Synthesis of Some Thiazole-, 1,3,4-Thiadiazole-, and 4*H*-1,2,4-Triazole Derivatives of Pyrazolo[3,4-*b*]quinoline

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Three novel series of pyrazolo[3,4-*b*]quinolines were perpared, namely: 1-(3-substituted-4-phenylthiazolin-2-ylidene)hydrazinocarbonylmethyl-1*H*-pyrazolo[3,4-*b*]quinolines **3a-d**; 1-(5-substituted amino-1,3,4-thiadiazol-2-yl)methyl-1*H*-pyrazolo[3,4-*b*]quinolines **4b-d**, and 1-(4-substituted-4*H*-5-thioxo-1,2,4-triazole-3-yl)methyl-1*H*-pyrazolo[3,4-*b*]quinolines **5a-d**. These compounds were prepared by cyclization of the new key intermediates 1-(substituted thiocarbamoylhydrazinocarbonyl)methyl-1*H*-pyrazolo[3,4-*b*]quinolines **2a-d**. The alkylthio, aralkylthio **6a-f** as well as the *Mannich* bases **8a-f** derived from compounds **5a-d** were also prepared. The structures of the new compounds were elucidated by elemental analyses, IR, ^{1}H-NMR-, and mass spectra. The antimicrobial as well as inotropic and chronotropic activities were studied.

Synthese von neuen Thiazol-, 1,3,4-Thiadiazol- und 4*H*-1,2,4-Triazol-Derivaten des 1*H*-Pyrazolo[3,4-*b*]chinolins

Drei neue Serien von Pyrazolo[3,4-*b*]chinolinen wurden hergestellt, nämlich: 1-(3-substituierte-4-Phenylthiazolin-2-yliden)hydrazinocarbonylmethyl-1*H*-pyrazolo[3,4-*b*]chinoline **3a-d**; 1-(5-substituierte Amino-1,3,4-thiadiazol-2-yl)methyl-1*H*-pyrazolo[3,4-*b*]chinoline **4b-d** und 1-(4-substituierte-4*H*-5-thiono-1,2,4-triazole-3-yl)methyl-1*H*-pyrazolo[3,4-*b*]chinoline **5a-d**. Diese Verbindungen waren durch Cyclisierung der neuen Schlüsselprodukte, der 1-(substituierten Thiocarbamoylhydrazinocarbonyl)methyl-1*H*-pyrazolo[3,4-*b*]chinoline **2a-d** zugänglich. Die Alkylthio-, Aralkylthio-Verbindungen **6a-f** und die *Mannich*-Basen **8a-f**, die alle von den Verbindungen **5a-d** abstammen, wurden auch synthetisiert. Die Strukturen der neuen Verbindungen wurden durch Elementaranalyse, IR-, ^{1}H-NMR- und Massenspektren bestimmt. Die antimikrobielle, inotropische und chronotropische Aktivität wurden geprüft.

The biological activities of thiazoline, thiadiazole and triazole derivatives are doubtless. Thiazole derivatives exhibit antithydroid[1], antimicrobial[2], and antifungal activities[3]. Thiadiazole derivatives possess antihypertensive[4] and antimicrobial activities[5]. Triazoles exhibit antibacterial[6] and antiinflammatory activities[7]. On the other hand, different pharmacological activities have been reported for pyrazoloquinolines. Several pyrazolo[3,4-*g*] quinolines display dopaminergic activity[8]. The isomeric pyrazolo[3,4-*f*] quinolines, pyrazolo[4,3-*c*]quinolines and pyrazolo[3,4-*b*]quinolines possess antibacterial[9], tranquilizing[10], antiviral, and antimalarial acitivities[11-13]. Inotropic as well as chronotropic activities have been attributed to some quinoline derivatives[14,15].

These findings focused our interest to synthesize new compounds containing the thiosemicarbazide-, thiazoline-, thiadiazole- or triazole moiety joined to the 1*H*-pyrazolo[3,4-*b*]quinoline nucleus in order to study their antimicrobial as well as inotropic and chronotropic acitivities.

The target heterocycles were synthesized according to Scheme 1.

Thus, the new key intermediates 1-(substituted thiocarbamoylhydrazinocarbonyl)methyl-1*H*-pyrazolo[3,4-*b*] - quinolines **2a-d** were prepared by addition of 1-*H*-pyrazolo[3,4-*b*]quinoline-1-acetic acid hydrazide **1**[16] to alkyl-, aralkyl-, and arylisothiocyanate[17,18]. Cyclization of **2a-d** with phenacyl bromide[19] yielded the new 1-(3-substituted-4-phenylthiazolin-2-ylidene)hydrazinocarbonylmethyl-1*H*-pyrazolo[3,4-*b*]quinolines **3a-d**. When H_2SO_4 was the cyclizing agent[20], 1-(5-substituted amino-1,3,4-thiadiazol-2-yl)methyl-1*H*-pyrazolo[3,4-*b*]quinolines **4b-d** were formed. When compounds **2a-d** were cyclized by NaOH[21,22], 1-(4-substituted-5-thioxo-4*H*-1,2,4-triazole-3-yl) methyl-1*H*-pyrazolo[3,4-*b*]quinolines **5a-d** were obtained. Alkylation of compounds **5b-d** with alkyl or aralkyl halide gave the corresponding alkylthio or aralkylthio-derivatives **6a-f**. The new *Mannich* bases derived from compounds **5b-d**: 1-(1-substituted aminomethyl-4-aralkyl or aryl-5-thioxo-4*H*-1,2,4-triazole-3-yl)methyl-1*H*-pyrazolo[3,4-*b*]quinolines **8a-f** could not be prepared by classical Mannich reaction. These bases **8a-f** were prepared indirectly involving the reaction of **5b-d** with formalin[23] and then treating the produced 1-(1-hydroxymethyl-4-aralkyl or aryl-5-thioxo-4*H*-1,2,4-triazol-3-yl)methyl-1*H*-pyrazolo[3,4-*b*]quinolines **7b-d** with $SOCl_2$. The chloromethyl derivatives so produced, being unstable, were reacted directly with the proper secondary amine to afford the required *Mannich* bases **8a-f**.

Biological evaluation

A) Preliminary Antimicrobial Testing

The antimicrobial activity of the new products was tested by the agar diffusion method[24]. A 0.2% solution in propylene glycol was used. The test organisms were *Staphylococcus aureus* NCTC 4163, *Escherichia coli* NCTC 5933, and *Candida albicans* 3501. 0.1% streptomycin in propylene glycol was used as a standard. The inhibition zones against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* were 15-20 mm; 15-20 mm; and 14-19 mm, respectively, whilst streptomycin resulted in a zone of 29; 25; 13 mm. Compounds **6f, 8c, 8e** and **8f** were inactive against *Staphylococcus aureus*; compound **6f** was inactive against *Escherichia coli*; whereas compounds **3c, 6b, 6e**

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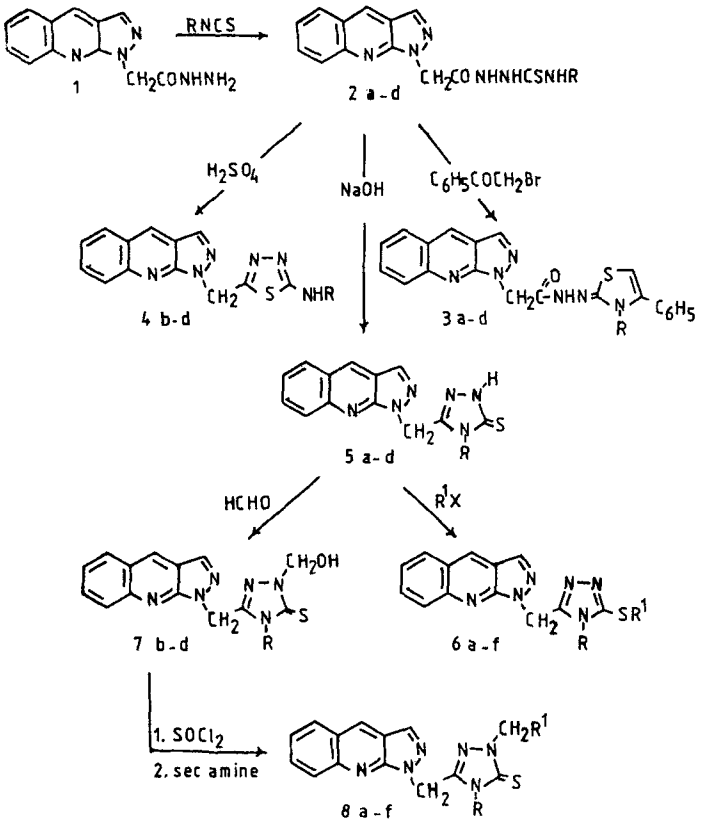

und **6f** were inactive against *Candida albicans*. So none of the prepared compounds was superior to streptomycin in these tests against *S. auveus* and *E. coli*.

B) Inotropic and Chronotropic evaluation

All compounds were preliminarly tested for their inotropic and chronotropic effects on isolated *Toad's* heart[25].

The frog heart was suspended in a 15 ml bath containing Ringer solution kept at 37°C, 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 the used concentrations has no effect on the heart.

Compound **2b** possese s a mild positive inotropic activity while **6a** and **8f** demonstrated mild negative inotropic effects. The remaining compounds showed 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. - ^{1}H-NMR-spectra: Varian EM-360L and Bruker 200 MHz spectrometers, TMS as intern. standard, chem. shift in δ (ppm). - Mass spectra: Mat-711 spectrometer, inlet temp. ca. 200°C, ionization energy 70 EV. - Analytical data: Microanalytical Unit, Faculty of Science, Cairo, Egypt.

1-(Substituted thiocarbamoylhydrazinocarbonyl)methyl-1H-pyrazolo-[3,4-b]-quinolines **2a-d**

To a solution of 1H-pyrazolo[3,4-b]quinoline-1-acetic acid hydrazide (**1**) (0.24 g, 0.001 mole) in ethanol (20 ml), the proper alkyl-, aralkyl-, and aryl isothiocyanate (0.001 mole) was added. The mixture was heated under reflux for 6-8 h, concentrated and cooled. The obtained precipitate was crystallized from ethanol. Products **2a-d** are listed in Table 1. - IR: 3340-3140 (NH); 1685 (C=O); 1615, 1570 (C=N, C=C); 1545, 1180, 1070, 960 cm^{-1} (N-C=S I, II, III, IV bands). - ^{1}H-NMR of **2b** (DMSO-d_6): 4.55 (d, J = 8 Hz, 2H, $CH_2C_6H_5$); 7.0-8.2 (m, 9H, Ar-H); 8.4 (s, 1H, pyrazoloquinoline H-4); 8.85 (s, 1H, pyrazoloquinoline H-3); 9.6, 9.9, 10.4 (three s, each 1H, three NH, D_2O exchange).

1-(3-Substituted-4-phenylthiazolin-2-ylidene)hydrazinocarbonylmethyl-1H-pyrazolo[3,4-b]quinolines (**3a-d**)

2a-d (0.001 mole) in ethanol (10 ml) and phenacyl bromide (0.2 g, 0.001 mole) were heated together under reflux for 2 h, concentrated and neutralized with sodium acetate solution. The precipitated was washed with water and crystallized from ethanol. The compounds so prepared are recorded in Table 2. - IR: 3240-3100 (br. band NH): 1680 (C=O); 1625, 1600, 1530, 1500 (C=N, δNH, C=C). - ^{1}H-NMR of **3a** ($CDCl_3$): 2.3 (broad s, 1H, NH; D_2O exchange); 4.2-4.4 (m; 2H, CH_2-CH=CH_2); 4.4-5.3 (m, 2H, CH_2-CH=CH_2); 5.4 (s, 2H, CH_2); 5.5-5.7 (m, 1H, CH_2-CH=CH_2); 7.1-8.2 (m, 10H, Ar-H); 8.3 (s, 1H, pyrazoloquinoline H-4); 8.6 (s, 1H, pyrazoloquinoline H-3). - MS of **3a**, m/z (%): 441 (32, $(M-H)^+$), 258 (5); 227 (55); 217 (37); 191 (11); 182 (23); 170 (23); 147 (90); 134 (5); 123 (30); 114 (100); 102 (55); 88 (75).

1-(5-Substituted amino-1,3,4-thiadiazol-2-yl)methyl-1H-pyrazolo[3,4-b]-quinolines **4b-d**.

2b-d (0.001 mole) were dissolved in cold pure conc. H_2SO_4 (3 ml) and stirred for 30 min at room temp., then poured into crushed ice. The precipitate was washed with water and crystallized from ethanol. The products

Table 1: 1-(Substituted thiocarbamoylhydrazinocarbonyl)methyl-1*H*-pyrazolo[3,4-*b*]quinolines **2a-d**.

Compound No.	R	Yield %	Mp °C	Molecular formula	Analyses C%	H%	N%	S%
2a	$CH_2CH{=}CH_2$	56	208-9	$C_{16}H_{16}N_6OS$	56.46	4.74	24.69	9.42
					56.1	5.0	24.3	9.2
2b	$CH_2C_6H_5$	30	185-6	$C_{20}H_{18}N_6OS$	61.52	4.65	21.52	8.21
					61.2	4.5	21.5	8.4
2c	C_6H_5	57	210-1	$C_{19}H_{16}N_6OS$	60.62	4.28	22.32	8.52
					60.5	4.5	22.0	8.4
2d	$C_6H_4CH_3$(p)	60	212-3	$C_{20}H_{18}N_6OS$	61.52	4.65	21.52	8.21
					61.2	4.7	21.9	8.1

Table 2: 1-(3-Substituted-4-phenylthiazolin-2-ylidene)-hydrazinocarbonylmethyl-1*H*-pyrazolo[3,4-*b*]quinolines **3a-d**.

Compound No.	R	Yield %	Mp °C	Molecular formula	Analyses C%	H%	N%	S%
3a	$CH_2{-}CH{=}CH_2$	40	178-9	$C_{24}H_{20}N_6OS$	65.44	5.58	19.08	7.28
					65.1	5.3	18.9	6.5
3b	$CH_2C_6H_5$	66	196-7	$C_{28}H_{22}N_6OS$	68.55	4.52	17.13	6.54
					68.2	4.2	17.2	6.5
3c	C_6H_5	28	144-5	$C_{27}H_{20}N_6OS$	68.05	4.23	17.63	6.72
					68.0	4.1	17.9	6.6
3d	$C_6H_4CH_3$(p)	53	101-2	$C_{28}H_{22}N_6OS$	68.55	4.52	17.13	6.54
					68.3	4.3	17.1	6.3

4b-d are summarized in Table 3. - IR: 3300, 3220 (NH); 1620, 1600, 1545 cm^{-1} (C=N, δ NH, C=C). - ^{1}H-NMR of compound **4c** (DMSO-d_6, 200 MHz): 5.95 (s, 2H, CH_2); 6.8-8.2 (m, 9H, Ar-H); 8.48 (s, 1H, pyrazoloquinoline H-4); 8.94 (s, 1H, pyrazoloquinoline H-3); 10.2 (s, 1H, NH).

1-(4-Alkyl, aralkyl or aryl-5-thioxo-4H-1,2,4-triazol-3-yl)methyl-1H-pyrazolo[3,4-b]quinolines **5a-d**

2a-d (0.001 mole) were heated in N NaOH (20 ml) for 1 h. The mixture was filtered while hot, poured into water and acidified with dilute HCl to

Table 3: 1-(5-Substituted amino-1,3,4-thiadiazol-2-yl)methyl-1*H*-pyrazolo[3,4-*b*]quinolines **4b-d**.

Compound No.	R	Yield %	Mp °C	Molecular formula	Analyses C%	H%	N%	S%
4b	$CH_2C_6H_5$	40	202-3	$C_{20}H_{16}N_6S$	64.50	4.33	22.56	8.61
					64.3	4.1	22.2	9.0
4c	C_6H_5	55	230-1	$C_{19}H_{14}N_6S$	63.67	3.94	23.45	8.94
					63.6	4.8	23.7	8.7
4d	$C_6H_4CH_3$(p)	77	205-6	$C_{20}H_{16}N_6S$	64.50	4.33	22.56	8.61
					64.1	4.2	22.4	8.9

pH 5. The precipitate was washed with water and crystallized from ethanol. Compounds 5a-d are listed in Table 4. - IR: 3460-3300 (NH); 1615, 1585 (C=N, C=C); 1570, 1270, 1020, 945 cm^{-1} (N-C=S, I, II, III, IV bands). - ^{1}H-NMR of **5a** ($CDCl_3$, 200 MHz); 4.8-5.11 (m; 2H, $-CH_2-CH=CH_2$); 5.0-5.1 (m, 2H, $CH_2-CH=CH_2$), 5.63-5.82 (m, 1H, $CH_2-CH=CH_2$); 5.87 (s, 2H, $N-CH_2$); 7.26-8.17 (m, 4H, arom., H-5,6,7,8); 8.31 (s, 1H, pyrazoloquinoline H-4); 8.66 (s, 1H-pyrazoloquinoline H-3); 11.33 (s, 1H, NH).

1-(5-Alkylthio or aralkylthio-4-aralkyl or aryl-4H-1,2,4-triazol-3-yl)-methyl-1H-pyrazolo[3,4-b]quinolines **6a-f**

To a solution of **5b-d** (0.001 mole) in 10% NaOH (10 ml), the proper alkyl or aralkyl halide (0.001 mole) was added. The mixture was stirred for 30 min at room temp. The precipitates of **6e** and **6f** were washed with water and crystallized from ethanol, whereas in case of compounds **6a-d**, an oily layer was formed, which was extracted into benzene, dried over Na_2SO_4, filtered, concentrated and the product was precipitated as its hydrochloride or picrate. Products **6a-f** are listed in Table 5. - IR: 1610, 1570, 1560, 1510 (C=N, C=C).

1-(1-Hydroxymethyl-4-aralkyl or aryl-5-thioxo-4H-1,2,4-triazol-3-yl)-methyl-1H-pyrazolo[3,4-b]quinolines **7b-d**

To a solution **5b-d** (0.001 mole) in dioxane (3 ml) formalin, solution 37% (3 ml) was added. The mixture was stirred at 50°C for 2 h and left overnight at room temp. Then it was concentrated, cooled and poured into water (20 ml). The precipitate was washed with water and crystallized from $CHCl_3$. The compounds so prepared are listed in Table 6. - IR: 3220 (OH); 1610, 1600, 1575, 1500 (C=N, C=C); 1240 cm^{-1} (C=S). - ^{1}H-NMR of **7d**

Table 4: 1-(4-Alkyl, aralkyl or aryl-5-thioxo-4*H*-1,2,4-triazol-3-yl)methyl-1*H*-pyrazolo[3,4-*b*]quinolines **5a-d**.

Compound No.	R	Yield %	Mp °C	Molecular formula	Analyses C%	H%	N%	S%
5a	$-CH_2-CH=CH_2$	62	196-7	$C_{16}H_{14}N_6S$	59.61	4.38	26.07	9.94
					59.3	4.7	25.8	9.6
5b	$CH_2C_6H_5$	53	218-9	$C_{20}H_{16}N_6S$	64.50	4.33	22.56	8.61
					64.3	4.0	22.2	8.5
5c	C_6H_5	90	>300	$C_{19}H_{14}N_6S$	63.67	3.93	23.45	8.94
					63.4	3.6	23.8	8.6
5d	$C_6H_4CH_3$(p)	70	189-90	$C_{20}H_{16}N_6S$	64.50	4.33	22.56	8.61
					64.3	4.7	22.5	8.6

Table 5: 1-(5-Alkylthio or aralkylthio-4-aralkyl or aryl-4*H*-1,2,4-triazol-3-yl)methyl-1*H*-pyrazolo[3,4-*b*]quinolines **6a-f**.

Compound No.	R	R^1	Yield %	Mp °C	Molecular formula	Analyses C%	H%	N%	S%
6a	$CH_2C_6H_5$	CH_3	71	140-1	$C_{21}H_{18}N_6S.HCl$	59.64	4.53	19.87	7.58
						59.3	4.3	19.5	7.4
6b	$CH_2C_6H_5$	$CH_2C_6H_5$	31	118-9	$C_{27}H_{22}N_6S.HCl$	64.98	4.65	16.84	6.42
						64.7	4.4	16.6	6.8
6c	C_6H_5	CH_3	23	123-4	$C_{20}H_{16}N_6S.$ $C_6H_3N_3O_7$	51.91	3.18	20.96	5.33
						51.9	3.0	20.8	5.2
6d	C_6H_5	$CH_2C_6H_5$	29	117-8	$C_{26}H_{20}N_6S.HCl$	64.39	4.36	17.33	6.61
						64.4	4.1	17.0	6.4
6e	$C_6H_4CH_3$(p)	CH_3	64	95-6	$C_{21}H_{18}N_6S$	65.26	4.69	21.75	8.3
						65.4	5.0	21.5	8.0
6f	$C_6H_4CH_3$(p)	$CH_2C_6H_5$	15	100-1	$C_{27}H_{22}N_6S$	70.11	4.79	18.17	6.93
						69.9	5.0	18.1	6.7

(DMSO-d_6/$CDCl_3$): δ 2.3 (s, 3H, CH_3); 3.6 (s, 2H, CH_2OH); 5.7 (s, 2H, CH_2); 6.7-7.7 (m, 8H, Ar-H); 8.0 (s, 1H, pyrazoloquinoline H-4); 8.3 (s, 1H, pyrazoloquinoline H-3).

1-(1-Substituted aminomethyl-4-aralkyl or aryl-5-thioxo-4H-1,2,4-triazole-3-yl)methyl-1H-pyrazolo[3,4-b]quinolines **8a-f**

7b-d (0.001 mole) in dry benzene (3 ml) and $SOCl_2$ (5 ml) were heated under reflux for 10-12 h. Excess $SOCl_2$ was removed in vacuo. The residue in dry benzene (2 ml) and the proper amine (0.005 mole) were heated together under reflux for 4-6 h. The precipitate was crystallized from benzene/petrol ether 60-80°C (3:1). The products obtained are recorded in Table 7. IR: 1640, 1615, 1520 (C=N, C=C); 1230 cm^{-1} (C=S).

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Table 6: 1-(1-Hydroxymethyl-4-aralkyl or aryl-5-thioxo-4*H*-1,2,4-triazol-3-yl)methyl-1*H*-pyrazolo[3,4-*b*]quinolines **7b-d**.

Compound No.	R	Yield %	Mp °C	Molecular formula	Analyses C%	H%	N%	S%
7b	$CH_2C_6H_5$	50	118-9	$C_{21}H_{18}N_6OS$	62.67	4.51	20.88	7.97
					62.4	4.7	21.0	8.1
7c	C_6H_5	70	160-1	$C_{20}H_{16}N_6OS$	61.84	4.15	21.63	8.25
					62.0	4.0	22.0	8.1
7d	$C_6H_4CH_3$(p)	65	152-3	$C_{21}H_{18}N_6OS$	62.67	4.51	20.88	7.97
					62.8	4.5	21.2	7.8

Table 7: 1-(1-Substituted aminomethyl-4-aralkyl or aryl-5-thioxo-4*H*-1,2,4-triazol-3-yl)methyl-1*H*-pyrazolo[3,4-*b*]quinolines **8a-f**

Compound No.	R	R^1	Yield %	Mp °C	Molecular formula	Analyses C%	H%	N%	S%
8a	$CH_2C_6H_5$	piperidino	20	190-1	$C_{26}H_{27}N_7S.2HCl$	57.56	5.39	18.07	5.91
						57.2	5.1	18.1	6.1
8b	$CH_2C_6H_5$	N-methyl-piperazino	25	140-1	$C_{26}H_{28}N_8S.2HCl$	56.01	5.42	20.10	5.75
						56.0	5.6	20.4	5.9
8c	C_6H_5	piperidino	90	170-1	$C_{25}H_{25}N_7S.2HCl$	56.82	5.15	18.55	6.07
						57.0	5.0	18.6	6.2
8d	C_6H_5	N-methyl-piperazino	75	101-2	$C_{25}H_{26}N_8S.2HCl$	55.25	5.19	20.62	5.9
						55.0	4.9	20.4	5.8
8e	$C_6H_4CH_3$ (p)	piperidino	79	95-6	$C_{26}H_{27}N_7S.2HCl$	57.56	5.39	18.07	5.91
						57.7	5.4	18.2	5.6
8f	$C_6H_4CH_3$ (p)	N-methyl-piperazino	52	104-5	$C_{26}H_{28}N_8S.2HCl$	56.01	5.42	20.10	5.75
						56.0	5.1	19.9	5.6

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