3 mmol) in ethylenediamine (2.0 mL, 1.79 g, 29 mmol) was kept for 2 h (TLC control, EtOAc—hexane, 3 : 1). The reaction solution was poured into water (50 mL) and extracted with EtOAc (3×30 mL). The organic layer was dried with $MgSO_4$ and the solvent was evaporated *in vacuo*. The residue was crystallized from ethanol. The yield was 0.05 g (63%), m.p. 280 °C.

Reactions of chloroacetanilides with ethylenediamine and elemental sulfur (general procedure for the preparation of 4,5-dihydroimidazole-2-carboxanilides). A mixture of sulfur (1.0 g, 30 mmol) and ethylenediamine (10 mL, 150 mmol) was stirred for 30 min until the dark-red solution was formed. Then chloroacetanilide (6 mmol) was added portionwise with stirring over 10 min. The reaction mixture was stirred for 30 min and poured into water (100 mL). The precipitate was filtered

Table 1. Characteristics of the synthesized monothiooxamides (**1c,h—t**)

Compound	Yield (%)	M.p./°C	Found / Calculated (%)			Molecular formula	^{1}H NMR (DMSO-d_6), δ	MS $[M]^+$, *m/z*
			C	H	N			
1c	89	60—61.5	61.19 60.99	6.67 6.82	11.73 11.85	$C_{12}H_{16}N_2OS$	0.90 (m, 3 H, Me); 1.30 (m, 2 H, —CH_2—); 1.63 (m, 2 H, —CH_2—); 3.60 (m, 2 H, —CH_2—); 7.10 (t, 1 H, H arom.); 7.35 (t, 2 H, H arom.); 7.75 (d, 2 H, H arom.); 10.30 (s, 1 H, NH); 10.85 (s, 1 H, NH)	236
1h	77	178—180	66.11 66.17	7.48 7.64	9.76 9.65	$C_{16}H_{22}N_2OS$	1.10—1.85 (m, 10 H, —CH_2—); 2.20 (s, 6 H, 2 Me); 4.18 (m, 1 H, —CH—); 7.10 (s, 3 H, H arom.)	290
1i	90	114—116	65.75 65.18	7.10 7.29	10.05 10.14	$C_{15}H_{20}N_2OS$		276
1j*	95	113—115	50.83 50.76	4.93 4.87	8.32 8.46	$C_{14}H_{16}N_2OSCl_2$	1.10—1.90 (m, 10 H, —CH_2—); 4.20 (m, 1 H, —CH—); 7.60 (d, 1 H, H arom.); 7.75 (d, 1 H, H arom.); 8.10 (s, 1 H, H arom.); 10.55 (s, 1 H, NH)	330, 332
1k	77	84—86	60.21 59.98	5.32 5.49	12.61 12.72	$C_{11}H_{12}N_2OS$	4.25 (d, 2 H, —CH_2—); 5.20 (t, 2 H, CH_2=); 5.90 (m, 1 H, CH); 7.15 (t, 1 H, H arom.); 7.35 (t, 2 H, H arom.); 7.75 (d, 2 H, H arom.); 10.40 (s, 1 H, NH); 10.95 (s, 1 H, NH)	220
1l	89	93—95	59.85 59.98	5.27 5.49	12.90 12.72	$C_{11}H_{12}N_2OS$	0.90 (s, 4 H, —CH_2—); 3.45 (m, 1 H, —CH—); 7.10 (t, 1 H, H arom.); 7.35 (t, 2 H, H arom.); 7.70 (d, 2 H, H arom.); 10.25 (s, 1 H, NH); 10.65 (s, 1 H, NH)	220
1m	67	129—131	61.25 60.99	6.85 6.82	11.73 11.85	$C_{12}H_{16}N_2OS$	1.65 (m, 6 H, 2 Me); 3.62 (q, 2 H, —CH_2—); 4.09 (q, 2 H, —CH_2—); 7.10 (t, 1 H, H arom.); 7.13 (t, 2 H, H arom.); 7.65 (d, 2 H, H arom.); 10.45 (s, 1 H, NH)	236
1n	77	54—56	64.60 64.71	7.90 7.97	10.16 10.06	$C_{15}H_{22}N_2OS$	0.9 (t, 3 H, Me); 1.3 (s, 8 H, —CH_2—); 1.65 (t, 2 H, —CH_2—); 3.65 (m, 2 H, —CH_2—); 7.15 (t, 1 H, H arom.); 7.40 (t, 2 H, H arom.); 7.75 (d, 2 H, H arom.); 10.35 (s, 1 H, NH); 10.95 (s, 1 H, NH)	278
1o	85	179—181	64.97 65.18	7.12 7.29	10.87 10.14	$C_{15}H_{20}N_2OS$	1.70 (s, 6 H, —CH_2—); 2.20 (s, 6 H, 2 Me); 3.75 (s, 2 H, —CH_2N); 4.15 (s, 2 H, CH_2N); 7.10 (s, 3 H, H arom.); 9.85 (s, 1 H, NH)	276
1p**	60	185—187	49.25 49.22	4.20 4.45	8.97 8.83	$C_{13}H_{14}N_2OSCl_2$	1.65 (s, 6 H, —CH_2—); 3.75 (s, 2 H, —CH_2N); 4.13 (s, 2 H, —CH_2N); 7.55 (d, 1 H, H arom.); 7.65 (d, 1 H, H arom.); 8.08 (s, 1 H, H arom.); 9.85 (s, 1 H, NH)	316, 318
1r	74	165—167	53.37 53.23	5.29 5.15	14.25 14.32	$C_{13}H_{15}N_3O_3S$	1.65 (s, 6 H, —CH_2—); 3.75 (s, 2 H, —CH_2N); 4.15 (s, 2 H, —CH_2N); 7.55 (t, 1 H, H arom.); 7.90 (d, 1 H, H arom.); 8.10 (d, 1 H, H arom.); 8.75 (s, 1 H, H arom.); 9.85 (s, 1 H, NH)	293
1s***	73	175—177	67.48 67.58	5.27 5.67	9.54 9.85	$C_{16}H_{16}N_2OS$	1.60 (d, 3 H, Me); 5.60 (q, 1 H, CH); 7.15 (t, 1 H, H arom.); 7.25—7.45 (m, 7 H, H arom.); 7.75 (m, 2 H, H arom.); 10.45 (s, 1 H, NH); 11.15 (s, 1 H, NH)	284
1t	78	174—176	63.10 62.87	6.37 6.49	11.10 11.28	$C_{13}H_{16}N_2OS$	0.90 (m, 4 H, —CH_2—); 2.15 (s, 6 H, 2 Me); 3.45 (m, 1 H, —CH—); 7.30 (s, 3 H, H arom.); 9.90 (s, 1 H, NH); 10.70 (s, 1 H, NH)	248

* Found (%): Cl, 21.30. Calculated (%): Cl, 21.40.
** Found (%): Cl, 22.45. Calculated (%): Cl, 22.35.
*** $[\alpha]_D^{15} = -4.80°$ (*c* 1.0, MeOH).

off, washed with water, dried, dissolved in acetone, and filtered to remove unconsumed sulfur. The acetone solution was concentrated and the residue was recrystallized from ethanol. The characteristics of the resulting 4,5-dihydroimidazole-2-carboxanilides **2a—i** are given in Table 2.

***N,N'*-Bis(2-anilino-2-oxothioacetyl)-1,2-ethylenediamine (4).** A mixture of sulfur (0.5 g, 15.6 mmol) and ethylenediamine (0.2 mL, 0.18 g, 2.9 mmol) was stirred for 30 min. Then the reaction mixture was added portionwise to a solution of chloroacetanilide **3a** (0.5 g, 12.9 mmol) in DMF (5 mL) over

Table 2. Characteristics of the synthesized 4,5-dihydroimidazole-2-carboxanilides (**2a—i**)

Compound	Yield (%)	M.p./°C	Found / Calculated (%)			Molecular formula	^{1}H NMR (DMSO-d_6), δ	MS, *m/z*
			C	H	N			
2a	72	195—196	63.32 63.48	5.95 5.86	22.41 22.21	$C_{10}H_{11}N_3O$	3.75 (s, 4 H, 2 $-CH_2-$); 7.05 (t, 1 H, H arom.); 7.30 (t, 2 H, H arom.); 7.57 (d, 2 H, H arom.)	188 $[M-1]^+$
2b*	80	236—238	53.51 53.70	4.40 4.51	18.83 18.79	$C_{10}H_{10}ClN_3O$	3.65 (s, 4 H, 2 $-CH_2-$); 7.35 (d, 2 H, H arom.); 7.80 (d, 2 H, H arom.); 10.40 (s, 1 H, NH)	223, 225 $[M]^+$
2c	63	280—281	44.81 44.77	4.38 4.51	20.79 20.88	$C_{10}H_{12}N_4O_3S$	3.60 (s, 4 H, 2 $-CH_2-$); 4.0 (br.s, 4 H, NH); 7.75 (d, 2 H, H arom.); 7.95 (d, 2 H, H arom.)	267 $[M-1]^+$
2d	50	274—276	51.40 51.28	4.35 4.30	23.80 23.92	$C_{10}H_{10}N_4O_3$	3.25 (br.s, NH); 3.65 (s, 4 H, 2 $-CH_2-$); 8.05 (d, 2 H, H arom.); 8.25 (d, 2 H, H arom.)	234 $[M]^+$
2e	75	199—200	60.10 60.26	5.88 5.98	19.33 19.16	$C_{11}H_{13}N_3O_2$	3.25 (br.s, NH); 3.65 (s, 4 H, 2 $-CH_2-$); 3.73 (s, 3 H, —OMe); 6.90 (d, 2 H, H arom.); 7.65 (d, 2 H, H arom.)	219 $[M]^+$
2f	78	278—280	58.61 58.53	5.49 5.73	22.60 22.75	$C_{12}H_{14}N_4O_2$	2.00 (s, 3 H, Me); 3.65 (s, 4 H, 2 CH_2-); 7.10 (s, 1 H, NH); 7.50 (d, 2 H, H arom.); 7.65 (d, 2 H, H arom.); 9.90 (s, 1 H, NH); 10.20 (s, 1 H, NH)	246 $[M]^+$
2g**	52	185—186	46.85 46.54	3.49 3.51	16.29 16.28	$C_{10}H_9Cl_2N_3O$	3.25—3.40 (br.s, NH); 3.65 (s, 4 H, 2 $-CH_2-$); 7.55 (d, 1 H, H arom.); 7.75 (d, 1 H, H arom.); 8.10 (s, 1 H, H arom.)	257, 259 $[M]^+$
2h	65	120—122	65.10 65.01	6.36 6.45	20.53 20.68	$C_{11}H_{13}N_3O$	2.25 (s, 3 H, Me); 3.30 (br.s, NH); 3.63 (s, 4 H, 2 $-CH_2-$); 6.90 (d, 1 H, H arom.); 7.19 (t, 1 H, H arom.); 7.55 (t, 2 H, H arom.)	203 $[M]^+$
2i	74	158—161	66.43 66.34	6.98 6.96	19.28 19.34	$C_{12}H_{15}N_3O$	2.05 (s, 3 H, Me); 2.25 (s, 3 H, Me); 3.25 (br.s, NH); 3.65 (s, 4 H, 2 $-CH_2-$); 7.05 (m, 2 H, H arom.); 7.30 (d, 1 H, H arom.)	217 $[M]^+$

* Found (%): Cl, 15.73. Calculated (%): Cl, 15.85.
** Found (%): Cl, 27.55. Calculated (%): Cl, 27.47.

10 min. After 30 min (TLC control), the mixture was poured into water (50 mL). After 12 h, the precipitate that formed was filtered off, dried, dissolved in acetone, and filtered to remove unconsumed sulfur. The acetone solution was concentrated and the residue was recrystallized from ethanol. The yield was 0.40 g (36%), m.p. 198—200 °C. Found (%): C, 56.10; H, 4.39; N, 14.37. $C_{18}H_{18}N_4O_2S_2$. Calculated (%): C, 55.94; H, 4.69; N, 14.50. ^{1}H NMR, δ: 3.98 (m, 4 H, 2 $-CH_2-$); 7.25 (t, 2 H, 2 H arom.); 7.37 (t, 4 H, 4 H arom.); 7.75 (d, 4 H, 4 H arom.); 10.30 (s, 2 H, 2 NH); 11.00 (s, 2 H, 2 NH). MS, *m/z*: 386 $[M]^+$.

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