Non-Steroidal Antiinflammatory Agents, II[1]:

Synthesis of Novel Pyrazole and Pyrazoline Derivatives of 4(3H)-Quinazolinone

Nicht-steroidale Antiphlogistika, 2. Mitt.[1]: Synthese neuer Pyrazol- und Pyrazolin-Derivate des 4(3H)-Chinazolinons

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Antiinflammatory and/or analgesic activities have been ascribed to compounds containing the 4(3H)-quinazolinone[2,3] or pyrazole moiety[4-7]. Continuation to the previous work[1] in the field of the synthesis of non-steroidal antiinflammatory 4(3H)-quinazolinones, the present investigation deals with the synthesis of new compounds having the pyrazole or pyrazoline and 4(3H)-quinazolinone moieties in one molecule, hoping that such combination might improve their antiinflammatory activity.

α,β-unsaturated ketones when treated with hydrazine hydrate achieve cyclization to the corresponding pyrazoline derivatives[8,9], whereas, when arylhydrazines are used, pyrazole derivatives are formed[10-12].

In the present investigation, the designed compounds were prepared according to the reaction sequences outlined in the Scheme. The key intermediates **3a-h** were prepared by condensation of **1a-d**[13-15] with the arylglyoxals[16,17] **2a,b**. Heating **3a-h** with hydrazine hydrate in EtOH for 15 min afforded the pyrazoline derivatives **4a-h**. When heating was prolonged for 12 h, the 3-amino derivative **5** was obtained. This might be due to cyclization of the side chain as well as hydrazinolysis at the 3-position[18,19]. The formation of the pyrazoline derivatives **4a-h** was confirmed by IR- and ^{1}H-NMR-spectra as well as by the preparation of the N-acyl derivatives **6a-c**. On the other hand, when **3a-h** were heated with arylhydrazines in ethanol or glacial acetic acid, the pyrazole derivatives **7a-x** were the products.

The IR, ^{1}H-NMR and mass spectra of some representative examples are concordant with the expected structures (Experimental Part).

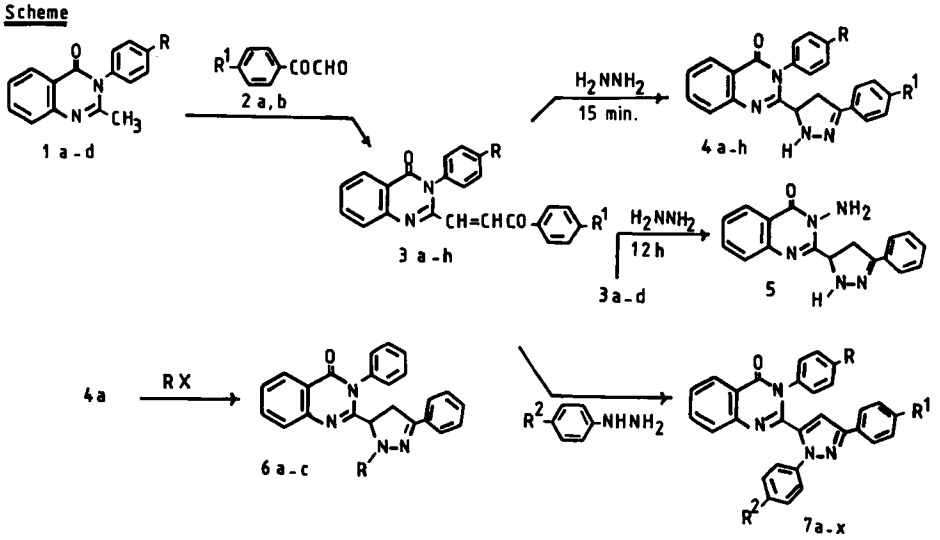
Antiinflammatory Activity

The local antiinflammatory activity of **3c, 4c, 7a,** and **7s,** as representative examples, was evaluated applying the cotton pellet granuloma bioassay in rats[20]. The results (Table 5) indicate that compounds **4c, 7a,** and **7s** significantly inhibit the granuloma formation at a dose level 3mg/cotton pellet, whereas **3c**, the open chain counterpart, displayed no activity. The percent granuloma inhibition by **4c** and **7s** was comparable to that of the reference standard Proquazone* at the same dose level: it can be concluded that the incorporation of both pyrazole or pyrazoline and 4(3H)-quinazolinone moieties in one frame results in compounds displaying antiinflammatory activity.

Experimental Part

Melting points: uncorrected. - IR (KBr): Beckman 4210 spectrophotometer. - ^{1}H-NMR: Varian EM 390L spectrometer in $CDCl_3$, chemical shift as δ (ppm). - Mass spectra: Finnigan 4510 GCMS, 70 eV. - Analytical data: Microanalytical Unit, Faculty of Science, Cairo University, Egypt.

Scheme



for a - x cf. Tables 1-4

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Table 1: 3-Aryl-2-(3-aryl-3-oxopropenyl)-4(3H)-quinazolinones **3a-h**

Compound No.	R	R^1	Yield* %	Mp °C	Molecular Formula	Analyses %, Calc./Found C	H	N	X
3a	H	H	90	248-50	$C_{23}H_{16}N_2O_2$ (352.40)	78.39 78.3	4.58 5.0	7.95 7.7	
3b	CH_3	H	94	250-52	$C_{24}H_{18}N_2O_2$ (366.42)	78.76 78.4	4.95 5.2	7.65 7.3	
3c	Cl	H	92	238-39	$C_{23}H_{15}ClN_2O_2$ (386.84)	71.41 71.1	3.91 4.1	7.24 7.0	9.16 8.9
3d	Br	H	88	254-55	$C_{23}H_{15}BrN_2O_2$ (431.29)	64.05 64.3	3.51 3.8	6.50 6.3	18.53 18.6
3e	H	CH_3	73	234-35	$C_{24}H_{18}N_2O_2$ (366.42)	78.76 78.9	4.95 5.0	7.65 7.4	
3f	CH3	CH_3	85	225-26	$C_{25}H_{20}N_2O_2$ (380.45)	78.93 79.2	5.30 5.2	7.36 7.4	
3g	Cl	CH_3	80	211-12	$C_{24}H_{17}ClN_2O_2$ (400.87)	71.91 72.2	4.27 4.5	6.99 7.2	8.48 8.5
3h	Br	CH_3	83	221-23	$C_{24}H_{17}BrN_2O_2$ (445.32)	64.73 64.5	3.85 4.1	6.29 6.0	17.94 17.8

Table 2: 3-Aryl-2-(3-aryl-4,5-dihydro-1H-pyrazol-5yl)-4(3H)-quinazolinones **4a-h**

Compound No.	R	R^1	Yield %	Mp °C	Molecular Formula	Analyses %, Calc./Found C	H	N	X
4a	H	H	94	210-11	$C_{23}H_{18}N_4O$ (366.43)	75.39 75.2	4.95 4.9	15.29 15.3	
4b	CH_3	H	74	186-88	$C_{24}H_{20}N_4O$ (380.45)	75.77 75.5	5.30 5.5	14.73 14.9	
4c	Cl	H	86	178-79	$C_{23}H_{17}ClN_4O$ (400.87)	68.91 68.7	4.27 4.3	13.98 13.8	8.84 9.0
4d	Br	H	80	172-74	$C_{23}H_{17}BrN_4O$ (445.32)	62.04 62.4	3.85 3.5	12.58 12.8	17.94 17.6
4e	H	CH_3	78	134-36	$C_{24}H_{20}N_4O$ (380.45)	75.77 75.9	5.30 5.2	14.73 14.6	
4f	CH3	CH_3	78	212-13	$C_{25}H_{22}N_4O$ (394.48)	76.12 76.2	5.62 5.7	14.20 14.2	
4g	Cl	CH_3	82	204-06	$C_{24}H_{19}ClN_4O$ (414.90)	69.48 69.5	6.62 6.4	13.50 13.6	8.55 8.2
4h	Br	CH_3	79	200-01	$C_{24}H_{19}BrN_4O$ (459.35)	62.76 63.0	4.17 3.8	12.20 12.3	17.40 17.2

3-Aryl-2-(3-aryl-3-oxopropenyl)-4(3H)-quinazolinones **3a-h**

To a solution of proper 3-aryl-2-methyl-4(3H)-quinazolinone **1a-d** (0.01 mole) in acetic anhydride (20 ml) was added an equimolar amount of phenyl- or p-tolylglyoxal **2a** or **2b**. The mixture was heated under reflux for 15 min and then allowed to attain room temp. The separated yellow product was washed with ethanol and crystallized from chloroform/ethanol (1:2), Table 1. - IR: 1690-1685 (C=O, quinazolinone), 1660 (C=O, side chain), 1615 (C=N) and 1570 (C=C). - ^{1}H-NMR spectrum of **3e**: 2.46 (s, 3H, CH_3), 6.97 (d, 1H, J = 16 Hz, CH=CHCO), 7.2-8.1 (m, 12H, two phenyls and H-6,7,8), 8.2 (d, 1H, J = 16 Hz, CH=CHCO), 8.4 (dd, J_1 = 8.5 Hz, J_2 = 1.7 Hz, 1H, quinazolinone H-5). The J value of CH=CH denotes E configuration. - Mass spectrum of compound **3c** (m/z): M^+ = 388/386 (19/54%).

3-Aryl-2-(3-aryl-4,5-dihydro-1H-pyrazol-5-yl)-4(3H)-quinazolinones **4a-h**

The appropriate **3a-h** (0.01 mole) and hydrazine hydrate (2g, 0.04 mole) in ethanol (30 ml) was heated under reflux for 15 min. Then it was concentrated and set aside overnight. The separated product was washed with water and crystallized from EtOH, Table 2. - IR: 3300-3290 (NH), 1690-1680 (C=O), 1635-1620 (C=N), 1545-1540 (δNH). - ^{1}H-NMR spectrum of **4a**: 2.73-3.8 (m, 2H, pyrazoline H-4), 4.60-4.93 (dd, J_1 = 10.5 Hz, J_2 = 7

Table 3: 3-Phenyl-2-(1-substituted-3-phenyl-4,5-dihydro-1H-pyrazol-5yl)-4(3H)-quinazolinones **6a-c**

Compound No.	R	Yield %	Mp °C	Molecular Formula	Analyses %, Calc./Found C	H	N	S
6a	CH_3CO	90	250-51	$C_{25}H_{20}N_4O_2$ (408.46)	73.51 73.4	4.94 5.0	13.72 14.0	- -
6b	C_6H_5CO	86	230-31	$C_{30}H_{22}N_4O_2$ (470.53)	76.58 76.7	4.71 4.4	11.90 11.8	- -
6c	CH_3SO_2	73	244-46	$C_{24}H_{20}N_4O_3S$ (444.52)	64.85 64.5	4.54 4.8	12.60 12.5	7.21 7.0

Table 4: 3-Aryl-2-(1,3-diaryl-1H-pyrazol-5-yl)-4(3H)-quinazolinones **7a-x**

Compound No.	R	R^1	R^2	Yield %	Mp °C	Molecular Formula	Analyses %, Calc./Found C	H	N	X
7a	H	H	H	80	210-12	$C_{29}H_{20}N_4O$ (440.51)	79.07 78.8	4.58 5.0	12.72 12.7	
7b	CH_3	H	H	69	205-07	$C_{30}H_{22}N_4O$ (454.54)	79.28 79.0	4.88 5.2	12.33 12.6	
7c	Cl	H	H	78	220-21	$C_{29}H_{19}ClN_4O$ (474.95)	73.34 73.1	4.03 3.7	11.80 11.8	7.46 7.0
7d	Br	H	H	72	138-40	$C_{29}H_{19}BrN_4O$ (519.40)	67.06 66.8	3.69 3.6	10.79 10.5	15.38 15.1
7e	H	CH_3	H	79	174-76	$C_{30}H_{22}N_4O$ (454.54)	79.28 79.1	4.88 4.9	12.33 12.7	
7f	CH3	CH_3	H	68	197-99	$C_{31}H_{24}N_4O$ (468.56)	79.47 79.7	5.16 5.1	11.96 11.8	
7g	Cl	CH_3	H	82	192-94	$C_{30}H_{21}ClN_4O$ (488.98)	73.69 73.6	4.33 4.6	11.46 11.8	7.25 7.0
7h	Br	CH_3	H	76	177-78	$C_{30}H_{21}BrN_4O$ (533.43)	67.55 67.3	3.97 4.1	10.50 10.6	14.98 14.7
7i	H	H	CH_3	72	178-80	$C_{30}H_{22}N_4O$ (454.54)	79.28 79.2	4.88 4.9	12.33 12.5	
7j	CH_3	H	CH_3	81	127-28	$C_{31}H_{24}N_4O$ (468.56)	79.47 79.2	5.16 5.3	11.96 11.6	
7k	Cl	H	CH_3	77	138-40	$C_{30}H_{21}ClN_4O$ (488.98)	73.69 73.7	4.33 4.4	11.46 11.6	7.25 7.2
7l	Br	H	CH_3	67	126-28	$C_{30}H_{21}BrN_4O$ (533.43)	67.55 67.3	3.97 4.2	10.50 10.2	14.98 14.9
7m	H	CH_3	CH_3	79	149-50	$C_{31}H_{24}N_4O$ (468.56)	79.47 79.3	5.16 4.8	11.96 11.7	
7n	CH3	CH_3	CH_3	75	122-24	$C_{32}H_{26}N_4O$ (482.59)	79.64 76.6	5.43 5.7	11.61 11.3	

Hz, 1H, pyrazoline H-5), 7.3-7.8 (m, 14H, two phenyls, NH and H-6,7,8), 8.3 (dd, J_1 = 8.5 Hz, J_2 = 1.7 Hz, 1H, quinazolinone H-5).

3-Amino-2-(3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)-4(3H)-quinazolinone (5)

A mixture of the appropriate **3a-d** (0.01 mole) and hydrazine hydrate (2 g, 0.04 mole) in EtOH (20 ml) was heated under reflux for 12 h. The mixture was concentrated and cooled. The product was filtered and crystallized from EtOH, yield 20 %, m.p. 201-03°C. - IR: 3315, 3295 (NH_2), 3145 (NH), 1690 (C=O), 1640 (C=N). - ^{1}H-NMR: 3.23-3.83 (m, 2H, pyrazoline, H-4), 4.36-4.7 (dd, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H, pyrazoline H-5), 7.20-7.93 (m, 11H, NH, NH_2, Ar-H), 8.2 (dd, J_1 = 8.5 Hz, J_2 = 1.7 Hz, 1H, quinazolinone H-5). - $C_{17}H_{15}N_5O$ (305.3) Calc. C 66.9 H 4.95 N 22.9 Found C 66.7 H 4.7 N 22.7.

cont. Table 4:

Compound No.	R	R^1	R^2	Yield %	Mp °C	Molecular Formula	Analyses %, Calc./Found C	H	N	X
7o	Cl	CH_3	CH_3	68	134-36	$C_{31}H_{23}ClN_4O$ (503.01)	74.02 73.9	4.61 4.5	11.14 11.0	7.05 7.0
7p	Br	CH_3	CH_3	82	138-39	$C_{31}H_{23}BrN_4O$ (547.46)	68.01 67.9	4.23 3.9	10.23 9.9	14.60 14.9
7q	H	H	Br	80	183-85	$C_{29}H_{19}BrN_4O$ (519.40)	67.06 66.8	3.69 3.5	10.79 10.5	15.38 15.5
7r	CH_3	H	Br	72	146-48	$C_{30}H_{21}BrN_4O$ (533.43)	67.55 67.5	3.97 4.3	10.50 10.2	14.98 14.6
7s	Cl	H	Br	76	130-32	$C_{29}H_{18}BrClN_4O$ (553.85)	62.89 62.8	3.28 3.6	10.12 9.9	Br: 14.43 14.5
7t	Br	H	Br	68	118-20	$C_{29}H_{18}Br_2N_4O$ (598.30)	58.22 58.3	3.03 3.3	9.38 9.1	26.71 26.4
7u	H	CH_3	Br	69	160-61	$C_{30}H_{21}BrN_4O$ (533.43)	67.55 67.2	3.97 4.3	10.50 10.2	14.98 15.3
7v	CH3	CH_3	Br	76	115-17	$C_{31}H_{23}BrN_4O$ (547.45)	68.01 68.2	4.23 4.0	10.23 10.0	14.60 14.9
7w	Cl	CH_3	Br	72	125-26	$C_{30}H_{20}BrClN_4O$ (567.87)	63.45 63.7	3.55 3.2	9.87 10.1	Br: 14.07 14.0
7x	Br	CH_3	Br	78	103-05	$C_{30}H_{20}Br_2N_4O$ (612.32)	58.85 59.0	3.29 3.5	9.15 9.3	26.10 25.9

Table 5: Effect of tested compounds on Granuloma formation

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	70.8 ± 5.00	-
4c	3	33.29 ± 2.6[b]	53.67
7a	3	46.5 ± 3.17[b]	35.28
7s	3	36.5 ± 3.17[b]	49.20

a. Data are given as means ± S.E. of 5 animals
b. Significantly different from control ($P < 0.001$)

3-Phenyl-2-(1-acetyl, benzoyl or methanesulphonyl)-4,5-dihydro-1H-pyrazol-5-yl)-4(3H)-quinazolinones **6a-c**

To a solution of **4a** (0.37 g, 0.001 mole) in pyridine (5 ml) was added the equivalent amount of acetyl chloride, benzoyl chloride or methanesulphonyl chloride. The mixture was heated on a boiling water-bath for 15 min, cooled and then poured onto crushed ice (20 g). The separated product was filtered, washed with water and crystallized from EtOH for **6a,c** or from chloroform-petroleum ether (60-80°C) for **6b**, Table 3. - IR of **6a,b**: 1690-1685 (C=O quinazolinone), 1660 (C=O amide), 1640-1630 (C=N). - IR of **6c**: 1690 (C=O quinazolinone), 1365, 1165 (SO_2), 1630 (C=N). - ^{1}H-NMR spectrum of **6a**: 2.4 (s, 3H, CH_3), 3.1-3.46 (m, 2H, pyrazoline H-4), 5.06 (dd, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H, pyrazoline H-5), 7.2-7.89 (m, 13H, two phenyls and H-6,7,8), 8.3 (dd, J_1 = 8.5 Hz, J_2 = 1.7 Hz, 1H, quinazolinone H-5). - ^{1}H-NMR spectrum of **6c**: 3.13-3.60 (m, 5H, CH_3 and pyrazoline H-4), 5.13 (dd, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H, pyrazoline H-5), 7.10-7.93 (m, 13H, two phenyls and H-6,7,8), 8.36 (dd, J_1 = 8.5 Hz, J_2 = 1.7 Hz, 1H, quinazoline H-5).

3-Aryl-2-(1,3-diaryl-1H-pyrazol-5-yl)-4(3H)-quinazolinones **7a-x**

To a solution of the appropriate **3a-h** (0.01 mole) in EtOH or glacial acetic acid (20 ml) was added the proper arylhydrazine hydrochloride (0.012 mole) and anhydrous sodium acetate (0.98 g, 0.01 mole). The mixture was heated under reflux for 6 h and then poured into cold water. The precipitate was filtered and crystallized from aqueous ethanol, Table 4. - IR: 1690-1685 (C=O), 1635-1610 (C=N). - ^{1}H-NMR spectrum of **7b**: 2.26 (s, 3H, CH_3), 6.83-7.76 (m, 18H, three phenyls, pyrazole H-4 and

quinazolinone H-6,7,8), 8.26 (dd, J_1 = 8.5 Hz, J_1 = 1.7 Hz, 1H, quinazolinone H-5). -

References

1 Part I: A.M. Farghaly, I. Chaaban, M.A. Khalil, and A.A. Bekhit, Archiv. Pharm. (Weinheim), in press (Ph710).
2 I.P. Singh, A.K. Saxena, J.N. Sinha, K.P. Phargava, and K. Shanker, Indian J. Chem. Sect. B *23*, 592 (1984).
3 R. Agarwal, C. Agarwal, C. Singh, and V.S. Misra, J. Chem. Soc. Pak. *6*, 89 (1984); C.A. *102*, 45870c (1985).
4 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).
5 P. Muller, H.G. Dammon, and B. Simon, Arzneim.-Forsch. *36*, 1399 (1986).
6 A.M. Farghaly, S.M. El-Khawass, M.A. Khalil, F.M. Sharabi, and T.T. Daabees, Pharmazie *36*, 93 (1981).
7 G. Picciola, G. Zavaglio, G. Carenini, P. Gentili, and G. Tempra-Gabbiati, Il Farmaco Ed.Sc. *39*, 371 (1984).
8 F. Stranss and A. Ackermann, Ber. Dtsch. Chem. Ges. *42*, 1813 (1916).
9 L. Mehr, E.I. Becker, and P.E. Spoerri, J. Am. Chem. Soc. *77*, 984 (1955).
10 K.v. Auwers and A. Kreuder, Ber. Dtsch. Chem. Ges. *58*, 1974 (1925).
11 R.G. Martin, U.S. Patent, 2,508,617 (1950); C.A. *44*, 9667i (1950).
12 H.M. Feid-Allah, Pharmazie, *36*, 754 (1981).
13 H. Stephen and B. Staskun, J. Chem. Soc. *1965*, 980.
14 H.W. Grimmel, A. Guenther, and J.F. Morgan, J. Am. Chem. Soc. *68*, 542 (1946).
15 K.H. Boltze, H.D. Dell, H. Lehwald, D. Lorenz, and M.R. Schweer, Arzneim. Forsch. *13*, 689 (1963).
16 H.A. Riley and A.R. Grey, Org. Synthesis *II*, 509 (1947).
17 H.v. Pechmann, Ber. Dtsch. Chem. Ges. *22*, 2560 (1889).
18 S.L. Mertsalov, N.N. Vereshchagina, and I. Ya Postovskii, Kim. Getersikl. Soedin., Akad. Nauk Latv. SSR, 2, 215 (1965), C.A. *63*, 56436 (1965).
19 N.S. Habib and M.A. Khalil, J. Pharm. Sci. *73*, 982 (1984).
20 R. Meier, W. Schuler, and P. Desaulles, Experientia *6*, 469 (1950).

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