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Note

Synthesis and biological evaluation of some new 4,5-dihydro-3-(2-aryl-indol-3-yl)-5-(4-chlorophenyl)-*N*[1]-phenylpyrazoles

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A facile and clean cyclization of indolylchalcone with phenyl hydrazine in glacial acetic acid occurs to afford 4,5-dihydro-3-(2-arylindol-3-yl)-5-(4-chlorophenyl)-N[1]-phenylpyrazoles **5a-e** in quantitative yield using 'Grindstone' technique. The results obtained indicate that, unlike classical heating, grinding method results in higher yields, shorter reaction time and cleaner reaction conditions. All the synthesized compounds have been characterized by their elemental analyses and spectral data (IR, ^{1}H NMR). Antibacterial and antifungal activity of all synthesized compounds have also been evaluated and some of them show promising results against *E. coli, S. aureus, C. albicans* and *A. niger*.

Keywords: Indolyl chalcone, 2-pyrazoline, Claisen-Schmidt condensation, grindstone chemistry, antimicrobial activity

Indoles, pyrazolines and allied derivatives are well known biologically important nitrogen containing heterocycles. Pyrazolines exhibit a plethora of bioactivities *viz*, COX-2 inhibitior[1], antiandrogenic[2], antibacterial[3], antifungal[4], antitumor[5], antidepressant[6], insecticidal[7], antidiabetic[8], photochemical[9], molluscicidal[10], antinociceptive[11] and antiamoebic activity[12]. In addition pyrazolines are also used in the treatment of Parkinson's, Alzheimer's disease and cerebral edema[13]. Besides being biologically active they are also used extensively as useful synthons in organic synthesis[14-16]. Indole derivatives also possess antibacterial and antifungal activities[17,18]. In view of this, it was planned to synthesize some new 4,5-dihydro-3-(2-arylindol-3-yl)-5-(4-chlorophenyl)-N[1]-phenylpyrazoles **5** containing both indole and pyrazoline moieties to get more potent compounds.

A classical synthesis of these compounds involves the base-catalyzed aldol condensation of aromatic ketones and aldehydes to give chalcones, which undergo a subsequent cyclization reaction with hydrazines affording 2-pyrazolines[19]. The combination of solvents, strong base and long reaction time period makes this method environmentally hazardous.

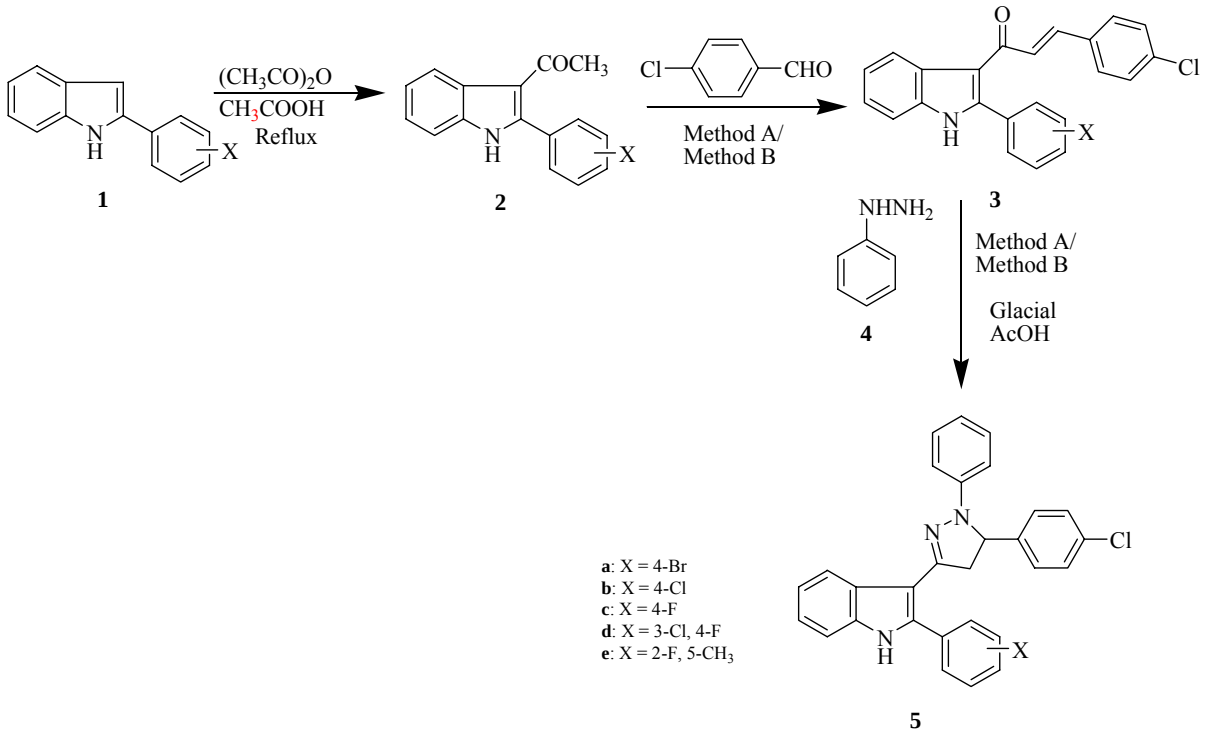
This provided the stimulus to synthesize new pyrazoline derivatives using classical as well as grindstone technique[20]. In grindstone technique reactions occur through generation of local heat by grinding of crystals of substrate and reagents by mortar and pestle. Reactions are initiated by grinding, with the transfer of very small amount of energy through friction. In some cases, a mixture of reactant and reagents turns to a glassy material. Such reactions are simple to handle, reduce pollution, comparatively cheaper to operate and may be regarded as more economical and ecologically favourable procedures in chemistry[21,22]. Solid state reactions occur more efficiently and more selectively than does the solution reaction, since molecules in a crystal are arranged tightly and regularly[23].

In the present work grindstone technique was used for the first time for the synthesis of titled compounds. This method is superior since it is eco-friendly, high yielding, requires no special apparatus, non-hazardous, simple and convenient. The significance of this approach is that chalcone and pyrazoline can both be obtained by grinding with a dramatic improvement in yield[24]. Further, the workup process is also simplified since there is no involvement of any volatile organic solvent to be removed but only requires pouring and washing in water.

Keeping these observations in view and in continuation to the earlier work on the synthesis of indole and pyrazole heterocycles[25-27] and as a part of the continuing programme in this area[28], a series of new 4,5-dihydro-3-(2-arylindol-3-yl)-5-(4-chlorophenyl)-N[1]-phenylpyrazoles have been prepared. To the best of the knowledge earlier reports do not exist on the synthesis of these pyrazolines. Their antibacterial and antifungal activities have also been evaluated and some of them show promising results.

Results and Discussion

Most products described herein were prepared by classical method as well as by grinding process. In the



Scheme I

classical method, a mixture of indolylchlalcone, phenylhydrazine and glacial acetic acid was heated to afford 4,5-dihydro-3-(2-arylindol-3-yl)-5-(4-chlorophenyl)-*N*[1]-phenylpyrazoles. In contrast, under solvent free conditions, the same reactants and catalytic amount of glacial acetic acid were ground together in a mortar and pestle to afford target compounds **5** in higher yield and lesser time (**Scheme I**).

Grinding together the solid aldehydes or ketones without addition of catalyst reveals an interesting phenomenon, in some cases a liquid melt is observed while in others the solid reagents remained in a discrete crystalline phase. More importantly, upon addition of the catalyst a rise in temperature (5-10°C) was recorded and the reaction was observed to take place in those systems that exhibit a phase change to a melt. Thus, the existence of a liquid phase is a prerequisite for reaction in those systems.

The physical and analytical data of compounds **5a-e** are given in **Table I**. Compounds **1-3** were characterized on the basis of their analytical and spectral data and were consistent with previous results[28].

In the IR spectra of **5a-e**, >N–H absorption appears as a broad band in the range of 3400-3310 cm^{-1}. Characteristic absorption due to >C=N group appears in the range of 1610-1600 cm^{-1} and aromatic –C=C– stretching vibrations are observed in the range of 1580-1560 cm^{-1}. The disappearance of absorption band from 1625-1605 cm^{-1} due to conjugated >C=O group of chalcone also confirms the formation of desired compounds **5a-e**.

The ^{1}H NMR spectra of **5a-e** exhibit a characteristic ABX pattern for the presence of two diastereotopic protons (non-equivalent) at C-4 and one proton at the C-5 position. These protons appear as three doublets of doublets. They show double doublet from δ 3.04-3.10 (due to α-C*H* at C-4) double doublet from δ 3.75-3.88 (due to β-C*H* at C-4) and double doublet from δ 5.21-5.41 (due to -*H* at C-5), each integrating for one proton. The aromatic resonance signal appears as a multiplet from δ 6.7-7.8 and a singlet due to >NH protons appears in the region of δ 7.7-8.0. Compound **5e** shows an additional singlet at δ 2.26 due to C*H*$_3$ protons. The IR and ^{1}H NMR data of 4,5-dihydro-3-(2-arylindol-3-yl)-5-(4-chlorophenyl)-N[1]-phenylpyrazoles are summarized in **Table I**.

In conclusion, by judicious choice of reaction conditions, it has been possible to enhance yields of desired products and make the procedure more eco-friendly, much simpler and faster than conventional procedure.

Table I — Physical, analytical and spectral characterization data of 4,5-dihydro-3-(2-arylindol-3-yl)-5-(4-chlorophenyl)-N[1]-phenylpyrazoles, **5a-e**

Compd	X	m.p. (°C)	Mol. Formula	Yield %		Found (%) (Calcd.)			^{1}H NMR δ ppm ($CDCl_3$)
				A	B	C	H	N	
5a	4-Br	121	$C_{29}H_{21}BrClN_3$	90	78	66.09 (66.08	3.98 3.96	7.97 7.98)	3.10 (dd, *J*=17.0, 7.1 Hz, 1H, C*H*$_2$ (Pyraz)), 3.81 (dd, *J*=16.5, 12.2 Hz, 1H, C*H* (Pyraz)), 5.36 (dd, *J*=12.5, 7.0 Hz, 1H, C*H*$_2$ (Pyraz)), 6.9-7.8 (m, Ar*H*, 17H), 7.9 (s, N*H*, 1H)
5b	4-Cl	118	$C_{29}H_{21}Cl_2N_3$	87	75	72.19 (72.20	4.35 4.37	8.71 8.70)	3.08 (dd, *J*=16.5, 6.9 Hz, 1H, C*H*$_2$ (Pyraz)), 3.85 (dd, *J*=16.3, 12.0 Hz, 1H, C*H* (Pyraz)), 5.21 (dd, *J*=12.1, 6.9 Hz, 1H, C*H*$_2$ (Pyraz)), 6.8-7.5 (m, Ar*H*, 17H), 7.7 (s, N*H*, 1H)
5c	4-F	130	$C_{29}H_{21}ClFN_3$	84	72	74.75 (74.76	4.51 4.50	9.02 9.01)	3.05 (dd, *J*=17.2, 7.2 Hz, 1H, C*H*$_2$ (Pyraz)), 3.75 (dd, *J*=17.1, 12.6 Hz, 1H, C*H* (Pyraz)), 5.24 (dd, *J*=12.3, 7.2 Hz, 1H, C*H*$_2$ (Pyraz)), 6.7-7.6 (m, Ar*H*, 17H), 7.8 (s, N*H*, 1H)
5d	3-Cl, 4-F	146	$C_{29}H_{20}Cl_2FN_3$	91	79	69.60 (69.61	4.00 4.01	8.40 8.42)	3.04 (dd, *J*=17.1, 7.1 Hz, 1H, C*H*$_2$ (Pyraz)), 3.75 (dd, *J*=16.9, 12.4 Hz, 1H, C*H* (Pyraz)), 5.30 (dd, *J*=12.0, 7.1 Hz, 1H, C*H*$_2$ (Pyraz)), 6.8-7.7 (m, Ar*H*, 16H), 7.9 (s, N*H*, 1H)
5e	2-F, 5-CH_3	125	$C_{30}H_{23}ClFN_3$	83	71	75.07 (75.04	4.79 4.75	8.75 8.78)	2.26 (s, C*H*$_3$, 3H), 3.06 (dd, *J*=16.4, 6.8 Hz, 1H, C*H*$_2$ (Pyraz)), 3.88 (dd, *J*=16.2, 11.9 Hz, 1H, C*H* (Pyraz)), 5.41 (dd, *J*=12.2, 7.0 Hz, 1H, C*H*$_2$ (Pyraz)), 6.7-7.6 (m, Ar*H*, 19H), 8.0 (s, N*H*, 1H)

Table II — Antibacterial activity of 4,5-dihydro-3-(2-arylindol-3-yl)-5-(4-chlorophenyl)-N[1]-phenylpyrazoles, **5a-e**

Compd	Mean value of area of inhibition in mm (800 ppm) IZ(AI)		Mean value of area of inhibition in mm (400 ppm) IZ(AI)		Mean value of area of inhibition in mm (200 ppm) IZ(AI)	
	S. aureus	*E. coli*	*S. aureus*	*E. coli*	*S. aureus*	*E. coli*
Streptomycin	12	10	10	08	7.8	6.2
5a	10 (0.83)	14 (1.40)	09 (0.90)	11.4 (1.42)	6.7 (0.86)	9.7 (1.56)
5b	12 (1.0)	10 (1.0)	08 (0.80)	08 (1.0)	7.7 (0.99)	6.2 (1.0)
5c	14 (1.17)	11 (1.10)	11.9 (1.19)	09 (1.12)	8.9 (1.14)	7.0 (1.13)
5d	13 (1.08)	08 (0.80)	10 (1.0)	06 (0.75)	8.7 (1.11)	5.0 (0.81)
5e	11 (0.92)	12 (1.20)	11.1 (1.11)	9.9 (1.24)	8.5 (1.09)	7.5 (1.20)

IZ = Inhibition area (zone) excluding diameter of disc
AI (Activity Index) = Inhibition area of sample / inhibition area of standard

Antimicrobial activity

All the synthesized compounds **5a-e** were screened for their antimicrobial activity against gram negative bacteria *Escherichia coli,* gram positive bacteria *Staphylococcus aureus* and fungi *Candida albicans* and *Aspergillus niger* at 200, 400 and 800 ppm concentration by disk diffusion method[29]. Streptomycin and ketoconazole are used as reference compounds for evaluation of antibacterial and antifungal activities, respectively.

A perusal of the results revealed that substituent present at *p*-position of phenyl ring at 2-position of indole moiety affects the observed activity *viz*, *p*-fluoro substituent resulted in higher activty against *S. aureus*, *p*-bromo substituents resulted in higher activty against *E. coli* while *p*-chloro substituent resulted in higher activity against *C. albicans* and methyl substituent resulted in higher activty against *A. niger* at various concentrations. The results obtained are presented in **Table II** and **III**.

Table III — Antifungal activity of 4,5-dihydro-3-(2-arylindol-3-yl)-5-(4-chlorophenyl)-N^1-phenylpyrazoles, **5a-e**

Compd	Mean value of area of inhibition in mm (800 ppm) IZ(AI)		Mean value of area of inhibition in mm (400 ppm) IZ(AI)		Mean value of area of inhibition in mm (200 ppm) IZ(AI)	
	C. albicans	*A. niger*	*C. albicans*	*A. niger*	*C. albicans*	*A. niger*
Ketoconazole	10	09	08	07	07	06
5a	11 (1.10)	12 (1.33)	8.9 (1.11)	9.2 (1.31)	7.8 (1.11)	7.9 (1.31)
5b	07 (0.70)	08 (0.89)	5.0 (0.62)	6.0 (0.86)	3.0 (0.49)	4.0 (0.67)
5c	13 (1.30)	06 (0.67)	10.6 (1.32)	4.1 (0.59)	9.0 (1.28)	-
5d	09 (0.90)	12 (1.33)	6.8 (0.85)	9.0 (1.28)	5.7 (0.81)	7.6 (1.27)
5e	12 (1.20)	13 (1.44)	9.6 (1.20)	9.3 (1.33)	8.4 (1.20)	8.0 (1.33)

IZ = Inhibition area (zone) excluding diameter of disc
AI (Activity Index) = Inhibition area of sample / inhibition area of standard

Experimental Section

All the melting points were determined in open glass capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model-557 and Nicolet Magna Model-750 spectrometer in KBr pellets. ^{1}H NMR spectra were recorded on Bruker DRX 300 NMR (300 MHz FT NMR) spectrometer using TMS as internal standard and $CDCl_3$ as solvent (chemical shift in δ, ppm). The homogeneity of the compounds was checked by TLC using silica gel-G as adsorbent. UV light or iodine vapour accomplished visualization. 2-Arylindoles were prepared by the method of Joshi *et al*.[30] 3-Acetyl-2-aryl-1*H*-indoles **2** were prepared by the literature method[31] and 3-Aryl-1-(2-aryl-1*H*-indol-3-yl)) prop-2-en-1-ones **3** were prepared by the method of Pathak *et al.*[28] All liquid reagents were distilled before use.

Synthesis of 4,5-dihydro-3-(2-arylindol-3-yl)-5-(4-chlorophenyl-N^1-phenylpyrazoles, 5

Method A: A mixture of 3-aryl-1-(2-aryl-1*H*-indole-3-yl)prop-2-en-1-one **3** (10 mmol), phenylhydrazine **4** (10 mmol) and 2,3-drops of glacial CH_3COOH was ground together in a mortar using a pestle to generate orange red coloured tacky solid within 20-40 min through grinding. The reaction proceeds exothermically (indicated by rise in temperature of 5-10°C). After the reaction was complete (when no starting material was detectable by TLC analysis), the solid was poured into ice cold water and the precipitate obtained was separated by filtration. The filtrate was washed well with water, dried and purified by recrystallization from ethanol to afford orange coloured crystals of the pure product.

Method B: A mixture of 3-aryl-1-(2-aryl-1*H*-indol-3-yl) prop-2-en-1-one **3** (10 mmol), phenyl hydrazine **4** (10 mmol) and 2,3-drops of glacial CH_3COOH was refluxed in absolute ethanol (50 mL) for 6 hr. The reaction mixture was concentrated *in vacuo* and the solid so obtained was filtered and the residue was subjected to column chromatography over silica gel G as stationary phase and solvents of increasing polarity as mobile phase.

All the other compounds were synthesized by similar methods and their physical, analytical and spectral characterization data are given in **Table I**.

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