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Synthesis and Pharmacological Studies of Some Pyrone and Benzodifuran Derivatives

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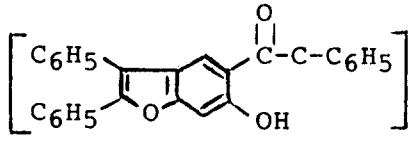
The michael adducts **2a,b** were obtained from the reaction of the phenylacetyl derivative **1** with benzaldehyde and p-anisaldehyde respectively. **2a** and **2b** were subjected to react with cyanoethanoic acid hydrazide, malononitrile, cyanothioacetamide, cyanoacetamide and 1,1,3-tricyano-2-amino propene to yield **4a-h** and **5a,b** respectively. Hydrogen peroxide oxidation of **2a,b** gave the aurone derivative **6a,b**. The pyrone derivatives **8a,b** were obtained from **2a,b** by addition of chloroacetyl chloride followed by dehydrochlorination.

Key words: Chalcones, Michael aducts, Antiinflammatory agents, Anticoagulants.

INTRODUCTION

Benzofuran derivatives are widely used as coronary vasodilators (Anrep *et al.*, 1949), in the therapy of cerebral arteriopathies (Fauran *et al.*, 1970). Some are known to have antibacterial (Ismail *et al.*, 1977; Hishmat *et al.*, 1977; Nomura *et al.*, 1978; Ismail *et al.*, 1985) and antiparasitic, analgesic and antiinflammatory activities (El-Diwani *et al.*, 1988).

Claisen-Schmidt condensation of 1-(2,3-diphenyl-6-hydroxybenzofuranyl)-2-phenyl-ethanone **1** (Hishmat *et al.*, 1987) with p-nitrobenzaldehyde or p-methoxybenzaldehyde using piperidine as base yielded the propenone, derivative **2** together with a minor amount of the pyrone derivative **3**. The mass spectrum of **2a** showed a molecular ion $[M+H]^+$ at *m/e* 538 and 402 as base peak for the fragment:



Its p.m.r. spectrum (200 MHz, $CDCl_3$) showed signals at δ 6.8-7.4 ppm (17H, m, 15 aromatic protons+1 vinyl proton+H-7) and at δ 7.9-8.2 ppm (5H, m, 4H of the p-nitrophenyl moiety+H-4). The mass spectra of **2b** and **3b** show the same M^+ at *m/e* 522.

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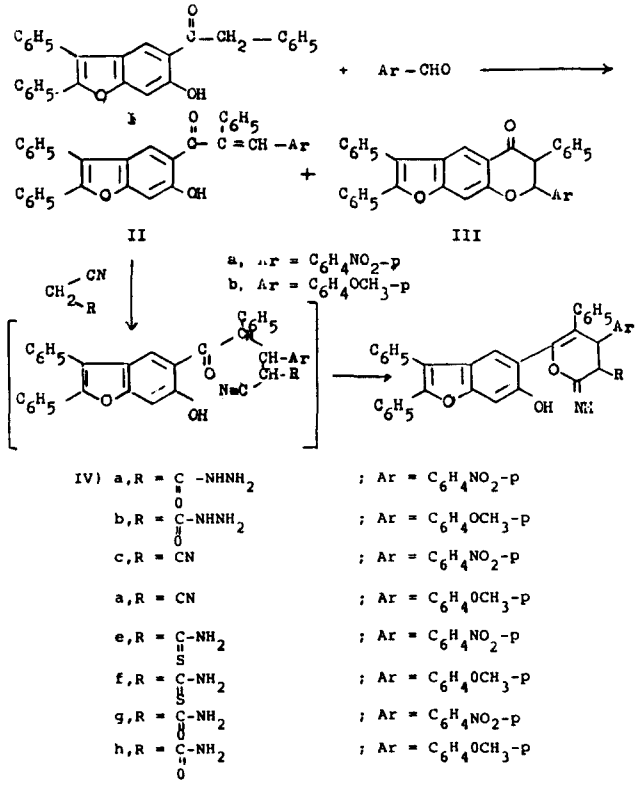
The p.m.r. spectrum of **3b** ((90 Hz, $CDCl_3$) revealed the presence of signals at δ 3.6 ppm (3H, s, OCH_3), δ 4.0 ppm (1H, d, H-7, J=10 Hz), δ 5.0 ppm (1H, d, H-6, J=10 Hz), δ 6.77 ppm (2H, d, protons ortho to OCH_3, J=8 Hz), δ 6.97-7.77 ppm (18H, m, 15 aromatic protons+H-9+2 protons meta to OCH_3), δ 8.08 ppm (1H, s, H-4).

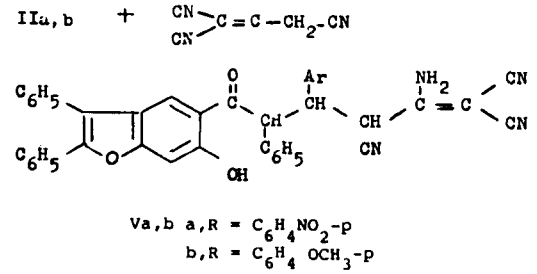
Michael addition of **2a** and **2b** with active methylene compounds using triethyl amine as base yielded the Michael adducts *via* 1,2-addition on the double bond followed by cyclization of the cyano group with the carbonyl group to give the iminopyran derivative as shown in Scheme 1. The reaction of **2a** and **2b** with cyanoethanoic acid hydrazide, malononitrite, cyanothioacetamide, cyanoacetamide in presence of triethyl amine afforded the 2-imino-3,4-dihydropyran derivatives. The chalcones **2a** and **2b** when treated with 1,1,3-tricyano-2-amino propene gave open-chain products **5a,b** respectively (Scheme 2).

Oxidation of chalcones **2a** and **2b** using alkaline hydrogen peroxide produced an aurone cyclic structure. It proceeded probably *via* the attack of the O^- ion on the α-carbon atom of the epoxide to form the corresponding benzodifuran derivatives **6a,b** as shown in Scheme 3. The p.m.r spectrum of **6a** ($CDCl_3$, 200 MHz) showed signals from δ 6.81-8.25 ppm as a great multiplet (21H, 15 phenyl protons, 4 p-nitrophenyl, H-4 and H-7), a singlet at δ 4.08 ppm (1H, tertiary CH) and a broad singlet at δ 1.85 ppm (1H, alcoholic OH).

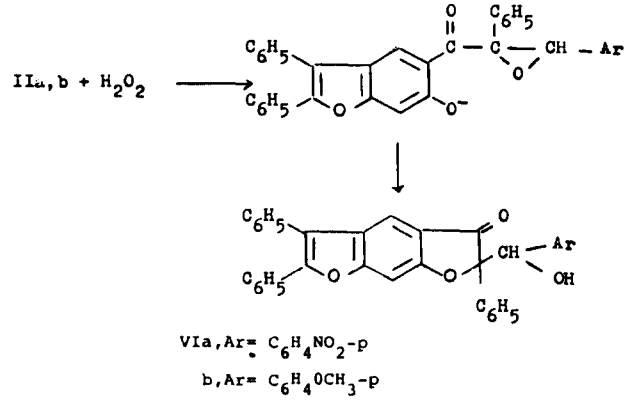
The reaction of **2a,2b** with chloracetyl chloride and triethylamine in dry benzene produced the corresponding 4,5,6-trisubstituted pyrone derivatives **8a,b** *via* a



Scheme 1.



Scheme 2.



Scheme 3.

1,4-cycloaddition product **7a,b** which in presence of triethylamine undergoes dehydrochlorination to **8** as shown in Scheme 4. The p.m.r spectrum of **8b** (200 MHz, $CDCl_3$) revealed the C_3 proton of the pyrone ring as a singlet at δ 8.0 ppm, a singlet at δ 3.8 ppm (3H, OCH_3), two doublets at δ 6.5, 6.8 ppm (2H, ortho anisyl protons, δ J=10 Hz), a multiplet at δ 7.2-7.2 ppm (19H, 15 phenyl protons+2 anisyl protons+ H-4 and H-7) and a singlet at δ 12.5 ppm (1H, OH proton).

EXPERIMENTAL METHODS

All melting points were uncorrected. The infra red spectra were recorded on a Unicam SP 1000 Spectra photometer. The p.m.r spectra were run on a varian (M-390 spectrometer at 90 or 200 MHz), using TMS as internal standard in $CDCl_3$ or DMSO. Mass spectra were recorded on mass spectrometers MS 30 and M 59 (AEI) at 70 eV.

Reaction of 2,3-diphenyl-6-hydroxybenzofuran with aromatic aldehydes

General procedure: A mixture of **1** (0.01 mole), aromatic aldehydes (0.01 mole), and **2** drops of piperidine in 20 ml of chloroform was refluxed for 7 hours then the solvent was evaporated under reduced pressure. The solid so obtained was crystallized from absolute ethanol.

1-(2,3-diphenyl-6-hydroxy-5-benzofuranyl)-2-phenyl-3-(3'-nitrophenyl) propen-1-one 2a: was obtained as orange crystals, mp. 122°C; yield ca. 60% (Found: C, 78.20; H, 4.30; N, 2.59. $C_{35}H_{23}NO_5$ requires C, 78.21; H, 4.28; N, 2.60%).

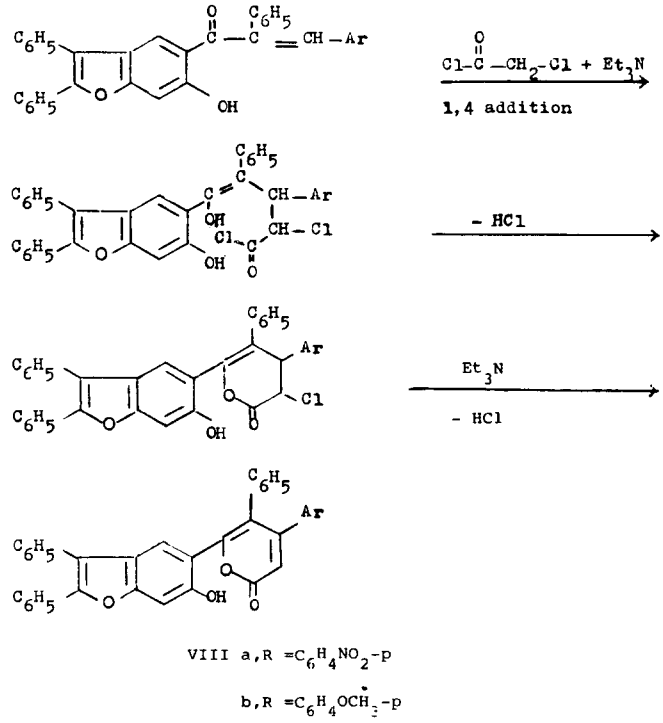
7-(p-nitrophenyl)-6,7-dihydro-2,3,6-triphenyl-5H-furo (3,2-g) 1 benzopyran-5-one 3a: was obtained by concentration of the mother liquor as pale yellow crystals, mp. 192°C; yield ca. 20% (Found: C, 78.20; H, 4.20; N, 2.58. $C_{35}H_{23}NO_5$ requires C, 78.21; H, 4.28; N, 2.60%).

1-(2,3-diphenyl-6-hydroxy-5-benzofuranyl)-2-phenyl-3-anisyl-propen-1-one 2b: was obtained as canary yellow crystals, mp. 186°C; yield ca. 70% (Found: C, 82.74; H, 50.00. $C_{36}H_{26}O_4$ requires C, 82.76; H, 44.98%).

7-anisyl-6,7-dihydro-2,3-triphenyl-5H-furo (3,2-g) 1 benzopyran-5-one 3b: was formed by concentration of the mother liquor as pale yellow crystals, mp. 147°C; yield ca. 10% (Found C, 82.70; H, 44.94. $C_{36}H_{26}O_4$ requires C, 82.76; H, 4.98%).

Reaction of the chalcones with active methylene compounds

General procedure: A suspension of **2a** or **b** (0.01



Scheme 4.

mole) in absolute ethanol (20 ml) was treated with an equimolar amount of the active methylene compound and then triethylamine (3 drops) were added. The reaction mixture was refluxed for 3 hours (TLC control). The solvent was evaporated under reduced pressure and the solid so obtained was crystallized from ethanol.

3-carboxyhydrazino-2-imino-4-(p-nitrophenyl)-5-phenyl-6-(2',3'-diphenyl-6'-hydroxy-5'-benzofuranyl)-3,4-dihydropyran 4a: was obtained as pale yellow crystals, mp. 178℃ yield ca. 60%. (Found: C, 71.61; H, 4.41; N, 8.86. $C_{38}H_{28}N_4O_6$ requires C, 71.69; H, 4.40; N, 8.80%).

3-carboxyhydrazino-2-imino-4-anisyl-5-phenyl-6-(2',3'-diphenyl-6'-hydroxy-5'-benzofuranyl)-3,4-dihydropyran 4b: formed pale yellow crystals, mp. 195℃; yield ca. 50%. (Found: C, 75.37, H, 5.05; N, 6.77. $C_{39}H_{31}N_3O_5$ requires C, 75.36; H, 4.99, N, 6.76%)

3-cyano-2-imino-4-(p-nitrophenyl)-5-phenyl-6-(2',3'-diphenyl-6'-hydroxy-5'-benzofuranyl)-3,4-dihydropyran 4c: formed brown crystals, mp. 118℃; yield ca. 50% (Found C, 75.63; H, 4.15; N, 6.94. $C_{38}H_{25}N_3O_5$ requires C, 75.62, H, 4.14; N, 6.96).

3-cyano-2-imino-4-anisyl-5-phenyl-6-(2',3'-diphenyl-6'-hydroxy-5-benzofuranyl)3,4-dihydropyran 4d: was obtained in ca 50% yield as brown crystals, mp. 106-108℃ (Found C, 79.55; H, 4.77; N, 4.52. $C_{39}H_{28}N_2O_4$ requires C, 79.59; H, 4.66; N, 4.76%).

Table I. Antiinflammatory effect of tested compounds in chronic and acute models of experiments

Group	Oedema	Pellet wt/gm	Ulcer No.
Control	49.9± 2.37	0.0750± 0.004	
2a	17.6± 0.91**	0.034± 0.0037**	2
2b	60.3± 2.47	0.083± 0.004	0
4a	56.6± 3.13	0.058± 0.008**	0
4g	27.2± 2.76**	0.041± 0.003**	0
4h	30.5± 1.37**	0.053± 0.003**	1
5a	42.5± 1.90*	0.042± 0.003**	0
5b	58.7± 2.78	0.049± 0.004**	0
8a	58.3± 4.30	0.054± 0.003**	3
8b	44.4± 2.44	0.038± 0.020**	1
Indomethacin	20.4± 2.05**	0.028± 0.002**	1.2

*p<0.05; **p<0.01

3,4,5,6-tetrasubstituted-3,4-dihydropyran derivatives

4e: was obtained as dark brown crystals, mp. 140-142 ℃; yield ca. 660% (Found C, 71.59; H, 4.27; N, 6.54; S, 5.01. $C_{38}H_{27}N_3O_5S$ requires C, 71.58; H, 4.23; N, 6.59; S, 5.02%).

4f formed dark brown crystals, mp. 121℃; yield ca. 70% (Found C, 75.26; H, 4.84; N, 4.48; S, 5.16. $C_{39}H_{30}N_2O_4S$ requires C, 75.24; H, 44.82; N, 4.50; S, 5.14%).

4g was obtained in ca. 52% yield as yellow crystals, mp. 114℃ (Found C, 73.40; H, 4.35; N, 6.70. $C_{38}H_{27}N_3O_6$ requires C, 73.42; H, 4.34; N, 6.76%).

4h formed yellow crystals, mp. 156℃; yield ca. 65%. (Found C, 77.24; H, 5.00; N, 4.60. $C_{39}H_{30}N_2O_5$ requires C, 77.22; H, 4.95; N, 4.62%).

The tricyano derivatives

5a was obtained as dark brown crystals, mp. 130℃; yield ca. 58% (Found C, 73.55; H, 4.05; N, 10.44. $C_{41}H_{27}N_5O_5$ requires C, 73.54; H, 4.03; N, 10.46%).

5b was obtained in ca. 54% yield as dark brown crystals, mp. 134℃ (Found C, 77.02; H, 4.56; N, 8.50. $C_{42}H_{30}N_4O_4$ requires C, 77.06; H, 4.58; N, 8.56%).

Oxidation of 2a,b with hydrogen peroxide

General procedure: A mixture of equimolar amounts of **2a,b** and hydrogen peroxide (15%) in methanol (20 ml) and sodium hydroxide solution (10 ml) (16%) was well stirred for 6 hours, then kept one day in the refrigerator. The precipitate formed was filtered and crystallized from the proper solvent.

The aurone derivatives

6a was crystallized from ethanol as yellow crystals, mp. 160℃; yield ca. 50% (Found C, 75.76; H, 4.20; N, 2.49. $C_{35}H_{23}No_6$ requires C, 75.94; H, 44.15; N, 2.53 %).

6b, formed white crystals from methanol, mp. 180℃;

Table II. Anticoagulant effect of tested compounds after 3 days of administration 0.2 mmol dose

Group	CT min	BT min	Plat No./10^3	Fib. g/L
Control	1.18± 0.08	3.75± 0.21	386.5± 13.6	2.20± 0.45
2a	0.87± 0.05	1.79± 0.10	574.3± 29.4**	7.00± 0.51**
2b	2.79± 0.07**	5.82± 0.25**	191.8± 17.9**	2.60± 0.72
4a	0.77± 0.06**	2.55± 0.39	449.7± 29.8	3.0± 0.46
4g	2.12± 0.41	5.93± 0.72	405.0± 19.5	8.00± 0.48**
4h	4.03± 0.46**	12.2± 1.16**	369.3± 27.9	6.00± 0.46**
5a	2.38± 0.16**	7.40± 0.33**	645.7± 25.6**	0.02± 0.01**
5b	2.19± 0.17**	5.00± 0.05**	193.5± 16.8**	2.40± 0.66
8a	1.26± 0.03	3.40± 0.27	427.7± 17.3	3.40± 0.23
8b	1.41± 0.08	2.99± 0.46	375.5± 17.9	0.40± 0.08

Table II. Anticoagulant effect of tested compounds after 7 days of administration

Group	CT min	BT min	Plat No./10^3	Fib. g/L
Control	1.20± 0.06	3.13± 0.34	356.7± 21.6	2.40± 0.48
2a	1.11± 0.08	1.22± 0.14**	297.0± 15.5*	8.00± 0.44**
2b	2.81± 0.07**	6.45± 0.26	706.3± 26.4**	2.00± 0.64
4a	1.87± 0.10	1.84± 0.23**	530.0± 38.9**	4.00± 0.24*
4g	3.34± 0.35**	4.78± 0.24**	497.5± 27.4**	10.00± 0.91
4h	2.63± 0.25**	4.18± 0.16*	425.0± 27.1	7.00± 27.10*
5a	2.01± 0.14**	7.37± 0.34*	309.3± 15.3	0.07± 0.01**
5b	2.30± 0.12**	4.11± 0.10*	597.7± 23.3**	5.00± 0.19**
8a	0.68± 0.06	4.68± 0.56	535.3± 17.2**	2.90± 0.36
8b	1.31± 0.16	3.04± 0.46	466.2± 18.6	0.30± 0.05

yield ca. 53% (Found C, 80.30; H, 44.82. $C_{36}H_{26}O_5$ requires C, 80.29; H, 4.83).

Reaction of 2a,b with chloroacetyl chloride and triethylamine

General procedure: A mixture of each of **2a,2b** (0.01 mole) in dry benzene 20 ml was treated with an equimolar amount of chloroacetyl chloride and triethylamine (97). The reaction mixture was then refluxed for a period of 24 hours. (The progress of the reaction was followed up by TLC). The precipitate formed was purified by several washings with anhydrous diethyl ether, the hygroscopic product so obtained **7a,b** was directly dehydrochlorinated with an equimolar amount of triethylamine. The reaction mixture was then refluxed for 6 hours, (the progress of the reaction was followed up by TLC) then evaporated *in vacuo*. The precipitate so formed was crystallized from the proper solvent.

4,5,6-trisubstituted pyrone derivatives

8a was crystallized from ethanol as brown crystals, mp. 196℃; yield ca. 50%. (Found C, 77.00; H, 4.00; N, 2.40; $C_{37}H_{23}NO_6$ requires C, 76.94; H, 3.98; N, 2.42 %).

8b gave borwn crystals by TLC (eluent petroleum ether 60-80℃: ether ratio 7:3). mp. 222℃; yield ca. 40%. (Found C, 81.10; H, 4.60. $C_{38}H_{26}O_5$ requires, C, 81.13; H, 4.62%).

Antiinflammatory effects

Animals: Male albino rats were obtained from the animal house colony from the National Research Center, Dokki, Egypt. They were weiged individually and the average weights ranged between 100 and 120 gm. They were kept on standard laboratory diet and water was provided ad lib.

Animals were divided into groups each of six animals.

Group I: control group recieved 1 ml of 20% propylen glycol in water in oral dose.

Group II: recieved indomethacin 20 mg/kg b.wt. weight as positive control. Groups III-XII: recieved the tested compounds in 0.2 mmol/kg body weight (Beetz *et al.*, 1982) in 20% propylene glycol.

The acute and chronic antiinflammatory effect of tested compounds were done according to the methods described by Winter *et al.* (1962) and Meier *et al.* (1950) respectively the mean percent oedema and mean gain in pellet's weight were calculated and compared with that of the control. Results were statistically analysed using student T test. Table I ulcerogenic activity was done according to Corell *et al.* (1979) (Table I).

Table III. Effect on haemogram after 1 week

Group	PCV. %	HB. g/100 ml	RBC. No.×10⁶	WBC. No.×10³	D.L.C. (No.×10³) L.	N.	M.	EO.	B.
2a	49.17**	19.23**	6.33**	7.40**	3.77**	2.48*	0.99	0.14	0.02
	1.23	0.77	0.32	0.50	0.26	0.16	0.08	0.65	0.01
2b	39.30	12.10	5.03**	13.17**	7.34	4.18**	1.43	0.21	0.00
	0.99	0.43	0.26	0.52	0.46	0.40	0.23	0.10	0.00
4a	43.70**	16.82**	7.40**	6.40**	3.63**	1.89	0.72	0.20**	0.00
	0.92	0.69	0.47	0.52	0.25	0.19	0.12	0.02	0.00
4g	46.50**	13.70**	6.00**	6.90**	4.63**	1.15**	1.01	0.13*	0.00
	0.76	0.33	0.29	0.71	0.42	0.16	0.16	0.05	0.00
4h	55.50**	15.70**	6.60**	6.63**	4.28**	1.52*	0.71**	0.10**	0.02
	0.67	0.76	0.28	0.48	0.34	0.20	0.06	0.004	0.02
5a	11.00*	17.30**	5.34**	6.83**	9.64**	4.66**	2.22**	0.29*	0.17
	1.15	0.83	0.42	0.42	0.51	0.18	0.14	0.11	0.08
5b	39.20	12.42	4.40	15.75**	8.26	5.66**	1.70*	0.00	0.00
	1.01	0.47	0.27	1.05	0.57	0.91	0.26	0.00	0.00
8a	38.30	11.62	5.53**	9.87	4.88**	3.78**	1.21	0.00	0.00
	1.15	0.35	0.29	0.55	0.14	0.37	0.15	0.00	0.00
8b	39.80	16.20**	6.50**	4.50**	3.04**	0.98**	0.37**	0.11	0.00
	1.51	0.56	0.31	0.38	0.24	0.10	0.07	0.02	0.00
Control	39.30	11.92	3.52	10.40	6.95	2.26	0.98	0.00	0.00
	1.02	0.15	0.34	0.53	0.32	0.22	0.06	0.00	0.00

*p<0.05; **p<0.01; No. of rats=6

Table III. Effect on haemogram after 2 week

Group	PCV. %	HB. g/100 ml	RBC. No.×10⁶	WBC. No.×10³	D.L.C. (No.×10³) L.	N.	M.	EO.	B.
2a	39.80	13.50	7.60**	14.02**	7.72**	4.50**	1.67	0.13	0.00
	2.00	0.60	0.20	0.40	0.36	0.25	0.12	0.08	0.00
2b	3.00*	11.10	5.00	10.40	6.91	1.80*	1.58	0.11	0.00
	1.00	0.30	0.20	0.97	0.88	0.18	0.18	0.06	0.00
4a	36.70	11.70	4.50	9.78	5.40	3.17	1.08	0.14	0.00
	1.00	0.50	0.30	0.48	0.37	0.20	0.10	0.06	0.00
4g	38.80	13.00*	3.90**	6.87**	4.62**	1.15**	0.94	0.17	0.00
	1.10	0.50	0.18	0.28	0.17	0.10	0.08	0.04	0.00
4h	37.50	11.05	3.90**	6.33**	3.28**	1.97*	0.87	0.13	0.08
	1.12	0.71	0.20	0.28	0.11	0.12	0.10	0.05	0.05
5a	45.50**	14.50**	6.40**	11.37	5.93	3.92*	1.36	0.15	0.00
	2.00	0.60	0.20	0.18	0.32	0.28	0.15	0.06	0.00
5b	37.80	12.20	5.20	10.60	7.27	1.78*	1.37	0.17	0.00
	1.30	0.50	0.20	0.62	0.62	0.10	0.17	0.09	0.00
8a	34.80	41.90	4.80	10.27	6.98	2.04**	0.93	0.32	0.00
	0.90	0.20	0.20	0.70	0.49	0.27	0.12	0.08	0.00
8b	40.00	12.00	5.50	16.08**	11.58	2.93	1.30	0.31	0.00
	1.30	0.40	0.20	1.16	0.93	0.17	0.22	0.11	0.00
Control	37.00	11.40	5.20	9.85	5.78	2.69	1.21	0.18	0.00
	1.20	0.50	0.20	0.73	0.27	0.30	0.17	0.07	0.00

The anticoagulant effect

Male albino rates weighing (100-110 g b.wt.) were divided into 10 groups, six animals in each. Group I: used as a control group and recieved 1 ml of 20% propyrlene glycol in water dialy oral dose. The other groups recieved 2 mmol/kg b.wt. daily oral dose of the tested compounds in 20% propylene glycol.

The anticoagulant effects of the tested compounds were evaluated using the whole-blood clotting time, bleeding time, platlet count and fibrinogen concentration (Kaneko and Cornelius, 1971).

Blood samples were obtained from the retro-orbital

venous plexus of each rat, collected in a clean tube containing EDTA anticoagulant, to evaluate the Haemogram according to standard techniques described in Jain (1986).

PHARMACOLOGICAL RERULTS

The results revealed that compounds **2a**,**4h**,**g** and **5a** have significantly decreased the oedema and granuloma tissue in acute and chronic models of experiment $p<0.01$. Compounds **4a**, **5b** and **8a**,**b** showed an antiinflammatory effect in the chronic model only while failed to produce an acute effect. Compound **2b** had no effect. In comparison to Indomethacin, the widely used antiinflammatory drug, compound **2a** was the only one to be more potent while the other compounds showed less potency.

Fortunately most of the tested compounds were devoid of ulcerogenic activity except **a**,**b** and **5a** which showed little evidence of ulcers.

The results in Table **2** showed that compounds **2b**, **4g**,**h** and **5a**,**b** caused prolonged clotting and bleeding time. This indicated that such compounds have anticoagulant effect. Compounds **2b** and **5b** showed an increase in clotting time (CT), bleeding time (BT) and a decrease in platelet number so its anticoagulant effect is due to thrombocytopenia.

Compound **5a** showed prolonged CT and BT with a decrease in fibrinogen conc. (hypofibrinogenaemia) and an increase in platelet number which may be explained by a platelet dys function, a deffect in interensic system and or common pathway.

In **4g** and **4h** prolonged CT and BT were shown to be accompanied by an increase in fibrinogen conc. various explanations had been offered: excess of lower molecular weight fibrinogen (Lipinski *et al.*, 1971), abnormal aggregation of fibrin monomers (Lane *et al.*, 1977), abnormal high content of sialic acid in fibrinogen (Martinez and Kwasniak, 1977) or abnormality of AX chains (Weinstein and Deykin, 1979).

Table III showed the effect of these compounds on blood elements (haemogram). No toxic symptoms were observed on haemogram for the studied compounds.

Antiinflammatory, anticoagulant, ulcerogenic activity and effect on blood elements were studied on the new synthesized compounds **2a**,**b**, **4a**,**h** and **5a**,**b** showed a significant anticoagulant effect. All compounds were devoid of ulcerogenic effect or any toxic effects on heamogram.

It was found that the nitro group in the para position of the phenyl ring has an important role in the antiinflammatory activity as we noticed that **2a** has a significant antiinflammatory effect while **2b** failed to show any effect.

The iminopyran and pyrone derivatives of **2b** were more potent antiinflammatory than the opened chain chalcone **2b**. The same relation was found for the anticoagulant effect, where **4h** was found to be more active than **2b**. The cyano group present as a substituent in the iminopyran ring of **4a** has abolished the anticoagulant while the amide group in the same position has increased it.

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