NEW BENZOFURANS AS POTENTIAL ANTIINFLAMMATORY AGENTS.

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ABSTRACT

2-Acetylbenzofuran (A) and 2-acetyl-7-methoxybenzofuran (B) react with different aromatic aldehydes to give chalcone analogues. These in turn interact with hydrazine hydrate (85%), methylhydrazine, phenylhydrazine, and 4-nitrophenylhydrazine in different solvents to afford the corresponding pyrazoline derivatives. The structure of these compounds have been established from analytical data, IR spectra, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. The antiinflammatory testing of six of the newly prepared compounds showed that two of them (1f, 3e) produce antiinflammatory effect

INTRODUCTION

Many benzofuran derivatives have been reported as antitubercular[1], anthelmintic[2], antifungal and antibacterial[3] agents. During the past two decades considerable evidance has been accumulated to demonstrate the efficiency of benzofuran derivatives as antiinflammatory and uricosuric agents. Among these active compounds are furofenac[4] benzarone[5] and furobufen[6]. More studies described the synthesis and the marked antiinflammatory activity of some benzofuran derivatives that contain a benzoyl functional group[7] and various 2-(4-substituted phenyl)benzofuran derivatives[8]. In the latter investigation,[8] several series of compounds were prepared containing a benzofuran and\or 7-methoxybenzofuran

moiety attached to a pyrazoline of known potentiating antiinflammatory activity as in tantum[9] and pirazolac[10].

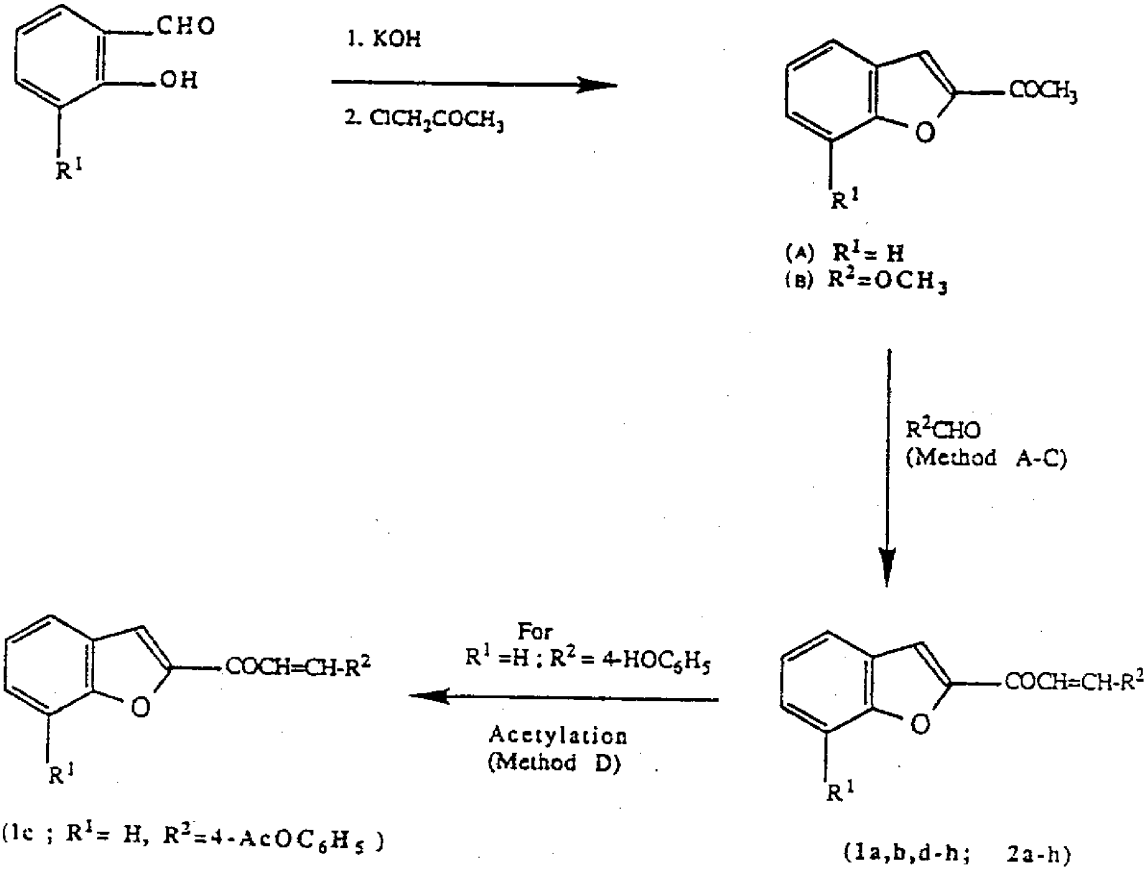
DISCUSSION

The syntheses of the chalcone analogues described herein were accomplished by the condensation of 2-acetylbenzofuran (A)[11] and 2-acetyl-7-methoxybenzofuran (B)[12] with the appropriate aldehyde in ethanol (70%) in the presence of 10% aq. sodium hydroxide (scheme 1). In the case of compound 1d, 2a,and 2d, the reaction did not proceed at room temperature, but a good yield was obtained when the mixture was heated in the presence of sodium hydroxide (10%). Experiments showed that 4-hydroxybenzaldehyde did not react with (A) or (B) even after four days at room temperature using 10% aq. sodium hydroxide, or after refluxing for 10 hours using 10% sodium hydroxide, undoubtedly becouse of the reduced carbonyl electrophilicity. Therefore, the reaction was repeated in the presence of an acid catalyst (conc. sulfuric acid). Compound 1c was prepared by treating 1a with acetic anhydride in the presence of 2N sodium hydroxide.

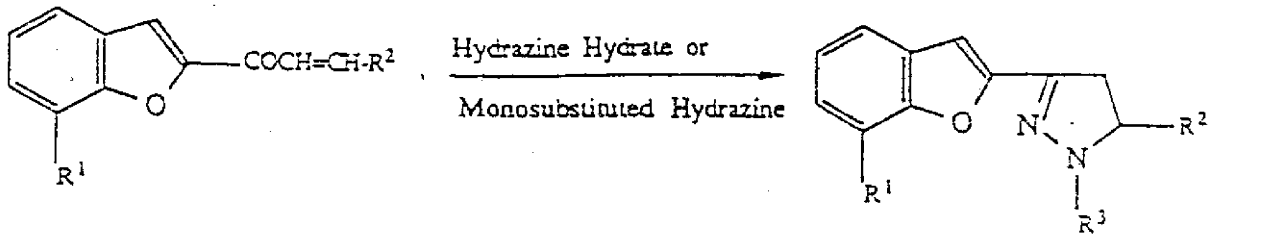
The structures of 1-(2-benzofuryl or 7-methoxy-2-benzofuryl)-3-aryl propen-1-one were determined by microanalysis and some of them were studied by IR, ^{1}H NMR and\or ^{13}C NMR and mass spectroscopy. The IR spectra of α,β-unsaturated compounds showed that the bands of the carbonyl groups were shifted somewhat to lower frequency as compound 1g had a peak at 1664 cm^{-1} (in the case of 2-acetylbenzofuran and 2-acetyl-7-methoxybenzofuran, it was at 1677 cm^{-1})[13]. The mass spectroscopy of the α,β-unsaturated compounds was consistant with the assinged structure and did not show the formation of reaction products between 1 mole of the aldehyde and 2 mole of (A) or (B).

The availability of an α,β-unsaturated ketone system in 1-(2-benzofuryl and 7-methoxy-2-benzofuryl)-3-aryl propen-1-one (1a-h, 2a-h) permitted a direct approach to a variety of pyrazolines by reaction with hydrazine hydrate (85%),

Scheme 1



Scheme 2.



R^3 = H, CH_3, C_6H_5 or 4-$NO_2C_6H_4$

(3a-j; 4a-f; 5a-c; 6a-c; 7a-d; 8a-d; 9a-b and 10a-b)

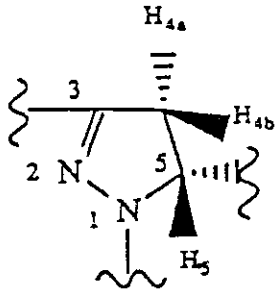
methylhydrazine, phenylhydrazine and 4-nitrophenylhydrazine (scheme 2). 3 (or 5)-(2-Benzofuryl or 7-methoxy-2- benzofuryl) -5(or 3)-aryl pyrazoline or 5(or 3)-aryl-1-substituted pyrazoline (3a-c, 3e-h, 3j, 4c-f, 5a-b and 6b-c) were obtained in the presence of a base (piperidine) or an acid (acetic or dil. sulfuric acid). Trials had been made to run the previous reaction in the presence of conc. sulfuric acid but were unsuccesseful. No conditions could be found to achieve cyclization of the chalcones and 2,4-dinitrophenylhydrazine, either in the presence of piperidine or conc. sulfuric acid.

Most of the selected pyrazoline compounds showed characteristic bands corresponding to C=N (1678-1613 cm^{-1}) and C-N (1250-1227 cm^{-1}) in the IR using a nujol mull. The structures were further confirmed using proton and ^{13}C magnetic resonsnce (Tables I and II). The C-4 methylene protons and the C-5 proton of some selected pyrazoline derivatives were assigned and the couplings ($J_{4,5}$) were calculated (Table I).

To confirm the cyclization to pyrazoline derivatives a DEPT[14] (distortionless enhancement by polarization transfer) ^{13}C NMR spectrum of 3(or 5)-(2-benzofuryl)-5(or 3)-(2,5-dimethoxyphenyl) pyrazoline (3g) was employed for the assignment of resonance signals. The molecular formula of 3g is $C_{19}H_{18}N_2O_3$ (mol. wt. 322). As may be seen from this structure, the total number of carbon is 19, quaternary carbons, 7; CH_3, 2 ; CH_2, 1; and CH, 9. The DEPT ^{13}C NMR spectrum of 3g in $(CD_3)_2SO$ is consistant with the proposed structure, although two quaternary carbon signals as well as two CH_3 carbons are apparently magnetically equivalent (Table 11). In particular, the starting material (1e) has no CH_2 group while the DEPT spectrum of 3g confirmed the presence of a CH_2. The structures of chalcone and pyrazoline derivatives were further confirmed by electron impact mass spectrometry. For example, 1e showed the following peaks (m\z, R.A., %) ($C_{19}H_{16}O_4$, M., 308, 23.92%), (M+1, 309, 5.29%), ($C_{19}H_{16}O_4$-OCH_3, 277, 100%), ($C_{18}H_{13}O_3$-C_9H_8O, 145, 17.32%), ($C_9H_5O_2$-CO, 117, 1.22%), (C_8H_5O-CO, 89, 24.29%),

Table I

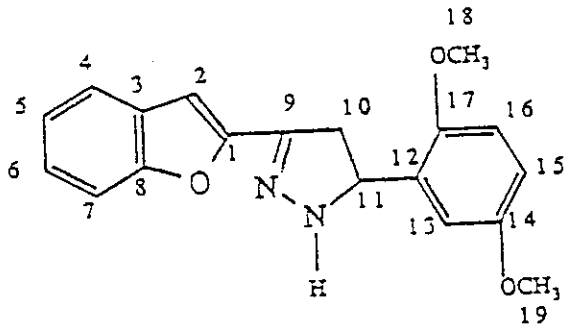
^{1}H NMR AND THE COUPLING CONSTANTS OF SOME SELECTED PYRAZOLINE DERIVATIVES



Comp. no.	NMR data (ppm)	J(Hz)		
		4a,5 (trans)	4b,5 (cis)	4a,4b (gem)
3f	δ7.9 (broad S, 1H, NH, exchangeable); 7.64-7.20 (m, 8H, ArH and ArH of benzofuran); 5.11-5.01 (dd, 1H, H_5); 3.63-3.50 (dd, 1H, H_{4b}); 3.12-2.99 (dd, 1H, H_{4a}); 6.76 (S, 1H, H-3 of benzofuran).	10.8	9.3	16.2
5b	δ7.57-7.22 (m, 8H, ArH and ArH of benzofuran); 6.6 (S, 1H, H-3 of benzofuran); 4.27-4.15 (dd, 1H, H_5); 3.52-3.39 (dd, 1H, H_{4b}); 3.01-2.93 (dd, 1H, H_{4a}); 2.88 (S, 3H, N-CH_3).	14.4	10.2	16.0
8d	δ7.25-7.00 (m, 11H, thiophene (3), ArH (5), ArH of benzofuran (3); 6.80 (S, 1H, H-3 of benzofuran); 5.65-5.56 (dd, 1H H_5); 4.02 (S, 3H, 7-OCH_3), 3.95-3.81 (dd, 1H, H_{4b}); 3.42-3.30 (dd, 1H, H_{4a}).	12.0	6.5	17.0
9a	δ7.6-6.8 (m,12H, ArH (8), ArH of benzofuran (4); 6.9 (S, 1H, H-3 of benzofuran); 5.47-5.38 (dd, 1H, H_5); 4.03-3.88 (dd, 1H, H_{4b}); 3.78 (S, 3H, ϕ-OCH_3); 3.32-3.20 (dd, 1H, H_{4a}).	12.1	5.3	17.3

Table II

^{13}C NMR DATA of 3-(or 5)-(BENZOFURYL)-5-(or 3)-(2,5-DIMETHOXYPHENYL) PYRAZOLINE in DIMENTHYL SULFOXIDE-d_6.



Type of Carbons	No. of Signals	Corresponding Carbons	Ppm (δ)
C	6	1, 3, 8, 9, 12, 14, 17 *	154.3 - 128.2
CH	1	* 11	58.05
CH	8	2, 4, 5, 6, 7, 13, 15, 16	124.8 - 111.0
CH_2	1	10	55.8
CH_3	1	18, 19 * *	55.3
Total	17	19	

* A DEPT analysis revealed six rather than the expected seven signals in the quaternary carbon region, undoubtedly resulting from accidential equivalence of two signals.

* * The two OMe carbons may be magnetically equivalent as C No. 14 & 17.

(C_6H_4 ,76, 6.83%). In the case of 3f, the electron impact analysis showed the following peaks: (m\z, R.A., %), ($C_{18}H_{13}F_3N_2O$, M, 330, 100%), (M+1, 331, 20.11%), ($C_{18}H_{13}F_3N_2O$ - $C_7H_4F_3$, 185, 25.21%), ($C_{11}H_9N_2O$ - N_2, 157, 7.71%), ($C_{11}H_9O$ - CH_2, 143, 5.87%), ($C_{10}H_7O$ - C_2H_2, 117, 2.08%), (C_8H_5O - CO, 89, 7.43%), (C_6H_4, 76, 2.98%). The last three peaks in compounds 1e and 3f are consistant with the fragmentation pattern of most benzofuran.[15]

Biological activity;

Evaluation of the antiinflammatory activity of some benzofuran derivatives was carried out using adjuvant-induced arthritis in rats[16]. Albino rats (150-200g) of either sex were injected subcutaneously with 0.05 ml of Freund's complete adjuvant into the plantar tissue of the right hind paw. The dorsoplantar thickness of the paws was measured initially and then every two days using a paw edema meter. Ten days after injection of the adjuvant, rats developed systemic polyarthritis, as indicated by swelling of the non-injected (left) paw and increase in its thickness and were divided into groups each 5-6 rats. Compounds 1b, 1f, 2g, 3e, 4a, and 9a were given in a dose of 30 mg/Kg orally once daily for 8 days The dorsoplantar thickness of the left non-injected paw at day 10 after adjuvant injection was considered as 100% and the % change in the thickness was calculated for each animal after treatment. Table (111) shows the activity of compound 1f and compound 3e as antiinflammatory agents. Compound 3e showed the highest activity and compound 1f also produced significant activity when compared with the control and indomethacin groups. On the other hand, compounds 1b, 2g, 4a and 9a did not produce any significent reduction in the thickness of the paw of adjuvant arthritic rats using the paw edema meter.

Table III

THICKNESS OF THE PAW OF ADJUVANT ARTHRITIC RATS (in ml) USING PAW EDEMA METER FOLLOWING ADMINISTRATION OF COMPOUNDS 1f and 3e.

Item	Control		Indomethacin 30 mg / kg		Compound (1f) 30 mg / kg		Compound (3e) 30 mg / kg	
	L[a]	R[b]	L	R	L	R	L	R
Mean (in ml)	3	3.2	2.4	2.4	2.7	2.9	2.4	2.1
S.E.±	± 0.14	± 0.08	± 0.027	± 0.03	± 0.08	± 0.1	± 0.11	± 0.04
P[c]			<0.001	<0.001	<0.05	<0.05	<0.05	<0.00
inhibn, %			93.1	94.8	49.5	38.2	61.3	83.0

[a] L = Left Paw [b] R = Right Paw P = Probability.

[c] Statistical significance of the data was estimated using the student T test.

EXPERIMENTAL.

Infrared studies were carried out on Unicam SP1000 spectrometer either in CCl_4 or dispersed in a Nujol mull. The ^1H NMR and\or ^{13}C NMR spectra were recorded on an IBM FT200 NMR speectrometer in $CDCl_3$ or $(CD_3)_2SO$ with TMS as an internal standard. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analysis were performed by Desert Analytic Laboratories, Tucson, Arizona, and the microanalysis unit at Cairo University, Egypt. All thin layer chromatography was performed on precoated sheets of silica gel 60F254, layer thickness 2mm using a toluene/EtOAc (7:3) or CH_3CN/ H_2O (8:2) system.

General methods for preparation of:
1-(2-Benzofuryl or 7-methoxy-2-benzofuryl)-3-aryl propen-1-one(1a-h, 2a-h):

Method A: A mixture of (A) and (B) (0.01 mole) and the appropriate aldehyde (0.015 mole) was dissolved in warm ethanol (30 ml). When the reaction reached room temperature, water (20 ml) was added, and the solution was set aside for two hours. Ten percent NaOH (1-5 ml) was added dropwise and the solution was left at room temperature from 2 to 24 hours. During this time TLC determined that all the starting material had reacted. The product, which crystallized from the reaction mixture, was collected, washed with 70% aq. ethanol, dried, and crystallized from the suitable solvents (Table IV).

Method B: To a mixture of (A) or (A) (0.01 mole) and the appropriate aldehyde (0.015 mole) in ethanol (20 ml) was added 10% NaOH (5 ml). The reaction mixture was heated under reflux and the reaction was followed by TLC. After 3 hours, the reaction mixture was cooled to ambient temperature. The precipitated solid was collected, washed with 50% aq. ethanol, dried and crystallized from the suitable solvents (Table IV).

Method C: A mixture of (A) or (B) (0.01 mole) and the appropriate aldehyde (0.015 mole) was dissolved in glacial acetic acid (20 ml), and to the cooled solution, 2 ml of conc.

Table IV

Physical and Analytical Data for :

1- (2- BENZOFURYL or 7- METHOXY -2- BENZOFURYL) -3- ARYLPROPEN -1- ONE (1 a - h , 2 a - h)

Compd no.	R^1	R^2	Formula (MW)	Method	Reaction Time	Solvent of Crystn.*	MP. °C	Yield %	Analysis % Calcd. (Found) C	H	N
1a	H	4-HOC_6H_4-	$C_{17}H_{12}O_3$ (204)	C	24	E	240-242	60	77.27 (77.11)	4.54 (4.57)	
1b	H	4-$CH_3OC_6H_4$-	$C_{18}H_{14}O_3$ (278)	A	20	E	120-122	75	77.69 (77.73)	5.03 (4.97)	
1c	H	4-$CH_3COOC_6H_4$-	$C_{19}H_{14}O_4$ (306)	D	10 min	H+F	156-158	70	74.50 (74.42)	4.57 (4.46)	
1d	H	3,4-$(OCH_2O)C_6H_3$-	$C_{18}H_{12}O_4$ (292)	B	3	K	158-160	75	73.97 (73.60)	4.10 (3.90)	
1e	H	2,5-$(CH_3O)_2C_6H_3$-	$C_{19}H_{16}O_4$ (308)	A	4	G	92-94	70	74.04 (74.13)	5.14 (5.10)	
1f	H	4-$CF_3C_6H_4$-	$C_{18}H_{11}F_3O_2$ (316)	A	2	E	170-172	80	68.37 (68.62)	3.47 (3.50)	
1g	H	2-C_4H_3S-	$C_{15}H_{10}O_2S$ (254)	A	6	E	130-132	85	70.86 (70.89)	3.93 (3.97)	
1h	H	3-C_5H_4N-	$C_{16}H_{11}NO_2$ (249)	A	3	N	228-230	90	77.12 (76.80)	4.41 (4.51)	5.62 (5.57)
2a	OCH_3	4-HOC_6H_4-	$C_{18}H_{14}O_4$ (294)	B	3	O	202-204	50	73.48 (73.12)	4.75 (4.51)	
2b	OCH_3	4-$CH_3OC_6H_4$-	$C_{19}H_{16}O_4$ (308)	A	17	M+F	102-104	75	74.04 (74.02)	5.19 (5.15)	
2c	OCH_3	2,5-$(CH_3O)_2C_6H_3$-	$C_{20}H_{18}O_5$ (338)	A	2	E	124-126	70	71.02 (70.97)	5.53 (5.26)	
2d	OCH_3	4-$O_2NC_6H_4$-	$C_{18}H_{13}NO_5$ (323)	B	3	E	198-200	65	66.98 (66.40)	4.02 (3.90)	4.33 (4.22)
2e	OCH_3	4-$CF_3C_6H_4$-	$C_{19}H_{13}F_3O_3$ (346)	A	5	E+F	156-158	70	65.91 (65.86)	3.75 (3.66)	
2f	OCH_3	2-C_4H_3O-	$C_{16}H_{12}O_4$ (268)	A	24	K	136-138	70	71.64 (71.54)	4.47 (4.57)	
2g	OCH_3	2-C_4H_3S-	$C_{16}H_{12}O_3S$ (284)	A	4	L+F	135-137	75	67.61 (67.56)	4.22 (4.24)	
2h	OCH_3	3-C_5H_4N-	$C_{17}H_{13}NO_3$ (279)	A	5	E	188-190	70	73.13 (72.90)	4.65 (4.38)	5.01 (4.93)

* E = Acetic acid, F = Water, G = Isopropanol, H = Acetone, K = Ethanol, L = Dioxane, M = Methanol, N = Dimethylformamide, O = Hexane.

sulfuric acid was added. the produced solution was left at room temperature for 24 hours. At the end of the reaction, the precipitated crystals were collected, washed with 50% aq. ethanol, dried and crystallized three times from acetic acid using charcoal (Table IV).

General method for preparation of:

1-(2-Benzofuryl)-3-(4-acetoxyphenyl)propen-1-one (1c):

Method D. To a solution of 1-(2-benzofuryl)-3-(4-hydroxy phenyl)propen-1-one (1a) (0.264 g, 0.001 mole) in sodium hydroxide (20 ml, 2N), crushed ice (5g), and then acetic anhydride (0.153 g, 0.0015 mole) were added. The mixture was shaken vigorously for 10 minutes until all starting material disappeared as judged by TLC. The yellow precipitate was filtered, washed with water, and crystallized from ethanol to give 0.244 g (80%); mp 156-158^{0} (Table IV).

General method for preparation of:

3 (or 5)-(2-Benzofuryl or 7-methoxy-2-benzofuryl)-5 (or 3)-arylpyrazoline or 1-methylpyrazoline (3a-i, 4a-f, 5a-c, and 6a-c):

Method A: 1-(2-Benzofuryl or 7-methoxy-2-benzofuryl) -3-aryl propen-1-one (0.01 mole) was dissolved or suspended in ethanol or isopropanol (10 ml). Hydrazine hydrate or methyl hydrazine (0.015 mole) was added followed immediately by 5 drops of piperidine. The mixture was refluxed for 4 hours under nitrogen until the TLC indicated the disappearance of starting material. The reaction mixture was concentrated in vacuo. The precipitate resulting from concentration or dilution with water was filtered, dried and recrystallized (Table V).

Method B. 1-(2-Benzofuryl or 7-methoxy-2-benzofuryl) -3-aryl propen-1-one (0.01 mole) was dissolved or suspended in a mixture of isopropanol (10 ml) and glacial acetic acid (2 ml). TO that mixture hydrazine hydrate or methylhydrazine (0.015 mole) was added and the solution was refluxed for 6 hours under nitrogen. During this time, TLC determined that all starting material had reacted. The reaction mixture was then

Table V

Physical and analytical Data for :

3-(or 5) - (2-BENZOFURYL or 7-METHOXY-2-BENZOFURYL) -5-(or 3)- ARYLPYRAZOLIN or -5-(or 3)- ARYL -1- SUBSTITUBD PYRAZOLINE

(3 a-j, 4 a-f, 5 a-c, 6 a-c, 7 a-d, 8 a-d, 9 a-b, and 10 a-b)

Compd. No.	R^1	R^2	R^3	Formula (MW)	Method	Solvent of Crysn.*	MP.°C	Yield %	Analysis Calcd. (Found) C	H	N
3a	H	C_6H_5-	H	$C_{17}H_{14}N_2O$ (262)	A	E+D	114+116	60	77.87 (77.60)	5.33 (5.23)	10.68 (10.52)
3b	H	4-HOC_6H_4-	H	$C_{17}H_{14}N_2O_2$ (278)	A	G+D	180-182	70	73.39 (73.23)	5.03 (4.98)	10.06 (9.92)
3c	H	4-$CH_3OC_6H_4$-	H	$C_{18}H_{16}N_2O_2$ (292)	A	E+D	124-126	85	73.98 (74.09)	5.47 (5.47)	9.60 (9.51)
3d	H	4-$O_2NC_6H_4$-	H	$C_{17}H_{13}N_3O_3$ (307)	B	F	178-180	60	66.46 (66.43)	4.23 (4.10)	13.67 (13.42)
3e	H	4-ClC_6H_4-	H	$C_{17}H_{13}ClN_2O$ (269.5)	A	E	118-120	85	68.83 (68.74)	4.38 (4.35)	9.44 (9.31)
3f	H	4-$CF_3C_6H_4$-	H	$C_{18}H_{13}F_3N_2O$ (330)	A	E+D	138-140	85	65.47 (65.17)	3.93 (3.80)	8.48 (8.42)
3g	H	2,5-$(CH_3O)_2C_6H_3$-	H	$C_{19}H_{18}N_2O_2$ (322)	A	E	155-157	65	70.82 (70.85)	5.58 (5.63)	8.69 (8.62)
3h	H	2-C_4H_3O-	H	$C_{15}H_{12}N_2O_2$ (252)	A	C+D	115-117	65	71.44 (71.34)	4.75 (4.65)	11.12 (10.99)
3i	H	3-C_5H_4N-	H	$C_{16}H_{13}N_3O$ (263)	B	E+D	205-207	55	73.01 (72.95)	4.93 (4.83)	15.96 (15.60)
3j	H	2-C_4H_3S-	H	$C_{15}H_{12}N_2OS$ (268)	A	E+D	110-112	90	67.16 (66.93)	4.47 (4.42)	10.44 (10.33)
4a	OCH_3	C_6H_5-	H	$C_{18}H_{16}N_2O_2$ (292)	B	F	138-140	60	73.98 (73.83)	5.47 (5.42)	9.58 (9.32)
4b	OCH_3	4-$CH_3OC_6H_4$-	H	$C_{19}H_{18}N_2O_3$ (322)	B	H	116-118	80	70.82 (70.79)	5.58 (5.44)	8.69 (8.52)
4c	OCH_3	4-ClC_6H_4-	H	$C_{18}H_{15}ClN_2O_2$ (326.5)	A	E+D	126-128	85	66.18 (66.13)	4.59 (4.53)	8.57 (8.42)
4d	OCH_3	4-$CF_3C_6H_4$-	H	$C_{19}H_{15}F_3N_2O_2$ (360)	A	E	172-174	90	63.35 (63.30)	4.16 (3.96)	7.77 (7.69)
4e	OCH_3	2,5-$(CH_3O)_2C_6H_3$-	H	$C_{20}H_{20}N_2O_4$ (352)	A	H	102-104	75	68.20 (68.12)	5.67 (5.60)	7.95 (7.83)
4f	OCH_3	2-C_4H_3S-	H	$C_{16}H_{14}N_2O_2S$ (298)	A	E	118-120	75	64.43 (64.43)	4.69 (4.71)	9.39 (9.32)
5a	H	4-$CH_3OC_6H_4$-	CH_3	$C_{19}H_{18}N_2O_2$ (306)	A	E+D	136-138	75	74.52 (74.20)	5.87 (5.78)	9.14 (9.00)
5b	H	4-ClC_6H_4-	CH_3	$C_{18}H_{15}ClN_2O$ (310.5)	A	E	135-137	70	69.58 (69.28	4.82 (4.62)	9.01 (8.82)
5c	H	2-C_4H_3S-	CH_3	$C_{16}H_{14}N_2OS$ (282)	B	E+D	153-155	70	68.08 (67.93)	4.96 (4.60)	9.92 (9.86)
6a	OCH_3	4-ClC_6H_4-	CH_3	$C_{16}H_{17}ClN_2O_2$ (340.5)	B	G+D	130-132	65	66.97 (66.78)	4.98 (7.87)	8.22 (8.20)
6b	OCH_3	4-$CF_3C_6H_4$-	CH_3	$C_{20}H_{17}F_3N_2O_2$ (347)	A	J+D	130-132	70	64.19 (64.25)	4.54 (4.63)	7.48 (7.38)
6c	OCH_3	2-C_4H_3S-	CH_3	$C_{17}H_{16}N_2O_2S$ (312)	B	J+D	120-122	70	65.83 (65.55)	5.12 (5.23)	8.97 (8.79)

Table V (Continued)

Comp no.	R^1	R^2	R^3	Formula (MW)	Method	Solvent of Crystn.*	MP, °C	Yield %	Analysis % Calcd. (Found) C	H	N
7a	H	4-ClC_6H_4-	C_6H_5-	$C_{23}H_{17}ClN_2O$ (372.5)	A	E	142.144	80	74.10 (73.96)	4.56 (4.60)	7.51 (7.45)
7b	H	4-$CF_3C_6H_4$-	C_6H_5-	$C_{24}H_{17}F_3N_2O$ (406)	A	E+D	132.134	85	70.93 (70.86)	4.18 (4.00)	6.89 (6.62)
7c	H	2,5-$(CH_3O)_2C_6H_3$-	C_6H_5-	$C_{25}H_{22}N_2O_3$ (398)	A	E	155.157	75	75.39 (75.14)	5.52 (5046)	7.03 (6.98)
7d	H	2-C_4H_3S-	C_6H_5-	$C_{21}H_{16}N_2OS$ (344)	A	E	152.154	75	73.28 (73.15)	4.64 (4.63)	8.13 (7.94)
8a	OCH_3	4-ClC_6H_4-	C_6H_5-	$C_{24}H_{19}ClN_2O_2$ (402.5)	A	C+D	160.162	85	71.57 (71.53)	4.71 (4.60)	6.95 (6.84)
8b	OCH_3	4-$CF_3C_6H_4$-	C_6H_5-	$C_{25}H_{19}F_3N_2O_2$ (436)	A	E+D	145.147	75	68.82 (68.68)	4.35 (4.20)	6.42 (6.20)
8c	OCH_3	2,5-$(CH_3O)_2C_6H_3$-	C_6H_5-	$C_{26}H_{24}N_2O_4$ (352)	A	H	132.134	70	68.20 (67.95)	5.67 (5.35)	7.95 (7.90)
8d	OCH_3	2-C_4H_3S-	C_6H_5-	$C_{22}H_{18}N_2O_2S$ (374)	A	E	142.144	80	70.59 (70.33)	4.80 (4.75)	7.48 (7.50)
9a	H	4-$CH_3OC_6H_4$-	4-$NO_2C_6H_4$-	$C_{24}H_{19}N_3O_4$ (413)	B	K+D	208.210	55	69.75 (69.50)	4.59 (4.46)	10.16 (10.01)
9b	H	4-ClC_6H_4-	4-$NO_2C_6H_4$-	$C_{23}H_{16}ClN_3O_3$ (417.5)	B	K+D	268.270	60	66.13 (65.82)	3.83 (3.75)	10.05 (10.10)
10a	OCH_3	4-$CH_3OC_6H_4$-	4-$NO_2C_6H_4$-	$C_{25}H_{21}N_3O_5$ (443)	B	K+D	172.174	50	67.73 (67.54)	4.73 (4.62)	9.47 (9.34)
10b	OCH_3	4-ClC_6H_4-	4-$NO_2C_6H_4$-	$C_{24}H_{18}ClN_3O_4$ (447.5)	B	K+D	195.197	55	64.41 (64.23)	4.02 (4.20)	9.38 (9.40)

* C = Dioxane, D = Water, E = Ethanol, F = Acetic acid, G = Methanol, M = Isopropanol, J = Acetone, K = Dimethylformamide.

evaporated under reduced pressure and triturated with water (20 ml). The resulting precipitate was filtered, dried and recrystallised (Table V).

General methods for preparation of:
3 (or 5)-(Benzofuryl or 7-methoxy-2-benzofuryl)-5 (or 3)-aryl 1-phenyl pyrazoline or 1-(4-nitrophenyl)pyrazoline (7a-d, 8a-d, 9a-b and 10a-b):

Method A: A mixture of 1-(2-benzofuryl or 7-methoxy-2-benzofuryl)-3-aryl propen-1-one (0.01 mole), isopropanol (10 ml), phenylhydrazine (0.01 mole) and 5 drops of piperidine was heated under reflux for 6 hours until all starting material disappeared (TLC). The mixture was cooled and concentrated under reduced pressure. The precipitate formed after concentration was filtered and dried. The remaining solvent was removed in vacuo and the solid residue was washed with water, filtered, washed with ethanol and petroleum ether ($60-90^0$) and dried. Both the products were recrystallized using the appropriate solvent (Table V).

Method B: To a mixture of 1-(2-benzofuryl or 7-methoxy -2-benzofuryl)-3-(4-chloro or 4-methoxyphenyl)propen-1-one (0.01 mole) in ethanol (10 ml) was added 2.5 ml of an acid solution of 4-nitrophenylhydrazine (prepared by dissolving 0.01 mole of 4-nitrophenylhydrazine in a mixture of 1 mL conc. sulfuric acid and 1.5 mL of water). The mixture was heated under reflux for 6 hours, then stirred overnight. The resulting precipitate was filtered, washed with ethanol and crystallized twice from dimethylformamid-water (7:3). The yields ranged from 50% to 60% (Table V).

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REFERENCES

1. R.G.child, R.G. Wilkinson, and A.S.Tomcufcik; U.S.Patent 4,006,234 (1977); Chem. Abstr.,87, 6031d (1977).
2. R. Cavier, R. Royer, R. Rips, and L.Rene; Chem. Ther., 4, 21, (1969); R. Cavier, R. Royer, R. Rips, and L.Rene; Chem. Abstr., 70 , 113868s (1969).
3. F. Pan and G.A. Wiese, J. Am. Pharm. Assoc., Sci. Ed. 49, 259, (1960); F. Pan and T.C. Wang, J. Chinese Chem. Soc., Series II, 8,220 (1961); F. Pan and T.C. Wang, J. Chinese Chem. Soc., Series II, 8, 374 (1961).
4. G.F. Tamagnone and F. DeMarchi, German Patent, 2, 526, 089 (1975) (Brit.); G.F. Tamagnone and F. DeMarchi, Chem. Abstr., 84, 135469q (1976).
5. F. Chaillet, G. Barchewitz, R. Charlier, A. Guilbert, M. Cololt, and G. Deltour, Arzneim-Forsch, 20, 1032 (1970).
6. R.Martel, T. Rochefort, J. Klicius, and T.Dobson , Can. J. Physiol. Pharmacol., 52, 669 (1974).
7. P.D. James, A.A. Neil, and J.T. albert. J. Med. Chem., 29, 2326 (1986).
8. M.M. El-Kerdawy and A.M. Abdelal, Arch. Pharm. Chem., Sci. Ed.,II, 129 (1983).
9. I. Roser and M. Bullard, Med. Pharmacol. Exp., 16, 25 (1967).
10. S. Kadowaki, K. Sugasawa, and S. Mizogami, Jap. J. Pharmacol., 39, 188 (1985); G. Katona, Curr. Ther. Res., 37, (1985).
11. R. Stormer, C.W. Chydenius, and E. Schinn, Berichte der Deutschen Chemischen Gesellschaft, 57, 72 (1924); ibid, Chem. Abstr., 18, 2160; R. Stormer, Justus Liebig's Annalen der Chemie, 312, 237 (1901) ; R. Stormer and M.Schaeffer, Berichte der Deutschen Chemischen Gesellschaft, 36, 2863 (1903).
12. M. Bisagni, N. P. Buu-Hoi, and R. Royer , J. Chem. Soc.,173 (1964).
13. L.H. Briggs, N.D. Colerook, J. Chem. Soc., 2458 (1960).

14. D.M. Doddrell, D.T. Pegg and M.R. Bendall, J. Magn. Reson., 48, 323 (1982); D.T. Pegg, D.M. Doddrell and M.R. Bendall, J. Chem. Phys., 77, 2745 (1982).
15. B. Willhalm , A.F. Thomas and F. Gantshi, Tetrahedron, 25, 2407 (1969).
16. B.B.Newbould, Brit. J. Pharmacol. Chemother., 21, 127 (1963).

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تشيد مشتقات جديدة من نواة البنزوفيوران لتجربتها أقربازينيا كمضادات للالتهابات

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تم فى هذا البحث تحضير العديد من مشتقات ٢ - (أو ٥) (٢ - بنزوفيوريل أو ٧ - ميثوكسى بنزوفيوريل) - ٥ - (أو ٣) اريل بيرازولين ، مبتدأ بتفاعل ٢ - اسيتيل أو ٢ - اسيتيل - ٧ - ميثوكسى بنزوفيوران مع بعض الألدهيدات العطرية المختلفة لتعطى مشتقات الشالكون المناسبة.

أما تفاعل مشتقات الشالكون الناتجة مع هيدرات الهيدرازين ، ميثيل الهيدرازين فينيل الهيدرازين و ٤ - نيتروبنزوفينيل الهيدرازين فقد أعطى البيرازولين المقابل.

وقد تم التعرف على التركيب الكيميائي للمركبات المشيدة بواسطة التحاليل الدقيقة والطيفية ، وقد وجد أن لبعض هذه المركبات تأثير قوى كمضادات للالتهابات بالمقارنة بالاندوميثاسين.