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Synthesis of 1-(2'-Hydroxybenzoyl)-5-(Substituted Phenyl)-3-(2'-Methylindolyl)-2-Pyrazolines as Anti Inflammatory Agents

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1-(2'-hydroxybenzoyl)-5-(substituted phenyl)-3-(2'-methylindolyl)-2-Pyrazolines were prepared by the cyclocondensation of 2-methyl-3-indolyl substituted chalcones with salicylic acid hydrazide through Michael condensation, which in turn were synthesized by the reaction of 3-acetyl-2-methylindole and substituted aromatic aldehydes. These compounds were screened for antiinflammatory activity, ulcerogenic potential, CVS activity and acute toxicity. Compound 1-(2'-hydroxybenzoyl)-5-(2'-fluorophenyl)-3-(2'-methylindolyl)-2-pyrazoline showed the most potent antiinflammatory activity.

The pyrazoline derivatives have been reported to possess bactericidal[1], fungicidal[2], anticonvulsant[3], antiparkinsonian[4], anthelmentic[5] and antiinflammtory activities[6-9]. Further, indole derivatives such as indomethacin and tenidap[10] were also found to possess potent antiinflammatory activity. It was thought worthwhile to incorporate the indole moiety in pyrazoline heterocyclic system. This led us to synthesize a series of 1-(2'-hydroxybenzoyl)-5-(substitutedphenyl)-3-(2'-methylindolyl)-2-pyrazolines (9-16) through Michael condensation with a view to obtain potent antiinflammatory agents.

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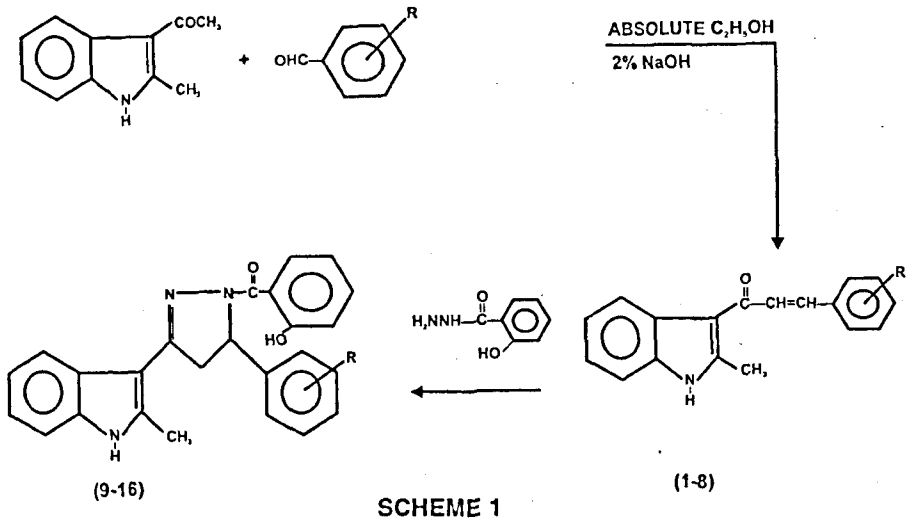
Melting points were recorded in open capillary tubes and are uncorrected. The purity of the compounds was verified on silica gel G plates using benzene and methanol (8:2) as elutent. IR spectra were recorded in KBr on Perkin-Elmer 157 Spectrophotometer (υ_{mac} in Cm^{-1}). ^1H-NMR spectra (90 MHz) in $CDCl_3$ on a Perkin Elmer 32 spectrometer using TMS as internal reference standard (Chemical shift in δ ppm) and mass spectra on Jeol D-300. Physical and biological data of compounds (1-16) are given in table 1.

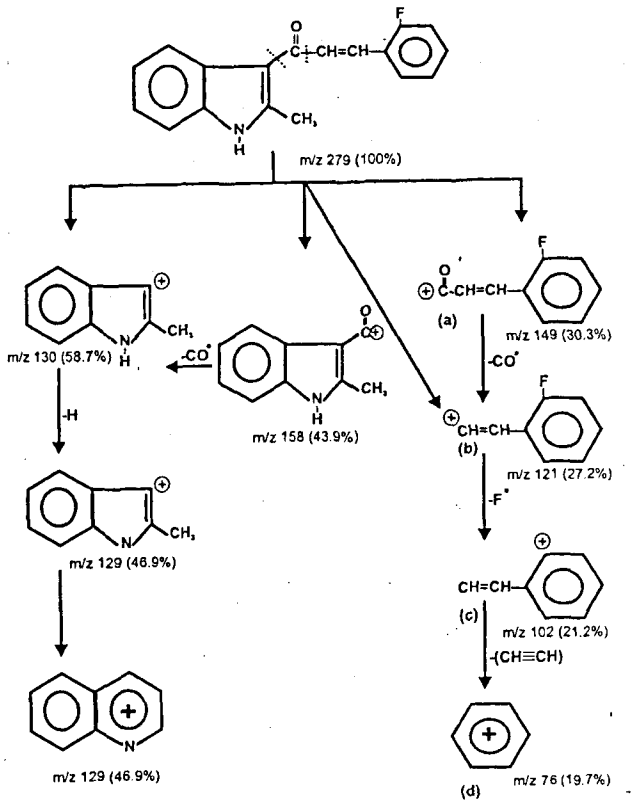
2-Methyl-3-indolyl-2-(fluorophenyl)chalcone (7) was prepared by adding a solution of 3-acetyl-2-methyl indole (0.01 mol) and 2-fluorobenzaldehyde (0.01 mol) in absolute ethanol (50 ml) in presence of 2% NaOH was refluxed for 8 h, concentrated, cooled and poured onto ice. The solid thus obtained was recrystallized from methanol/



SCHEME 1

water, m.p. 275°, yield, 70%, IR: 1720 (CO), 1670 (-CH=CH-), ^{1}H-NMR ($CDCl_3$) 8.2-7.8 (m, 8H, ArH), 9.2 (d, 1H,=CH-Ar) 6.85 (d, 1H, -COCH=), 5.5 (ss, 1H, indolic-NH proton exchangeable with D_2O), 2.5 (s, 3H,-CH_3 attached to the benzopyrazole nucleus) (Scheme 1).

The electron impact mass spectrum of compound 7 shows the molecular ion peak $[M]^+$ at m/z 279 (100%), $[M-1]^+$, (41.6%), $[M-15]^+$ (18%). The other important ions are at m/z 130 (58.7%), 129 (46.9%), 129 (46.9%), 158(43.9%), 149, (30.3%), 121 (27.2%) 102 (21.2%), 76 (19.7%). The ion $[b\text{-}c]^+$ for compound 7 is formed due to the ortho effect which is responsible for the rapid elimination of fluorine atom from (b). Similar ortho effect has been reported in substituted benzalacetones, (Schamdach *et al.*, 1981)[11] and in 2-substituted-[2'-(indol-3-yl-methylene)imino] chalcones (Kumar *et al.*, 1983)[12] (Scheme 2).



SCHEME 2

1-(2'-Hydroxybenzoyl)-5-(2'-fluorophenyl-3-(2'-methylindolyl)-2-pyrazoline (15) was prepared by adding to a solution of 7 (0.02 mol) in ethanol, salicyclic acid hydrazide (0.04 mol). The reaction mixture was refluxed for 12 h, distilled in vacuum and cooled. The separated solid was filtered, washed with ether and recrystallised from ethanol, m.p. 165°, yield 30%. IR 1520 (N-N), 3610 (-OH) 1710 (CO), 1660 (C=N), ^{1}H-NMR (TFA) δ 12.5 (ss, 1H, phenolic proton), 9.0-8.25 (m, 12H, ArH), 5.0 (d, 2H, -CH_2, of pyrazoline ring) 5.70 (ss, 1H, indolic proton exchangeable with D_2O), 6.75 (t, 1H-CH-Ar of pyrazoline ring), 2.5 (s, 3H, -CH_3 attached to indole nucleus). The electron impact mass spectrum of compound 15 shows the molecular ion peak $[M]^+$ at m/z 413 (39.3%), $[M-1]^+$ (25.8%), $[M-15]^+$ (15.3%). $[M-17]^+$ (25.7%). The other important ions are at m/z 130 (58.7%), 129 (46.9%), 156 (100%), 121 (34.8%), 292 (50.5%), 94 (57.5%), 66 (22.7%), 65 (33.3%) (Scheme 3). Compounds (1-6 and 8) and compounds (9-14 and 16) have been prepared by following the methods of preparation of compound 7 and 15 respectively.

TABLE 1 - PHYSICAL AND BIOLOGICAL DATA OF 2-METHYL-3-INDOLYL SUBSTITUTED CHALCONES (1-8) AND 1-(2-HYDROXYBENZOYL)-5-(SUBSTITUTEDPHENYL)-3-(2-METHYLINDOLY)-2-PYRAZOLINES (9-16)

Compound No.	R	M.P. O	Yield %	Molecular## Formula	%inhibition of oedema#	UD_{50}mg/kg p.o.	ED_{50}mg/kg p.o.
1.	2-OCH_3	186	50	$C_{19}H_{17}NO_2$	11.25**	-	-
2.	4-OCH_3	203	53	$C_{19}H_{17}NO_2$	6.25**	-	-
3.	2-Cl	176	60	$C_{18}H_{14}NOCl$	13.75**	-	-
4.	3-Cl	210	58	$C_{18}H_{14}NOCl$	7.50**	-	-
5.	4-Cl	263	65	$C_{18}H_{14}NOCl$	12.50**	-	-
6.	H	201	50	$C_{18}H_{15}NOF$	5.00**	-	-
7.	2-F	275	48	$C_{18}H_{14}NOF$	21.25**	-	-
8.	4-F	265	45	$C_{18}H_{14}NOF$	20.00**	-	-
9.	2-OCH_3	156	28	$C_{26}H_{23}N_3O_3$	15.55**	-	-
10.	4-OCH_3	165	30	$C_{26}H_{23}N_3O_3$	24.73**	-	-
11.	2-Cl	185	45	$C_{25}H_{20}N_3O_3Cl$	13.97**	-	-
12.	3-Cl	210	40	$C_{25}H_{20}N_3O_3Cl$	6.45**	-	-
13.	4-Cl	225	46	$C_{25}H_{20}N_3O_3Cl$	33.33**		- -
14.	H	186	25	$C_{25}H_{21}N_3O_2$	8.60**	-	-
15.	2-F	165	20	$C_{25}H_{20}N_3O_2F$	46.23**	200[a]	69.18[b]
16.	4-F	155	19	$C_{25}H_{20}N_3O_2F$	43.01**	-	-
Acetyl Salicylic Acid	-	-				158.5[a]	8.60**
Phenyl-butazone	-	-				-	75.86[b]
Indomethacin	-	-				-	4.00[c]

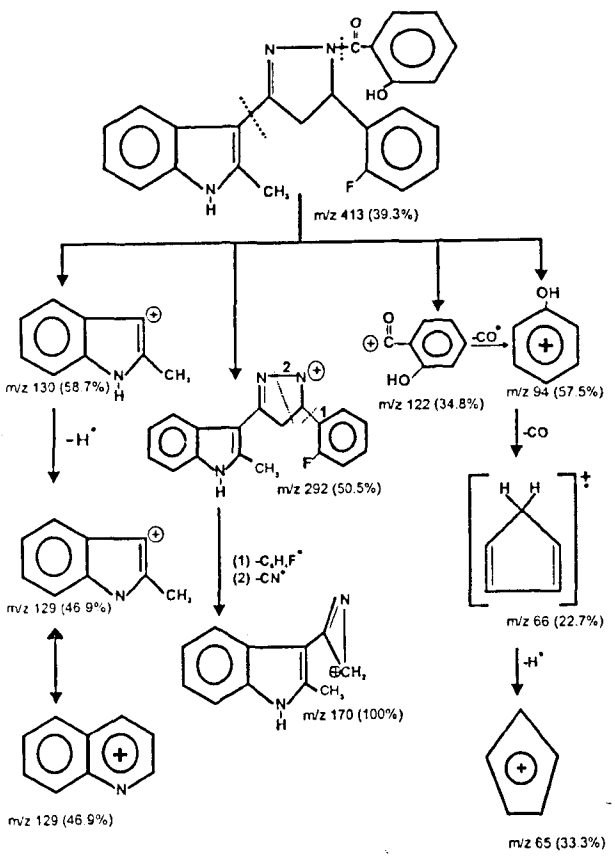
* P<0.01; # # C,H and N are within the limit of ±0.04% # all the compounds were tested at a dose of 50 mg/kg; (a) compound no. 15 and phenylbutazone were tested at three graded doses of 100, 200 and 300 mg/kg/oral for determing their UD_{50} (b) compound no. 15 and phenyl butazone (standard drug) were tested at three graded doses of 25,50 and 100 mg/kg/oral for determing their ED_{50}, while (c), Indomethacin was tested at three graded doses of 1.8, 3.6 and 5.4 mg/kg/oral to determine ED_{50}.

The pharmacological studies were conducted on adult albino rats (100-150 g), mice (20-25 g) and dogs (15-20 kg). The rats and mice were divided into batches of 6 animals.

Freshly prepared suspension of Carrageenin in 0.9% saline (0.05 ml) was injected under the planter aponeurosis of right paw of rats by method of Winter *et al.*[13] The animals were pretreated with test drugs given orally 1 h before the carrageenin. The volume of foot was measured by micropipette method described by Buttle *et al.*[14], 1 h before and 3 h after carrageenin treatment. The % antiinflammatory effect was calculated using the below given formula

$$\% \text{ antiinflammatory effect} = \frac{1 - D^t \times 100}{D^c}$$

Ulcerogenic activity was performed by method of Verma *et al*[15]. Behavioural effects were monitored by observing the animals for locomotor activity, hind limb weakness, head drop, loss of righting reflex and reactivity to sensory stimuli after oral administration of test com-



SCHEME 3

pounds in another group. Approximate LD_{50} values of some promising compounds were determined by observing 50% mortality after 24h[16]. Cardiovascular activity was conducted by method of Kumar *et al*[17].

All the compounds (1-16) have shown varying degrees of antiinflammatory activity (5.0 to 46.23%) and results are depicted in Table 1. The compound 15, 1-(2'-hydroxybenzoyl)-5-(2'-fluorophenyl)-3-(2'-methylindolyl)-2-pyrazoline showed the most effecient (46.23%) and dose dependent activity. It was therefore, further studied in detail for its antiinflammatory activity. Table 1 shows the results of compound 15 and standard drugs phenylbutazone (PBZ) and indomethacin. Interestingly this compound elicited more potent activity than PBZ at all the three doses tested but was found to be less potent when compared with indomethacin. This compound was also tested for ulcerogenic activity and found to be less ulcerogenic as compared to acetylsalicyclic acid (UD_{50} of compound 15 is 200 mg/kg i.p. and UD_{50} of acetyl salicylic acid is 158.5 mg/kg i.p.) (see Table 1).

Behavioural studies of this compound indicate that it induces mild retardation of locomotor activity at higher doses (>2000 mg/kg i.p.). This compound did not exhibit any change in blood pressure (B.P.) and pressor responses (carotid occlusion and noradrenaline) at a dose of 1 to 2 mg/kg i.v. while at a dose of 5 mg/kg, it showed a mild fall in blood pressure (20 mm of Hg) which is of short duration (5-10 min), without affecting pressor responses. In addition, effective dose of this compound is lesser (69.18%) than PBZ (75.66%) and higher than indomethacin (4.00) (see table 1). The ALD_{50} of the compound 15 could not be determined as no animal died upto>1500 mg/kg p.o. While for the rest of the compounds ALD_{50} was found to be > 1000 mg/kg.

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