Synthesis, Antimicrobial, Inotropic, and Chronotropic Activities of Novel 1,2,4-Triazolo[4,3-*a*]quinolines

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Starting from the 2-quinolylhydrazine **1** the title compounds were prepared according to Schemes 1 and 2. Some of them show activities described in the title of this paper.

Synthese, antimikrobielle, inotrope und chronotrope Eigenschaften neuer 1,2,4-Triazolo[4,3*a*-]chinoline

Ausgehend von dem 2-Chinolylhydrazin **1** werden die Titelverbindungen nach den Schemata 1 und 2 hergestellt. Einige Verbindungen zeigen die im Titel genannten Eigenschaften.

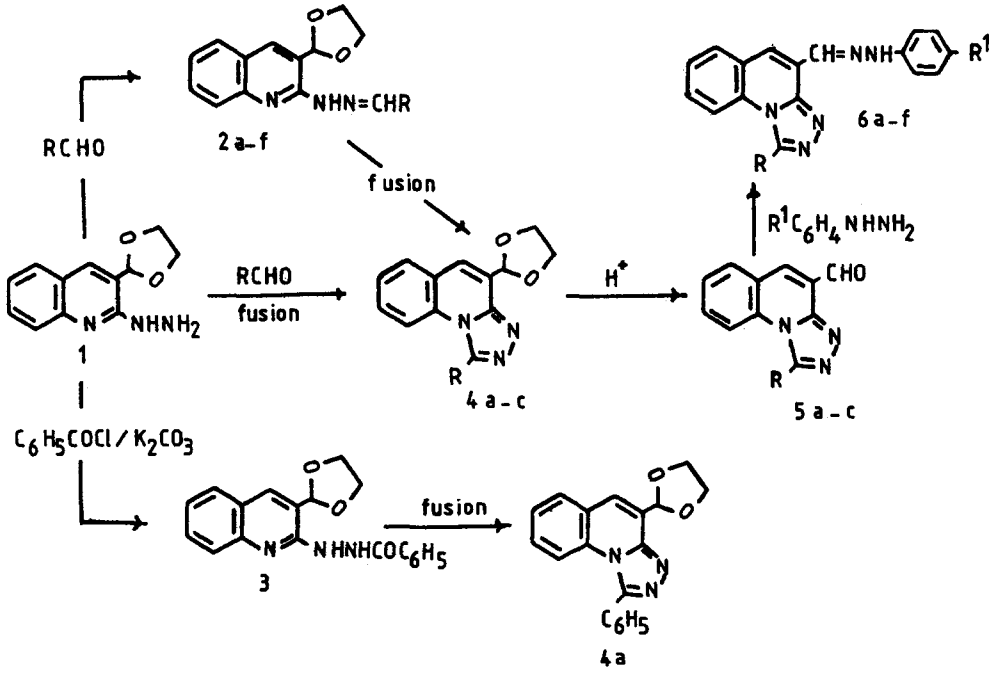
Triazoloquinolines exhibit antibacterial [1], antiallergic [2], antidepressant [3], and antiarrythmic [4] effects. In addition, inotropic as well as chronotropic activities have been attributed to some quinoline derivatives [5,6]

Therefore, this investigation is concerned with the synthesis of some substituted 1,2,4-triazolo[4,3-*a*]quinolines in order to study their antimicrobial, inotropic, and chronotropic activities.

Condensation of compound **1** [7] with aromatic aldehydes afforded 2-arylidenehydrazino derivatives **2a-f** which on fusion in presence of air underwent cyclodehydrogenation to give the triazolo[4,3-*a*]quinolines **4a-c**. **4a-c** were also prepared directly from **1** and the selected aldehyde by fusion.

Compound **4a** was also obtained by reacting compound **1** with benzoyl chloride in presence of base, the 2-benzoylhydrazino derivative **3** on fusion underwent cyclodehydration to form **4a**. Treatment of **4a-c** with 60% HCOOH [8] gave the 4-carbaldehyde derivatives **5a-c** which on condensation with arylhydrazines afforded the hydrazones **6a-f** (Scheme 1).

Cyclization of **1** with CS_2 in EtOH/NaOH or pyridine [9] gave the triazolo[4,3-a]quinoline-1-thione **7**. Treatment of **7** with 60% HCOOH followed by condensation of the carbaldehyde derivative **8** with phenylhydrazine gave the hydrazone **9**. The alkylthio-derivatives **10a-c** were prepared by alkylation of **7** with alkyl halides in alkaline medium. The bases **12a-d** were obtained by an indirect method as the application of *Mannich* reaction condition was unsuccessful. Thus treatment of **7** with formalin [10] and then reacting the hydroxymethyl derivative **11** with $SOCl_2$ followed by secondary amines gave the target compound **12a-d** (Scheme 2). The HCl liberated during the reaction cleaved the dioxolan ring to the free aldehyde.



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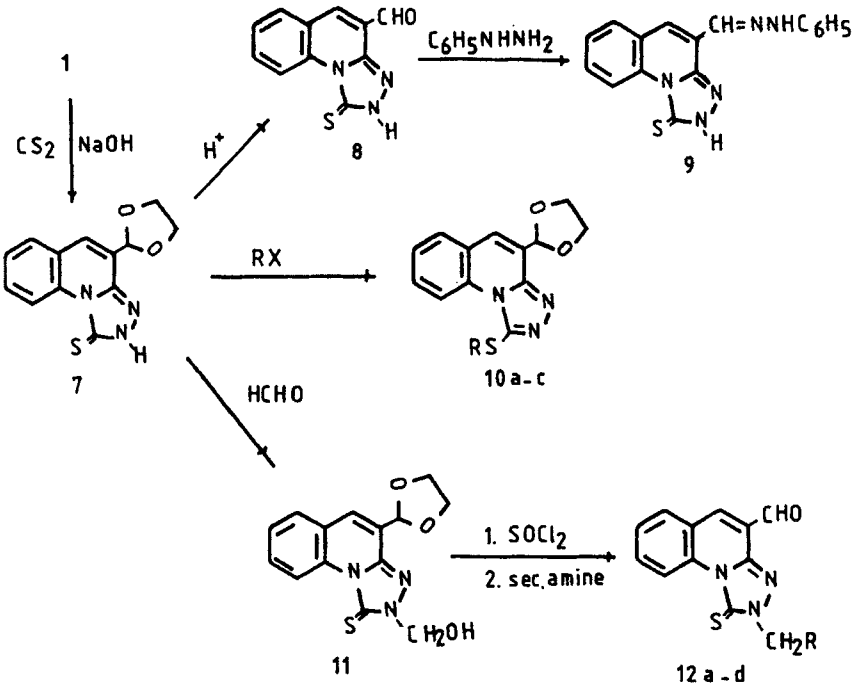

Biological Evaluation

A) *Antimicrobial Screening*

The compounds were evaluated by the agar diffusion technique [11] (0.2% solutions in propylene glycol). A 0.1% streptomycin solution in propylene glycol was used as standard. The inhibition zones against *Staphylococcus aureus* NCTC 4163; *Escherichia coli* NCTC 5933 and *Candida albicans* NCTC 3501 were 17-23 mm; 16-19 mm and 16-20 mm, respectively. **4b, 5a** and **6b** were inactive against *E. coli*, whereas **5a, 12c** were inactive against *E. coli*, and against *C. albicans*. Propylene glycol does not inhibit the test organisms. All compounds were less active than streptomycin against the tested organisms.

B) *Inotropic and Chronotropic Evaluation*

The compounds were preliminarily tested for inotropic and chronotropic effects on isolated Toad's heart [12], suspended in a 15 ml bath containing *Ringer* solution kept at 37°C and bubbled with carbogen. The compounds were dissolved in propylene glycol (2 mg/ml), then diluted with 3 ml of *Ringer* solution. The doses used were 5, 10, 20, 50 and 100 µg. Propylene glycol at this concentrations has no effect on the heart. Compound **5a** exhibited pronounced positive inotropic activity, whereas compound **12d** exhibited pronounced negative inotropic activity. The remaining compounds have no significant effect on the Toad's heart at the dose levels used.

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Experimental Part

Melting points: uncorrected. - IR spectra (Nujol): Beckman 4210 spectrophotometer. - ^{1}H-NMR spectra: Varian EM-360 L spectrometer and Brucker 200 MHz spectrometer, $CDCl_3$, TMS as int. standard, chemical shifts in δ (ppm). - Analytical data: Microanalytical Unit, Faculty of Science, Cairo University.

2-Arylidenehydrazino-3-(1,3-dioxolan-2-yl)quinolines **2a-f**

The mixture of compound **1** (0.23 g, 0.001 mole) in EtOH (5 ml) and of the proper aldehyde (0.001 mole) was heated under reflux for 10-15 min, cooled and poured into water. The precipitate was filtered and crystallized from the proper solvent (Table 1). - IR: 3300-3120 (NH); 1630-1620, 1660-1575, 1550-1510 (C=N, δ NH, C=C); 1260-1235, 1180-1160, 1150-1140, 1050-1030 cm^{-1} (C-O-C). - ^{1}H-NMR of compound **2a**: 4.1-4.3 (m, 4H, OCH_2CH_2O); 6.2 (s, 1H, CH); 7.2-7.9 (m, 11H, Ar-H and N=CH); 8.5 (s, 1H, NH, D-exchange).

2-Benzoylhydrazino-3-(1,3-dioxolan-2-yl)quinoline **3**

The suspension of **1** (0.23 g, 0.001 mole in chloroform, 20 ml), K_2CO_3 (0.5 g) and benzoyl chloride (0.14 g, 0.001 mole) was heated under reflux for 1 h, filtered, concentrated and cooled. The precipitate was filtered and crystallized from dioxane: m.p. 145-146°C; yield (0.23 g, 70%). - IR: 3400-3170 (NH); 1665 (C=O), 1640, 1575, 1510 (C=N, δ NH, C=C); 1270, 1160, 1120, 1060 cm^{-1} (C-O-C). - ^{1}H-NMR: 4.1-4.4 (m, 4H, OCH_2CH_2O); 6.0 (s, 1H, CH); 7.2-8.0 (m, 9H, Ar-H); 8.2 (s, 1H, quinoline H-4); 9.9 (br, s, 2H, 2NH, D-exchange). - $C_{19}H_{17}N_3O_3$ (335.4) Calcd. C 68.0 H 5.11 N 12.5 Found C 67.8 H 5.3 N 12.1.

1-Substituted-4-(1,3-dioxolan-2-yl)-1,2,4-triazolo[4,3-a]quinolines **4a-c**

Method I: The proper 2-arylidenehydrazino-3-(1,3-dioxolan-2-yl)quinoline **2a,e,f** (0.001 mole) was fused above its mp. for 1 h in presence of air. The product of fusion was crystallized from EtOH (Table 2).

Method II: A mixture of **1** (0.23 g, 0.001 mole) and the proper aldehyde (0.001 mole) was fused at 100°C in presence of air for 30 min. The product obtained after precipitation with water was crystallized from EtOH (Table 2).

Table 1: *2-Arylidenehydrazino-3-(1,3-dioxolan-2-yl)quinolines* **2a-f**

Comp. No.	R	Yield %	Mp°C Cryst.Solv.	Molecular Formula	Analyses % (Calc./Found) C	H	N
2a	C_6H_5	24	87- 88	$C_{19}H_{17}N_3O_2$	71.5	5.37	13.2
			Benzene	(319.4)	71.6	5.3	13.5
2b	$C_6H_3OCH_3$(m)-OH(p)	80	99-100	$C_{20}H_{19}N_3O_4$	65.7	5.24	11.5
			EtOH	(365.4)	66.0	5.4	11.8
2c	$C_6H_3(OCH_3)_2$ (m,p)	30	158-159	$C_{21}H_{21}N_3O_4$	66.5	5.58	11.1
			MeOH	(379.4)	66.1	5.3	11.0
2d*	2-Chloroquinol-3-yl	72	209-210	$C_{22}H_{17}ClN_4O_2$	65.3	4.23	13.8
			MeOH	(404.9)	65.4	4.6	13.8
2e	C_6H_4OH(o)	91	99-100	$C_{19}H_{17}N_3O_3$	68.0	5.11	12.5
			Dioxane	(335.4)	67.9	5.3	12.2
2f	$C_6H_4OCH_3$(p)	22	160-161	$C_{20}H_{19}N_3O_3$	68.7	5.48	12.0
			Dioxane	(349.4)	68.5	5.2	12.1

* Analysis % for Cl: Calcd. 8.8 Found 9.0

Table 2: *1-Substituted-4-(1,3-dioxolan-2-yl)-1,2,4-triazolo[4,3-a]quinolines* **4a-c**

Comp. No.	R	Yield* a	b	Mp°C	Molecular Formula	Analyses % (Calc./Found) C	H	N
4a	C_6H_5	50	72	116-117	$C_{19}H_{15}N_3O_2$	71.9	4.8	13.2
					(317.4)	71.8	4.6	13.4
4b	C_6H_4OH(o)	30	33	140-141	$C_{19}H_{15}N_3O_3$	68.5	4.54	12.6
					(333.3)	68.1	4.9	12.8
4c	$C_6H_4OCH_3$(p)	35	52	250-251	$C_{20}H_{17}N_3O_3$	69.2	4.93	12.1
					(347.4)	69.4	5.2	12.1

* The yield calculated according to a = *method I* b = *method II*

Table 3: *1-Substituted-1,2,4-triazolo[4,3-a]quinoline-4-carboxaldehydes* **5a-c**

Comp. No.	R	Yield %	Mp°C	Molecular Formula	Analyses % (Calc./Found) C	H	N
5a	C_6H_5	38	196-197	$C_{17}H_{11}N_3O$	74.7	4.06	15.4
				(273.3)	74.7	4.2	15.0
5b	C_6H_4OH(o)	38	200-201	$C_{17}H_{11}N_3O_2$	70.6	3.83	14.5
				(289.3)	70.9	3.6	14.2
5c	$C_6H_4OCH_3$(p)	76	171-172	$C_{18}H_{13}N_3O_2$	71.3	4.32	13.8
				(303.3)	71.0	4.0	13.5

IR: 1630-1620, 1530-1510 (C=N, C=C); 1260-1250, 1170-1160, 1120-1110, 1080-1060 (C-O-C). - ^{1}H-NMR of compound **4a**: 4.1-4.4 (m, 4H, OCH_2CH_2O); 6.6 (s, 1H, CH); 7.2-7.9 (m, 10H, Ar-H).

1-Phenyl-4-(1,3-dioxolan-2-yl)-1,2,4-triazolo[4,3-a]quinoline(**4a**) *from compound* **3**

3 (0.33 g, 0.001 mole) was fused above its mp. (150°C) for 1 h in a paraffin bath. The product was dissolved in EtOH, the solution was treated with charcoal, filtered, concentrated and the product was crystallized from ethanol; yield 0.19 g, (57%).

Analytical data of the product so obtained were identical with those of compound **4a** prepared by *methods I* and *II*.

1-Substituted-1,2,4-triazolo[4,3-a]quinoline-4-carboxaldehydes **5a-c**

The appropriate compounds **4a-c** (0.001 mole) were heated with 60% HCOOH (5 ml) for 15 min. The mixture was cooled and neutralized with Na_2CO_3 solution. The precipitate was filtered, washed with water and crystallized from benzene/petrol ether 60-80°C (Table 3). - IR (KBr): 1700-1690 (C=O, aldehyde); 1630-1615, 1540-1510 (C=N, C=C). - ^{1}H-NMR of compound **5a**: 7.1-8.1 (m, 9H, Ar-H); 8.3 (s, 1H, quinoline H-4); 10.9 (s, 1H, CHO).

1-Substituted-1,2,4-triazolo[4,3-a]quinoline-4-carboxaldehyde-p-substituted phenylhydrazones **6a-f**

The solution of **5a-c** (0.001 mole) and phenylhydrazine or ethyl p-hydrazinobenzoate-HCl (0.001 mole) in EtOH (5 ml) was heated under reflux for 30 min, concentrated and the separated product was crystallized from EtOH (Table 4). - IR: 3300-3220 (NH); 1630-1610, 1575-1540, 1530-1510 (C=N, δ NH, C=C). - ^{1}H-NMR of compound **6e**: 3.7 (s, 3H, OCH_3); 4.0 (br. s, 1H, NH); 7.1-8.3 (m, 15H, Ar-H and CH=N).

4-(1,3-dioxolan-2-yl)-1,2,4-triazolo[4,3-a]quinolines-1-thione (**7**)

The solution of compound **1** (2.3 g, 0.01 mole) in EtOH (20 ml) and NaOH (0.4 g, 0.01 mole) or in pyridine (40 ml) and CS_2 (30 ml) was

Table 4: *1-Substituted-1,2,4-triazolo[4,3-a]quinoline-4-carboxaldehyde-p-substituted phenylhydrazones* **6a-f**

Comp. No.	R	R^1	Yield %	Mp°C	Molecular Formula	Analyses % (Calc./Found) C	H	N
6a	C_6H_5	H	37	265-266	$C_{23}H_{17}N_5$	76.0	4.7	19.3
					(263.4)	75.7	5.0	19.0
6b	C_6H_5	$CO_2C_2H_5$	62	>300	$C_{26}H_{21}N_5O_2$	71.7	4.86	16.1
					(435.5)	71.4	5.0	16.1
6c	C_6H_4OH (o)	H	38	215-216	$C_{23}H_{17}N_5O$	72.8	4.52	18.5
					(379.4)	72.5	4.7	18.2
6d	C_6H_4OH (o)	$CO_2C_2H_5$	48	>300	$C_{26}H_{21}N_5O_3$	69.2	4.69	15.5
					(451.5)	69.2	4.8	15.2
6e	$C_6H_4OCH_3$ (p)	H	65	291-292	$C_{24}H_{19}N_5O$	73.3	4.87	17.8
					(393.5)	73.5	5.0	17.5
6f	$C_6H_4OCH_3$ (p)	$CO_2C_2H_5$	43	>300	$C_{27}H_{23}N_5O_3$	69.7	4.98	15.0
					(465.5)	69.3	4.8	15.0

Table 5: *1-Alkylthio or aralkylthio-4-(1,3-dioxolan-2-yl)-1,2,4-triazolo[4,3-a]quinolines* **10a-c**

Comp. No.	R	Yield %	Mp°C Cryst.Solv.	Molecular Formula	Analyses % (Calc./Found) C	H	N	Cl
10a	CH_3	34	161-162	$C_{14}H_{13}N_3O_2S$	58.5	4.56	14.6	11.2
			MeOH	(287.3)	58.5	4.8	14.7	10.8
10b	C_2H_5	33	247-248	$C_{15}H_{15}N_3O_2S$	59.8	5.02	13.9	10.6
			Benzene	(301.4)	59.9	5.1	14.0	10.7
10c	$CH_2H_6H_5$	33	151-152	$C_{20}H_{17}N_3O_2S$	66.1	4.71	11.6	8.8
			Dioxane	(363.4)	65.9	4.9	11.8	8.5

heated under reflux for 2 h, cooled and diluted with water. The pH was adjusted at 7 by dilute HCl, the precipitate was filtered, washed with water and crystallized from EtOH/$CHCl_3$ (4:1); m.p. 257-258°C; yield 1.8 g (66%). - IR: 3500, 3340 (NH): 1620, 1600, 1565 (C=N, δ NH, C=C); 1535, 1285, 1070, 950 (N-C=S, I, II, III, IV bands); 1255, 1150, 1110, 1050 cm^{-1} (C-O-C). - $C_{13}H_{11}N_3O_2S$ (273.3) Calcd. C 57.1 H 4.06 N 15.4 S 11.7 Found C 57.4 H 4.4 N 15.8 S 11.3.

1-Thioxo-1,2,4-triazolo[4,3-a]quinoline-4-carboxaldehyde (**8**)

The solution of **7** (2.7 g, 0.01 mole) in dioxane (3 ml) and 60% HCOOH (10 ml) was heated under reflux for 15 min, concentrated, cooled and neutralized with Na_2CO_3 solution. The yellowish orange precipitate was filtered, washed with water and crystallized from dioxane; m.p. 270-271°C; yield 2.1 g (92%). - IR: 3500, 3240 (NH); 1650 (C=O); 1610, 1585, 1510 (C=N, δ NH, C=C); 1535, 1285, 1070, 950 cm^{-1} (N-C=S, I, II, III, IV bands). - $C_{11}H_7N_3OS$, (229.3) Calcd. C 57.6 H 3.08 N 18.3 S 14.0 Found C 57.3 H 3.4 N 18.1 S 13.7.

1-Thioxo-1,2,4-triazolo[4,3-a]quinoline-4-carboxaldehyde-phenylhydrazone (**9**)

The solution of **8** (0.23 g, 0.001 mole) and phenylhydrazine HCl (0.14 g, 0.001 mole) in dioxane (5 ml) was heated under reflux for 1 h, cooled and neutralized with sodium acetate solution. The precipitate was filtered, washed with water and crystallized from $CH_3OH/CHCl_3$ (4:1). - IR: 3240, 3120 (NH); 1630, 1600, 1560, 1515 (C=N, δ NH, C=C); 1535, 1270, 1060, 985 cm^{-1} (N-C=S I, II, III, IV bands). m.p. 201-202°C; yield 0.1 g (31%). - $C_{17}H_{13}N_5S$ (319.4) Calcd. C 63.9 H 4.10 N 21.9 S 10.0 Found C 63.8 H 4.0 N 21.6 S 10.4.

1-Alkylthio-or aralkylthio-4-(1,3-dioxolan-2-yl)-1,2,4-triazolo[4,3-a]quinolines **10a-c**

A mixture of **7** (0.55 g, 0.002 mole) in methanolic $NaOCH_3$ (0.05 g Na in 15 ml of absol. methanol) and the proper alkyl halide or aralkyl halide (0.007 mole) was heated under reflux for 2 h. The mixture was concentrated, cooled and diluted with water. The product was crystallized from the proper solvent (Table 5). - IR: 1640-1625, 1580-1570, 1525-1510 (C=N, δ NH, C=C); 1230-1220, 1170-1150, 1065-1050 cm^{-1} (C-O-C). - ^{1}H-NMR of compound **10a** (200 MHz): 3.4 (s, 3H, CH_3); 4.0-4.3 (m, 4H, OCH_2CH_2O); 6.5 (s, 1H, CH); 7.3-8.4 (m, 4H, Ar-H); 8.7 (s, 1H, quinoline H-4).

4-(1,3-Dioxolan-2-yl)-2-hydroxymethyl-1,2,4-triazolo[4,3-a]quinoline-1-thione (**11**)

The solution of compound **7** (0.27 g, 0.001 mole) in dioxane (5 ml) and formalin solution 37% (2 ml) was stirred at 50°C for 2 h and left at room temp. overnight. Water was added, and the precipitate was crystallized from aqueous EtOH; m.p. 169-170°C; yield 0.14 g (46%). - IR: 3460 (OH); 1640, 1610, 1510 (C=N, C=C); 1220, 1135, 1110, 1060 (C-O-C); 1575, 1280, 1035, 970 cm^{-1} (N-C=S I, II, III, IV bands). - ^{1}H-NMR: 3.1 (s, 2H, CH_2OH); 4.0-4.3 (m, 4H, OCH_2CH_2O); 6.1 (s, 1H, CH); 7.4-7.7 (m, 5H, Ar-H); 10.6 (br.s, 1H, OH, D-exchange). - $C_{14}H_{13}N_3O_3S$ (303.3) Calcd. C 55.4 H 4.32 N 13.8 S 10.1 Found C 55.6 H 4.5 N 14.0 S 10.2.

2-Substituted aminomethyl-1-thioxo-1,2,4-triazolo[4,3-a]quinoline-4-carboxaldehydes **12a-d**

The solution of compound **11** (0.3 g, 0.001 mole) and $SOCl_2$ (5 ml) in dry benzene (3 ml) was heated under reflux for 10-12 h. Excess $SOCl_2$ was

Table 6: *2-Substituted aminomethyl-1-thioxo-1,2,4-triazolo[4,3-a]quinoline-4-carboxaldehydes* **12a-d**

Comp. No.	R	Yield %	Mp°C	Molecular Formula	Analyses % (Calc./Found) C	H	N	S
12a	piperdino	50	>300	$C_{17}H_{18}N_4OS$	51.1	5.05	14.0	8.0
				2HCl	51.0	5.1	14.2	8.3
				(399.3)				
12b	morpholino	54	140-141	$C_{16}H_{16}N_4O_2S$	47.9	4.52	13.9	8.0
				2HCl	47.7	4.3	13.7	7.8
				(401.3)				
12c	N-methylpiperazino	26	222-223	$C_{17}H_{19}N_5OS$	49.3	5.11	16.9	7.7
				2HCl	49.1	5.3	17.0	7.5
				(414.4)				
12d	$-N(CH_2C_6H_5)_2$	19	>300	$C_{26}H_{22}N_4OS$	61.1	4.73	10.9	6.3
				2HCl	61.0	4.5	10.6	6.1
				(511.5)				

removed by distillation under reduced pressure. To the residue a solution of the proper amine (0.005 mole) in dry benzene (3 ml) was added and the mixture was heated under reflux for 4-6 h. The precipitate was crystallized from benzene/petrol ether 60-80°C (3:1) (Table 6). - IR: 1720-1700 (C=O); 1640-1620, 1540-1510 (C=N, C=C); 1580-1570, 1300-1290, 1040-1030, 980-960 (N-C=S I, II, III, IV bands). - ^{1}H-NMR of compound **12d**: 3.7 (s, 6H, NCH_2 and two $CH_2C_6H_5$); 7.1-7.6 (m, 15H, Ar-H); 10.2 (s, 1H, CHO).

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