Non-Steroidal Antiinflammatory Agents

Synthesis of Novel 2-Pyrazolyl-4(3*H*)-Quinazolinones

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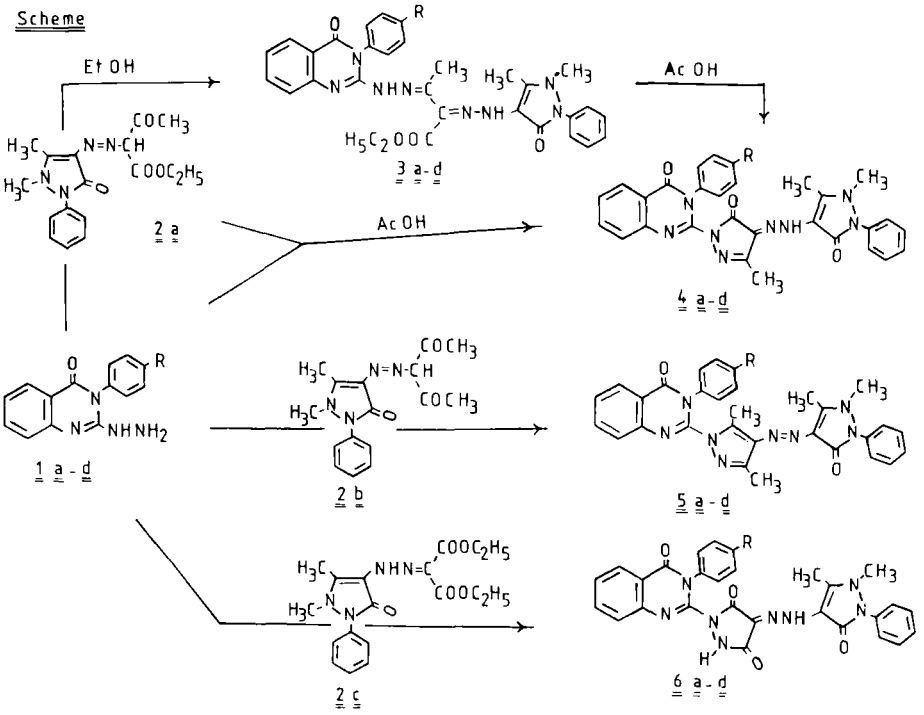
Four novel series of pyrazolyl-4(3*H*)-quinazolinones have been prepared through the reaction of 3-aryl-2-hydrazino-4(3*H*)-quinazolinones with antipyrylazo-derivatives of ethyl acetoacetate, acetylacetone or diethyl malonate. These series of compounds are 3-aryl-2-[1-ethoxycarbonyl-1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)hydrazono-2-propylidene]hydrazino-4(3*H*)-quinazolinones; 3-aryl-2-[4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)hydrazono-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl]-4(3*H*)-quinazolinones; 3-aryl-2-[4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)azo-3,5-dimethyl-1*H*-pyrazol-1-yl]-4(3*H*)-quinazolinones and 3-aryl-2-[4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)hydrazono-3,5-dioxo-pyrazolidin-2-yl]-4(3*H*)-quinazolinones. The antiinflammatory activity of some representatives of the prepared compounds was studied.

Nichtsteroidale entzündungshemmende Agentien: Synthese neuer Pyrazolyl-4(3*H*)-chinazolinone

Vier neue Serien von Pyrazolyl-4(3*H*)-Chinazolinonen wurden hergestellt durch die Reaktion von 3-Aryl-2-hydrazino-4(3*H*)-chinazolinonen mit Antipyrylazoderivaten von Ethyl-acetessigsäure, Acetylaceton oder Diethylmalonsäure. Diese Serien sind 3-Aryl-2-[1-Ethoxycarbonyl-1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)hydrazono-2-propylidene]hydrazino-4(3*H*)-chinazolinone; 3-Aryl-2-[4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)hydrazono-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl]-4(3*H*)-chinazolinone; 3-Aryl-2-[4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)azo-3,5-dimethyl-1*H*-pyrazol-1-yl]-4(3*H*)-chinazolinone und 3-Aryl-2-[4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)hydrazono-3,5-dioxo-pyrazolidin-2-yl]-4(3*H*)-chinazolinone. Die entzündungshemmende Aktivität von einigen repräsentativen Verbindungen wurde studiert.

Several compounds comprising a 4(3*H*)-quinazolinone moiety exhibit different biological activities, e.g. H_1, H_2-antihistaminic[1-3], antiinflammatory[4,5], anticonvulsant[6-8], antimicrobial[9-11], hypnotic[6], and CNS[12-13]-activities. Furthermore, the characteristic pharmacological activities of pyrazole derivatives are analgesic, antipyretic, and antiinflammatory[14-17].

Based on these facts, it was designed to synthesize compounds containing both the 4(3*H*)-quinazolinone and pyrazole moieties directly attached to each other in one and the same frame, in the hope that such an arrangement might produce compounds with higher antiinflammatory activity.



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The target compounds were prepared according to the presented scheme: Condensation of 3-aryl-2-hydrazino-4(3*H*)-quinazolinones[18] **1a-d** with ethyl antipyrylazoacetoacetate[19] **2a** in alcohol afforded the corresponding hydrazones **3a-d**. On heating **3a-d** in glacial acetic acid, they cyclized to the corresponding pyrazoline derivatives **4a-d**. Moreover, compounds **4a-d** were alternatively obtained by heating together under reflux **1a-d** and **2a** in glacial acetic acid. Likewise, heating **1a-d** with either antipyrylazoacetylacetone[16] **2b** or diethyl antipyrylhydrazonomalonate **2c** in glacial acetic acid led to the pyrazoles **5a-d** or pyrazolidindiones **6a-d**, respectively. The intermediates **2a-c** were prepared by coupling of diazotized aminoantipyrine with ethyl acetoacetate, acetylacetone or diethyl malonate, respectively.

The structures of the prepared compounds were confirmed by IR-, ^{1}H-NMR-, and elemental analyses (Experimental Part).

Antiinflammatory activity

The local antiinflammatory activity of compounds **3c**, **4c**, **5c**, and **6c** as representative examples was evaluated employing the cotton pellet granuloma bioassay in rats[20]. The results (Table 5 and Figure 1) indicate that all the tested compounds significantly inhibit the granuloma formation at a dose level of 3 mg/cotton pellet. The percent granuloma inhibitions produced by compounds **5c** and **6c** are comparable to that of the reference standard Proquazone* (1-isopropyl-7-methyl-4-phenyl-2(1*H*)-quinazolinone) at the same dose level.- From this study it can be concluded that combination of quinazolinone and pyrazole moieties in one and the same frame results in compounds with antiinflammatory activity comparable to that of Proquazone.

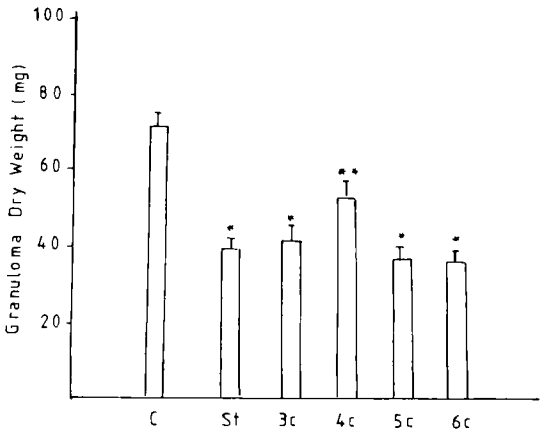

Figure 1: Effect of quinazolinones on granuloma formation. St: Proquazone, C: control. Each value represents the mean ± S.E. of six rats in an experimental group. (*) significantly different from control ($p < 0.001$), (**) significantly different from control ($p < 0.005$).

* Biarison,®Wander

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Experimental Part

Melting points: uncorrected.- IR spectra (KBr): Beckmann 4210 spectrophotometer.- ^{1}H-NMR: Varian EM 360 L spectrometer in $CDCl_3$, TMS as internal standard, chemical shift as δ (ppm).- Mass spectra: Finnigan 4510 GCMS, 70 eV.- Analytical data: Analytical Unit, Faculty of Science, Cairo University, Egypt.

Diethyl 1,5-dimethyly-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylhydrazonomalonate (**2c**)

To a cold well-stirred solution of 4-aminoantipyrine (10.2 g, 0.05 mole) in water (30 ml), acidified with H_2SO_4 (30%), was added dropwise a cold solution of $NaNO_2$ (4.14 g, 0.06 mole) in water (10 ml). An alcoholic solution of diethyl malonate (16.0 g, 0.1 mole) was then added with stirring, followed by saturated solution of sodium acetate. After standing for 3 h, the yellow precipitate was filtered, washed with water and crystallized from alcohol, m.p. 125-28°, yield 83%.- IR: 1720 (C=O, ester); 1670 (C=O of pyrazolidinone).- ^{1}H-NMR: 1.28 (t, J = 7 Hz, 6H, 2 CH_2-CH_3), 2.46 (s, 3H, pyrazolinone-C_5-CH_3), 2.96 (s, 3H, N-CH_3), 4.23 (q, J = 7 Hz, 4H, 2 CH_2-CH_3), 7.1-7.46 (m, 5H, Ar-H), 12.16 (s, 1H, NH, D-exchange).- $C_{18}H_{22}N_4O_5$ (374.40) Calc. C 57.7 H 5.92 N 15.0 Found C 57.7 H 6.1 N 14.7.

3-Aryl-2 [1-ethoxycarbonyl-1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)hydrazono-2-propylidene]-hydrazino-4(3H)-quinazolinones **3a-d**

To a solution of the appropriate **1a-d** (0.001 mole) in ethanol (30 ml) was added an equivalent amount of ethyl 4-antipyrylazoacetoacetate **2a** (0.34 g, 0.001 mole). The mixture was heated under reflux for 12 h and then left to attain room temp. The yellow product was crystallized from ethanol, Table 1.- IR: 3400-3300 (NH); 1700 (C=O, ester); 1680 (C=O, quinazolinone); 1670 (C=O, pyrazolinone); 1610 (C=N); 1530 (δNH); 1250; 1060 (C-O-C).- ^{1}H-NMR of **3a**: 1.30 (t, 3H, CH_2-CH_3), 1.93 (s, 3H, pyrazolinone-C_5-CH_3), 2.60 (s, 3H, N=C-CH_3), 3.00 (s, 3H, pyrazolinone-N-CH_3), 4.20 (q, 2H, CH_2-CH_3), 6.93-7.52 (m, 13H, 2 phenyls and quinazolinone-$C_{6,7,8}$ H), 8.03 (dd, $J_1 = 8$, $J_2 = 1.5$ Hz, 1H, quinazolinone-C_5-H), 9.80 (s, 1H, pyrazolinone-C_4-NH), 14.46 (s, 1H, quinazolinone-C_2-NH).- MS of **3c**: M^++2: 615(7.3), M^+: 613(22), 306(100).

3-Aryl-2-[4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-hydrazono-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]-4(3H)-quinazolinones **4a-d**

Method A

A solution of the appropriate **3a-d** (0.001 mole) in glacial acetic acid (15 ml) was heated under reflux for 2 h. The mixture was concentrated, cooled and poured into cold water (50 ml). The precipitated product was crystallized from aqueous alcohol, Table 2.

Method B

A mixture of equimolar amounts of the selected hydrazine **1a-d** (0.001 mole) and ethyl 4-antipyrylazoacetoacetate **2a** (0.34 g, 0.001 mole) in glacial acetic acid (15 ml) was heated under reflux for 3 h. The mixture was concentrated, cooled and poured into cold water (50 ml) with stirring. The

Table 1: *3-Aryl-2 [1-ethoxycarbonyl-1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl) hydrazono-2-propylidene]-hydrazino-4(3H)-quinazolinones* **3a-d**

Compd. No.	R	yield %	Mp °C	Molecular Formula	Analyses %, Calc. / Found C	H	N	Hal
3a	H	72	211-12	$C_{31}H_{30}N_8O_4$	64.4	5.23	19.4	-
				(578.6)	64.7	4.9	19.4	-
3b	CH_3	75	228-29	$C_{32}H_{32}N_8O_4$	64.9	5.44	18.9	-
				(592.6)	64.5	5.8	18.7	-
3c	Cl	78	221-23	$C_{31}H_{29}ClN_8O_4$	60.7	4.77	18.3	5.8
				(613.1)	60.4	4.8	18.6	5.6
3d	Br	83	214-15	$C_{31}H_{29}BrN_8O_4$	56.6	4.45	17.0	12.1
				(657.5)	56.3	4.3	16.7	12.0

Table 2: *3-Aryl-2[4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)hydrazono-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]-4(3H)-quinazolinones* **4a-d**

Compd. No.	R	Yield % *	**	Mp °C	Molecular Formula	Analyses %, Calc. / Found C	H	N	Hal
4a	H	82	67	247-49	$C_{29}H_{24}N_8O_3$	65.4	4.54	21.0	-
					(532.6)	65.6	4.3	20.9	-
4b	CH_3	87	78	232-33	$C_{30}H_{26}N_8O_3$	65.9	4.79	20.5	-
					(546.6)	66.1	5.0	20.6	-
4c	Cl	89	75	250-51	$C_{29}H_{23}ClN_8O_3$	61.4	4.09	19.8	6.3
					(567.0)	61.3	4.2	19.4	6.5
4d	Br	90	79	238-39	$C_{29}H_{23}BrN_8O_3$	57.0	3.79	18.3	13.1
					(611.5)	56.8	3.9	18.5	13.3

* Method A
** Method B

Table 3: *3-Aryl-2-[4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)azo-3,5-dimethyl-1H-pyrazol-1-yl]-4(3H)-quinazolinones* **5a-d**

Compd. No.	R	yield %	Mp °C	Molecular Formula	Analyses %, Calc. / Found C	H	N	Hal
5a	H	68	285-87	$C_{30}H_{27}N_8O_2$	67.8	5.12	21.1	-
				(531.6)	67.5	5.3	21.3	-
5b	CH_3	80	241-42	$C_{31}H_{29}N_8O_2$	68.2	5.36	20.5	-
				(545.6)	68.5	5.1	20.8	-
5c	Cl	72	>300	$C_{30}H_{26}ClN_8O_2$	63.7	4.63	19.8	6.3
				(566.0)	63.8	4.7	20.0	6.3
5d	Br	75	232-33	$C_{30}H_{26}BrN_8O_2$	59.0	4.29	18.3	13.1
				(610.5)	59.3	4.2	18.2	12.8

precipitated product was crystallized from aqueous ethanol, Table 2.- IR: 3300 (NH); 1690 (C=O, quinazolinone); 1675; 1660 (C=O, pyrazolinones); 1620 (C=N); 1530 (δNH).- ^{1}H-NMR of **4a** (DMSO-d_6): 2.03 (s, 3H, pyrazolinone-C_5-CH_3), 2.46 (s, 3H, pyrazolinone-C_3-CH_3), 3.26 (s, 3H, N-CH_3), 6.8-7.70 (m, 13H, 2 phenyls and quinazolinone-$C_{6,7,8}$ H), 8.10 (dd, 1H, quinazolinone-C_5-H), 9.36 (s, 1H, NH, D-exchange).

3-Aryl-2-[4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-azo-3,5-dimethyl-1H-pyrazol-1-yl]-4(3H)-quinazolinones **5a-d**

A mixture of the selected hydrazine **1a-d** (0.001 mole) and 4-antipyrylazoacetylacetone **2b** (0.31 g, 0.001 mole) in glacial acetic acid (15 ml) containing two drops of conc. H_2SO_4 was heated under reflux for 2 h. The mixture was allowed to cool, diluted with water and then carefully neutralized with ammonia. The separated solid was washed with water and crystallized from aqueous ethanol (Table 3).- IR: 1690 (C=O, quinazolinone); 1660 (C=O, pyrazolinone); 1640 (C=N); 1540 (N=N).- ^{1}H-NMR of **5a**: 2.3 (s, 3H, pyrazolinone-C_5-CH_3), 2.43 (s, 6H, pyrazole-C_3-CH_3 and C_5-CH_3), 3.00 (s, 3H, N-CH_3), 7.03-7.70 (m, 13H, 2 phenyls and quinazolinone-$C_{6,7,8}$ H), 8.03 (dd, 1H, quinazolinone-C_5-H).

3-Aryl-2-[4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-hydrazono-3,5-dioxo-2H-pyrazolidin-1-yl]-4(3H)-quinazolinones **6a-d**

A mixture of the proper hydrazine **1a-d** (0.001 mole) and the malonate derivative **2c** (0.37 g, 0.001 mole) in glacial acetic acid (15 ml) containing two drops of conc. H_2SO_4 was heated under reflux for 4 h. After cooling, the mixture was diluted with water and neutralized with ammonia. The

Table 4: *3-Aryl-2-[4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl) hydrazono-3,5-dioxo-2H-pyrazolidin-1-yl]-4(3H)-quinazolinones* **6a-d**

Compd. No.	R	yield %	Mp °C	Molecular Formula	Analyses %, Calc. / Found C	H	N	Hal
6a	H	72	>300	$C_{28}H_{22}N_8O_4$	62.9	4.15	21.0	-
				(534.5)	62.8	3.8	21.0	-
6b	CH_3	65	>300	$C_{29}H_{24}N_8O_4$	63.5	4.41	20.4	-
				(548.6)	63.5	4.2	20.7	-
6c	Cl	68	284-86	$C_{28}H_{21}ClN_8O_4$	59.1	3.72	19.7	6.2
				(569.0)	59.1	3.6	19.7	6.1
6d	Br	75	278-79	$C_{28}H_{21}BrN_8O_4$	54.8	3.45	18.3	13.0
				(613.4)	54.9	3.5	18.5	13.1

Table 5: Effect of tested compounds on granuloma formation[a]

Test Compounds	Dose mg/cotton pellet	Dry weight of granuloma (mg)	Granuloma inhibition %
Control	0	71.85 ± 3.52	-
Proquazone	3	39.20 ± 2.14[b]	45.44
3c	3	42.60 ± 2.54[b]	40.70
4c	3	53.00 ± 3.87[c]	26.23
5c	3	37.57 ± 2.90[b]	47.71
6c	3	37.22 ± 3.35[b]	48.19

a. Data are given as means ± S. E. of 6 animals.
b. Significantly different from control ($P > 0.001$)
c. Significantly different from control ($P > 0.005$)

product was filtered, washed with water and crystallized from aqueous ethanol, Table 4.- IR: 3320; 3250 (NH); 1690 (C=O, quinazolinone); 1670; 1660 (C=O, pyrazolinone and pyrazolidindiones); 1620 (C=N).- ^{1}H-NMR of **6b**: 2.46 (s, 3H, pyrazolinone-C_5-CH_3), 3.16 (s, 3H, N-CH_3), 7.20-7.90 (m, 13H, 2 phenyls, NH and quinazolinone-$C_{6,7,8}$ H), 8.10 (dd, 1H, quinazolinone-C_5-H), 8.56 (s, 1H, NH of pyrazolidine, D-exchange).- ^{1}H-NMR of **6d**: 2.46 (s, 3H, Ar-CH_3), 2.86 (s, 3H, pyrazolinone-C_5-CH_3), 3.30 (s, 3H, N-CH_3), 7.16-7.96 (m, 13H, 2 phenyls, NH and quinazolinone-$C_{6,7,8}$ H), 8.23 (dd, 1H, quinazolinone-C_5-H), 9.43 (s, 1H, NH, D-exchange).

Measurement of the Antiinflammatory Activity:

Adult male *Sprague-Dawley* rats (120-140 g) were maintained on standard laboratory conditions with water *ad libitum* and kept under controlled condition for one week prior to use and divided into groups (6 rats each). Cotton pellets (35 ± 1 mg) cut from dental rolls were impregnated with the test compounds in chloroform. Each pellet received 0.2 ml of the solution containing 3 mg of the test compound and the solvent was removed by evaporation. Each pellet was subsequently injected with 0.2 ml of an aqueous solution of antibiotics (1 mg penicillin G and 1.3 mg dihydrostreptomycin/ml). Two pellets were implanted subcutaneously one in each axilla of the rat under mild general anaesthesia. One group of animals received the standard reference proquazone and the antibiotic at the same dose level. Pellets containing only the antibiotic were similarly implanted in the control rats. Seven days later, the animals were sacrificed and the two cotton pellets, with their adhering granulomas, were removed, dried for 48 h at 60°C and weighed. The increment in dry weight (difference between the initial and the final pellet weights) was taken as a measure of granuloma formation. The mean dry weight of granuloma (± S.E.) was calculated for each group and the percentage reduction in dry weight of granuloma from control value was also calculated (Table 5 and Figure 1).

References

1 S. Büyüktimkin, N. Büyüktimkin, O. Özdemir, and S. Rollas, Arch. Pharm. (Weinheim) *322*, 49 (1989).
2 S. Büyüktimkin, A. Buschauer, and W. Schunack, ibid. *322*, 115 (1989).
3 N. Ogawa, T. Yoshida, T. Aratoni, E. Koshinaka, H. Kato, and Y. Ito, Chem. Pharm. Bull. *36*, 2955 (1988).
4 I. P. Singh, A. K. Saxena, J. N. Sinha, K. P. Bhargava, and K. Shanker, Indian J. Chem. Sect. B *23*, 592 (1984).
5 R. Agarwal, C. Agarwal, C. Singh, and V. Misra, J. Chem. Soc. Pak. *6*, 89 (1984); C.A. 102, 45870z (1985).
6 S. Büyüktimkin, Arch. Pharm. (Weinheim) *319*, 933 (1986).
7 M. J. Kornet, T. Varia, and W. Beaven, J. Heterocyclic Chem. *20*, 1553 (1983).
8 M. J. Kornet, Eur. J. Med. Chem. *21*, 529 (1986).
9 A. M. Farghaly, A. Mohsen, M. E. Omar, M. A. Khalil, M. A. Gaber, and H. Abou-Shleib, Eur. J. Med. Chem. *22*, 369 (1987).
10 N. S. Habib and M. A. Khalil, J. Pharm. Sci. *73*, 982 (1984).
11 A. Mohsen, M. A. Omar, S. A. Shams El-din, A. A. Ghobashy, and M. A. Khalil, Eur. J. Med. Chem. *16*, 77 (1981).
12 R. Lakhan and O. P. Singh, Arch. Pharm. (Weinheim) *318*, 228 (1985).
13 S. R. Nautiyal, V. R. Agarwal, and D. D. Mukerji, Indian J. Pharm. Sci. *50*, 26 (1988).
14 F. Bondavalli, O. Bruno, A. Ranise, P. Schenone, R. Russo, A. Loffreda, V. De Novellis, C. Lo Sasso, and E. Marmo, Il Farmaco - Ed. Sc. *43*, 1019 (1988).
15 P. Müller, H. G. Dammann, and B. Simon, Arzneim.-Forsch. *36*, 1399 (1986).
16 A. M. Farghaly, S. M. El Khawass, M. A. Khalil, F. M. Sharabi, and T. T. Daabees, Pharmazie *36*, 93 (1981).
17 G. Picciola, G. Zavaglio, G. Carenini, P. Gentili, and G. Tempra-Gabbiati, Il Farmaco - Ed. Sc. *39*, 371 (1984).
18 K. Kottke and H. Kuhmstedt, Pharmazie *33*, 19 (1978).
19 E. Emerson and J. Segal, J. Org. Chem. *13*, 535 (1948).
20 R. Meier, W. Schuler, and P. Desaulles, Experientia *6*, 469 (1950).

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