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Reactions of Some Cinnamoyl Benzofuran Derivatives with Activated Nitriles and their Biological Activity

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Abstract □ Several 4-cyano-1-benzofuranyl-1-butanone derivatives were synthesized and screened for potential antiinflammatory and analgesic activities. The effect of structural variation of these molecules on biological activities was systematically examined. Among these compounds V_a, V_c and VI_e were found to demonstrate a significant antiinflammatory effect. Compounds VI_e, V_a, I_d, I_b and VII_f were also significantly effective as analgesic ones.

Key words □ 4-Cyano-1-benzofuranyl-1-butanone derivatives, antiinflammatory activity, analgesic activity.

Benzofuran derivatives are known to possess coronary vasodilator properties[1]. Some derivatives are used in formulations of medicaments for therapy of cerebral arteriopathies[2]. Moreover some benzofuran derivatives show antibacterial activity as well as antiparasitic properties[3,4]. We have tried to find a novel type of analgesic agents having a potent antiinflammatory activity.

This paper deals with the synthesis of several derivatives of the chalcones I_{a-f} and the result of their primary pharmacological evaluation.

Chemistry

Michael addition of benzofuran chalcones with some active methylene compounds having a cyano group has been investigated. The chalcones I_{a-f}[5-8] when reacted with ω-cyano-acetophenone (II) in the presence of piperidine yielded the target compounds V_{a-f}.

The ^{1}H NMR spectrum of compound V_f revealed signals at δ 8.52 (1H, pyridine H-2,s), δ 8.4 (1H, pyridine H-6,d), δ 7.7-7.4 (5H, aromatic H,m), δ 7.4 (1H, furan H-2,d,J=2.1 Hz), δ 7.2 (1H,C_7-H,s), δ 7-7.2 (1H, pyridine H-5,m), δ 6.85 (1H, furan H-3,d,J=2.1 Hz), δ 6.65 (1H, pyridine H-4,d), δ 5.29 (1H, butanone H-4,d), δ 4.6-4.85 (1H, butanone H-3,m), δ 4.3 (2H, butanone H-2,d), δ 4.2 (3H,OCH_3,s).

The Michael adduct VI_f formed by reacting thiocyanoacetamide (III) with compound I_f showed the following signals in its ^{1}H NMR spectrum: δ 8.9-8.65 (3H,pyridine H-6,H-5 and H-2,m), δ 7.7 (1H, furan H-2,d), δ 7.0-7.3 (2H,pyridine H-4 and benzene H-7, m), δ 6.8 (1H,furan H-3,d), δ 4.2-3.3 (7H, OCH_3, 4 butanone protons, m).

The structure of the adducts VII_{a-f} produced from the reaction of the chalcones I_{a-f} with 1,1,3 -tricyano-2-aminopropene (IV) was confirmed by the ^{1}H NMR spectrum of VII_c which showed the signals δ 8.6 (1H, anisyl H-2,s), δ 8.05 (1H, anisyl H-6,d), δ 7.6 (1H,furan H-2,d), δ 7.3-7.5 (1H,

Table I. Infra red peaks of compounds V_{a-f}, VI_{a-f}, VII_{b-f} (cm^{-1})

Compound	OH	CN	C-C_6H_5 (C=O)	C-CH_2 (C=O)	C=N
V_a	3700-3400	2200	1690	1630	1620
V_b	3600	2200	1700	1630	1620
V_f	3600	2200	1700	1630	1620
	OH + NH_2	CN	C-CH_2 (C=O)	C=S	
VI_a	3600-3300	2200	1630	1070	
VI_e	3600-3300	2200	1630	1070	
VI_f	3600-3300	2210	1625	1070	
	OH + NH_2	CN	C-CH_2 (C=O)		
VII_b	3600-3400	2220	1620		
VII_c	3600-3400	2200	1620		
VII_d	3600-3400	2220	1620		
VII_f	3600-3300	2200	1620		

Table II. Michael adducts Va-f, VIa-f and VIIa-f

Comp	Solv. of Cryst.	M.P.	Yield %	Formula	Elemental analysis % Calcd. C	H	N	S	Found C	H	N	S
V_a	Methanol	220	80	$C_{28}H_{23}NO_6$	71.64	4.90	2.99		71.60	4.87	3.01	
V_b	Pet-ether*	90	85	$C_{27}H_{21}NO_5$	73.80	4.78	3.19		73.72	4.69	3.05	
V_c	Ether	124	90	$C_{29}H_{25}NO_7$	69.74	5.01	2.81		69.63	5.00	2.78	
V_d	Benzene	118	85	$C_{28}H_{23}NO_6$	71.64	4.90	2.99		71.50	4.85	2.81	
V_e	Dil. Acetic	80	90	$C_{27}H_{22}N_2O_6$	68.94	4.68	5.96		68.89	4.72	6.02	
V_f	Chloroform	126	85	$C_{26}H_{20}N_2O_5$	70.91	4.55	6.36		70.85	4.61	6.21	
VI_a	Benzene	220	80	$C_{22}H_{20}N_2O_5S$	62.26	4.72	6.60	7.55	62.30	4.68	6.54	7.42
VI_b	Chloroform-Pet-ether*	238	90	$C_{21}H_{18}N_2O_4S$	63.96	4.57	7.11	8.12	64.01	4.46	7.23	8.0
VI_c	Benzene	220	90	$C_{23}H_{22}N_2O_6S$	60.79	4.85	6.17	7.05	60.98	4.72	6.23	7.02
VI_d	Benzene	166	95	$C_{22}H_{20}N_2O_5S$	62.26	4.72	6.61	7.55	62.30	4.81	6.54	7.49
VI_e	Benzene	183	90	$C_{21}H_{19}N_3O_5S$	59.29	4.47	9.88	7.53	59.34	4.38	10.04	7.39
VI_f	Chloroform-Pet-ether*	above 270	95	$C_{20}H_{17}N_3O_4S$	60.76	4.30	10.63	8.10	60.71	4.25	10.28	8.05
VII_a	Ether	80	95	$C_{25}H_{20}N_4O_5$	65.79	4.39	12.28		65.88	4.44	12.02	
VII_b	Chloroform	155	90	$C_{24}H_{18}N_4O_4$	67.61	4.23	13.15		67.51	4.14	12.09	
VII_c	Benzene	190	95	$C_{26}H_{22}N_4O_6$	64.20	4.53	11.52		64.16	4.83	11.45	
VII_d	Abs. methanol	104	90	$C_{25}H_{20}N_4O_5$	65.79	4.39	12.28		65.74	4.65	12.32	
VII_e	Toluene	195	95	$C_{24}H_{19}N_5O_5$	63.02	4.16	15.32		62.95	4.23	15.27	
VII_f	Dil. Acetic	166	90	$C_{23}H_{17}N_5O_4$	64.64	3.99	16.39		64.59	4.04	16.46	

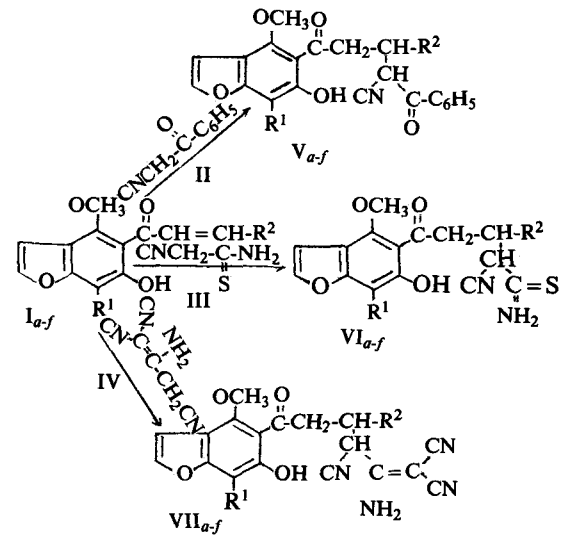
* Petroleum ether 60-80°

anisyl H-5,m), δ 7.0 (1H,anisyl H-4,d), δ 6.8 (1H,furan H-3,d), δ 4.3-4.8 (2H,two methine H,m) δ 4.6 (2H,-CH_2,d), δ 4.2, 3.9, 3.8 (9H, 3OCH_3,s), δ 1.2-1.6 (2H,NH_2,broad peak).

Various analytical data are shown in Table I and II.

Biology

Fig. 1 shows the antiinflammatory effect of compounds V_a, V_c, VI_e, I_{a-f}, III and phenylbutazone (in a decreasing order of activity). The starting compounds I_{a-f} and III showed no significant antiinflammatory effect except I_d and I_e. On the other hand, the introduction of ω-cyanoacetophenone group to the inactive compounds I_a and I_c produced active antiinflammatory compounds, *e.g.* V_a and V_c. It is of interest to note that compounds V_a and V_c have a OCH_3 group at the p-position in the benzofuran moiety (khellinone derivatives). This is in agreement with the findings of Fauran *et al.*[9,10] who found that some 6-aminoalkoxy-5-cinnamoyl-4,7-dimethoxybenzofuran (khellinone derivatives) possess antiinflammatory and analgesic ac-



I, V, VI, VII
a, $R^1 = OCH_3$ $R^2 = C_6H_5$
b, $R^1 = H$ $R^2 = C_6H_5$
c, $R^1 = OCH_3$ $R^2 = C_6H_4$-OCH_{3m}
d, $R^1 = H$ $R^2 = C_6H_4$-OCH_{3p}
e, $R^1 = OCH_3$ $R^2 = C_5H_4N_p$
f, $R^1 = H$ $R^2 = C_5H_4N_m$

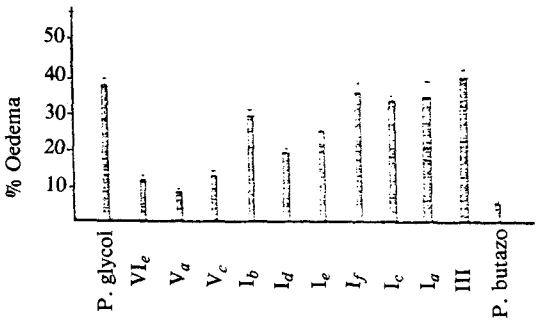


Fig. 1. Antiinflammatory effect of 500 and 100 mg/kg b. wt. benzofuran derivatives and phenylbutazon.

tivities. Moreover, the introduction of thiocyanoacetamide group to the khellinone derivative I_e increased the activity of VI_e.

Table III showed the significant activity of the compounds as analgesics in decreasing order (VI_e, V_a, I_d, I_b and VII_f). It was also observed that the introduction of the thiocyanoacetamide and cyanoacetophenone groups in the case of VI_e and V_a, respectively, increased the analgesic activity of I_e and I_a.

Table III. The analgesic activity of compounds VII_f, V_a, VI_e, I_b, I_d and paracetamol 500 mg/kg. B. wt

T Time (min)	Mean reaction time in seconds ± S.E. Compounds						
	P. glycol	VII_f	V_a	VI_e	I_b	I_d	Paracetamol
0	13.2	11.5	11.66	14.5	11	12.25	12.1
	0.93	0.64	1.25	1.32	0.4	0.75	1.35
10	11.2	11.64	21.6*	23.75*	9.0	10.75	24.31*
	0.67	0.85	2.5	0.62	0.7	1.2	1.2
20	14.2	9.75	21.25*	23.25*	32.5*	24.0*	26.07*
	0.61	1.02	1.7	1.1	1.4	0.7	3.1
30	12.0	14.75	20.75*	23.5*	28.7*	20.75	28.35**
	0.57	1.25	1.21	1.44	2.3	0.47	2.1
45	9.1	12.75**	19.5	23.25*	21.5*	13.5*	28.0*
	0.87	0.48	0.65	1.35	0.64	0.64	1.3
60	9.8	15.75*	18.5*	23.75*	15.0**	13.5*	22.6*
	0.77	0.85	0.69	1.1	1.4	0.61	0.5
120	9.0	13.25**	17.0*	21.0*	10.0	10.5	21.4*
	0.5	1.1	1.06	1.08	0.95	0.4	1.8

* Significantly different from normal control (p value at < 0.01) ** Significantly different from normal control (p value at < 0.05)

In conclusion the khellinone adducts (V_a, V_c and VI_e) showed more pronounced antiinflammatory effect while the activity of the visnaginone adducts was totally abolished.

Moreover, it has been observed that the adducts V_a, VI_e possess both antiinflammatory and analgesic activities.

EXPERIMENTAL SECTION

All m.p.'s are uncorrected. The IR spectra were recorded (KBr) on a Pye Unicam sp-1000 spectrophotometer. ^1H NMR were obtained in a Varian EM-390 90 MHz NMR spectrometer with Si Me_4 as internal standard. Elemental analysis were done by the microanalytical laboratory at National Research Center, Dokki-Cairo.

General Synthetic Procedure

0.01 Mol of the chalcone was dissolved in 20 m*l* abs. ethanol and 0.01 mol of the active methylene cyano compound was added then 2 drops of piperidine. The reaction mixture was refluxed for 5 hours. The solvent mixture was evaporated under vacuum and the solid so obtained was crystallized from the appropriate solvent (*cf.* Table II). All the Michael adducts are coloured compounds ranging from yellow to brown.

Anti-inflammatory activity

The antiinflammatory effect of I_{a-f}, III, V_a, V_c, V_d, VI_b, VI_e and VII_f was evaluated using the method described by Winter *et al.*[11]. Rats were divided into groups of 6-8 animals. The tested compounds were dissolved in 50% propylene glycol and were orally given 500 mg/kg B. Wt. to each group of rats. Phenylbutazone was given to another group while the control group was treated with propylene glycol. After 60 min. of administration rats were injected with 0.05 m*l*. of 1% solution of carageenen into the planter tissue of the hind pow. The volume of the injected pow was measured immediately after carageenen injection and 3 hrs. later the percentage of oedema increase was calculated.

Analgesic activity

The analgesic activity testing was investigated for all the tested compounds using the method described by Janssen *et al.*[12]. The reaction time was taken as the interval from the instant the mouse reaches the hot plate until it licks its feet or jumps out of the cylinder. Mice were divided into groups of 6-8 animals. The tested compounds (dissolved in 50% propylene glycol) and paracetamol were orally administered to groups of mice in doses of 500

mg/kg B. Wt. A separate group of animals was given 50% propylene glycol and used as control. The reaction time of each group was taken at 10, 20, 30, 40, 60 and 120 min. after administration of the tested materials.

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