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Original Article

Synthesis, characterization, antimicrobial and antitubercular activity of Some Pyrazoline derivatives from Chalcones bearing indane-1,3-dione as nucleus

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Abstract: A series of phenyl pyrazoline derivatives have been synthesized from chalcones of indane-1,3-dione. The substituted chalcones have already been synthesized and reported by us. The phenyl pyrazoline derivatives were synthesized by condensation of chalcone of indane-1,3-dione with phenyl hydrazine in basic medium in the presence of ethanol. The newly synthesized compounds (7a-f) have been characterized by IR and ^{1}H-NMR Spectroscopy and TLC. The new compounds have been evaluated for their antibacterial, antifungal and antitubercular activities.

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Introduction

Chalcones are an important class of natural products which are abundantly distributed in foods, fruits, vegetables and other plant products. They possess a variety of biological and pharmacological activities like anticancer, antitubercular [1, 2] analgesic, anti-inflammatory, antioxidant and antimicrobial [3, 4] activities. Chalcones have been used as intermediates for the preparation of many heterocyclic compounds having different therapeutic values. 3,5-disubstituted derivatives of phenyl pyrazolines have reported to possess varies biological and pharmacological activities like analgesic, anti-inflammatory, antipyretic, antitubercular, anticancer, anticonvulsant and antimicrobial activities.

Hence, in the present work, the synthesis of some new phenyl pyrazoline derivatives [5, 6] from chalcones [7, 8] of indane-1,3-dione has been carried out and the newly synthesized compounds have been evaluated for their antibacterial, antifungal and antitubercular activities [9].

Materials and methods

Instrumentation

All the reagents and chemicals used in this research work were of analytical grade. Melting points of the newly synthesized compounds were determined by open capillary method and are uncorrected. All the chemicals used for the research work were purchased from SD Fine Chemicals, Mumbai, India. IR Spectra of the compounds are recorded using (KBr) Bruker ALPHA FT-IR Spectrophotometer. ^{1}H-NMR Spectra of the compounds are recorded in $CDCl_3$ on BRUKER WM 400 MHz Spectrophotometer using TMS as internal standard. Microanalysis was performed on Carlo Erba EA-1108 element analyzer and are within ±1.0 % of the theoretical values. The reaction completion was identified by TLC using silica gel-G over precoated and preactivated glass plates with solvent system Ethyl acetate: Petroleum ether (3:1).

General procedure for the synthesis of new phenyl pyrazoline derivatives from chalcones of indane-1,3-dione:

An aromatic chalcone of indane-1,3-dione (0.001mol) was added to phenyl hydrazine (0.001mol). The mixture was condensed in basic medium viz. pyridine in the presence of ethanol (5 ml) at reflux temperature on water bath for 4-6 hrs. which resulted in the formation of corresponding phenyl pyrazoline derivatives [10-13]. The product formed was filtered under vacuum, dried and purified by recrystallization from ethanol (Scheme 1).

2-[5-(4-Flourophenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-indane-1,3-dione (7a):

Yield 60.0%; mp 162-165^0 C: IR (KBr) cm^{-1} ; 3029(C-H Str. Aromatic); 2920(C-H Str. Aliphatic); 1690(C=O Str.); 1597(C=N Str.); 1562(C=C Str.); 1230(C-N Str.) : ^{1}H NMR ($CDCl_3$) δ ppm; 3.40(s,1H,C-2-H); 3.85(1H,dd,C-4-H); 7.12(2H,d,J=8.8 Hz, C-2''' & 6'''-H); 7.43(1H,t,J=5.5 Hz, C-4'''-H); 7.61(2H,d,J=7.4 Hz, C-3'' & 5''-H); 7.71-7.76(2H,m, Ar-H); 7.80-7.84(2H,m, Ar-H); 8.08(2H,d,J=7.6 Hz, C-2'' & 6''-H); 8.50(2H,d,J=8.5 Hz, C-3''' & 5'''-H); Anal. Calcd. for $C_{24}H_{15}N_2O_2F$: C,75.4; H,3.92, N,7.32, F,4.97. Found: C,75.62; H,4.10; N,7.41; F,4.80.

2-[5-(2,6-dinitrophenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-indane-1,3-dione (7b):

Yield 58.0%; mp 161-163^0 C: IR (KBr) cm^{-1} ; 3042(C-H Str. Aromatic); 2908(C-H Str. Aliphatic); 1695(C=O Str.); 1606(C=N Str.); 1570(C=C Str.); 1234(C-N Str.) : ^{1}H NMR ($CDCl_3$) δ ppm; 3.37(s,1HC-2-H); 3.81(1H,dd,C-4-H); 6.48(2H,d,J=8.7 Hz, C-2''' & 6'''-H); 6.65(1H,t,J=5.4 Hz, C-4'''-H); 6.80(2H,d,J=8.1 Hz, C-3''' & 5'''-H); 7.54-7.59 (3H,m, Ar-H); 7.74-7.78(2H,m, Ar-H); 7.81-7.85 (2H,m, Ar-H); Anal. Calcd. for $C_{24}H_{14}N_4O_6$; C,63.43; H,3.08, N,12.33. Found: C,63.30; H,2.91, N,12.50.

2-[5-(4-Chloro-3-nitrophenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-indane-1,3-dione (7c):

Yield 59.0%; mp 183-185^0 C: IR (KBr) cm^{-1} ; 3047(C-H Str. Aromatic); 2910(C-H Str. Aliphatic); 1688(C=O Str.); 1610(C=N Str.); 1560(C=C Str.); 1224(C-N Str.); 847(C-Cl) : ^{1}H NMR ($CDCl_3$) δ ppm; 3.35(s,1H,C-2-H); 3.83(1H,dd,C-4-H); 6.53(2H,d,J=8.2 Hz, C-2''' & 6'''-H); 6.72(1H,t,J=5.1 Hz, C-4'''-H); 7.10(2H,d,J=8.3 Hz, C-3''' & 5'''-H); 7.73-7.77(2H,m, Ar-H); 7.79-7.84(2H,m, Ar-H); 7.62(2H,d,J=7.2 Hz, C-2'' & 6''-H); 8.06(2H,d,J=7.4 Hz, C- 5''-H); Anal. Calcd. for $C_{24}H_{14}N_3O_4Cl$: C,64.93; H,3.15, N,9.47. Found: C,65.10; H,3.00, N,9.54.

2-[5-(3-Fluoro-6-methoxyphenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-indane-1,3-dione (7d):

Yield 56.0%; mp 172-174^0 C: IR (KBr) cm^{-1} ; 3036(C-H Str. Aromatic); 2901(C-H Str. Aliphatic); 1683(C=O Str.); 1592(C=N Str.); 1572(C=C Str.); 1231(C-N Str.); 1165(OCH_3); 834(C-F) : ^{1}H NMR ($CDCl_3$) δ ppm; 3.31(s,1H,C-2-H); 3.79(s,3H, C-2 -OCH_3); 3.82(1H,dd,C-4-H); 6.57(2H,d,J=8.3 Hz, C-2''' & 6'''-H); 6.78(1H,t,J=5.4 Hz, C-4'''-H); 6.92(2H,d,J=8.6 Hz, C-3''' & 5'''-H); 7.75-7.79(2H,m, Ar-H); 7.81-7.84(2H,m, Ar-H); 7.28(1H,d,J=4.2 Hz, C-6''-H); 7.49(1H,d,J=3.8 Hz, C- 3''-H); 7.60(1H,d,J=4.0 Hz, C- 4''-H): Anal. Calcd. for $C_{25}H_{17}N_2O_3F$: C,72.81; H,4.12, N,6.76. Found: C,72.75; H,4.00, N,6.92.

2-[5-(2,6-dimethoxyphenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-indane-1,3-dione (7e):

Yield 58.0%; mp 160-162^0 C: IR (KBr) cm^{-1} ; 3030(C-H Str. Aromatic); 2915(C-H Str. Aliphatic); 1701(C=O Str.); 1599(C=N Str.); 1569(C=C Str.); 1229(C-N Str.); 1169(OCH_3) : ^{1}H NMR ($CDCl_3$) δ ppm; 3.34(s,1H,C-2-H); 3.82(s,6H,-OCH_3); 3.85(1H,dd,C-4-H); 6.64(2H,d,J=8.4 Hz, C-2''' & 6'''-H); 6.73(1H,t,J=5.2 Hz, C-4'''-H); 6.94(2H,d,J=8.6 Hz, C-3''' & 5''-H); 7.55-7.61(3H,m, Ar-H); 7.72-7.76(2H,m, Ar-H); 7.79-7.83(2H,m,Ar-H): Anal. Calcd. for $C_{26}H_{20}N_2O_4$: C,73.58; H,4.71, N,6.60. Found: C,73.76; H,4.52, N,6.43.

2-[5-(4-hydroxy-2,6-dimethoxyphenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-indane-1,3-dione (7f):

Yield 57.0%; mp 166-168^0 C: IR (KBr) cm^{-1} ; 3392(O-H Str.);3041(C-H Str. Aromatic); 2921(C-H Str. Aliphatic); 1693(C=O Str.); 1612(C=N Str.); 1565(C=C Str.); 1221(C-N Str.); 1158(OCH_3) : ^{1}H NMR ($CDCl_3$) δ ppm; 3.32(s,1H,C-2-H); 3.81(1H,dd,C-4-H); 3.94(s,6H,2X-OCH_3); 6.69 (2H,d,J=8.6 Hz, C-2''' & 6'''-H); 6.85(1H,t,J=5.5 Hz, C-4'''-H); 7.16(2H,d,J=8.9 Hz, C-3''' & 5''-H); 7.74-7.78(2H,m, Ar-H); 7.82-7.86(2H,m,Ar-H); 7.63(2H,d,J=7.3 Hz, C-3'' & 5''-H); 8.21(s,1H,Ar-OH): Anal. Calcd. for $C_{26}H_{20}N_2O_5$: C,70.90; H,4.54, N,6.36. Found: C,71.20; H,4.36, N,6.51.

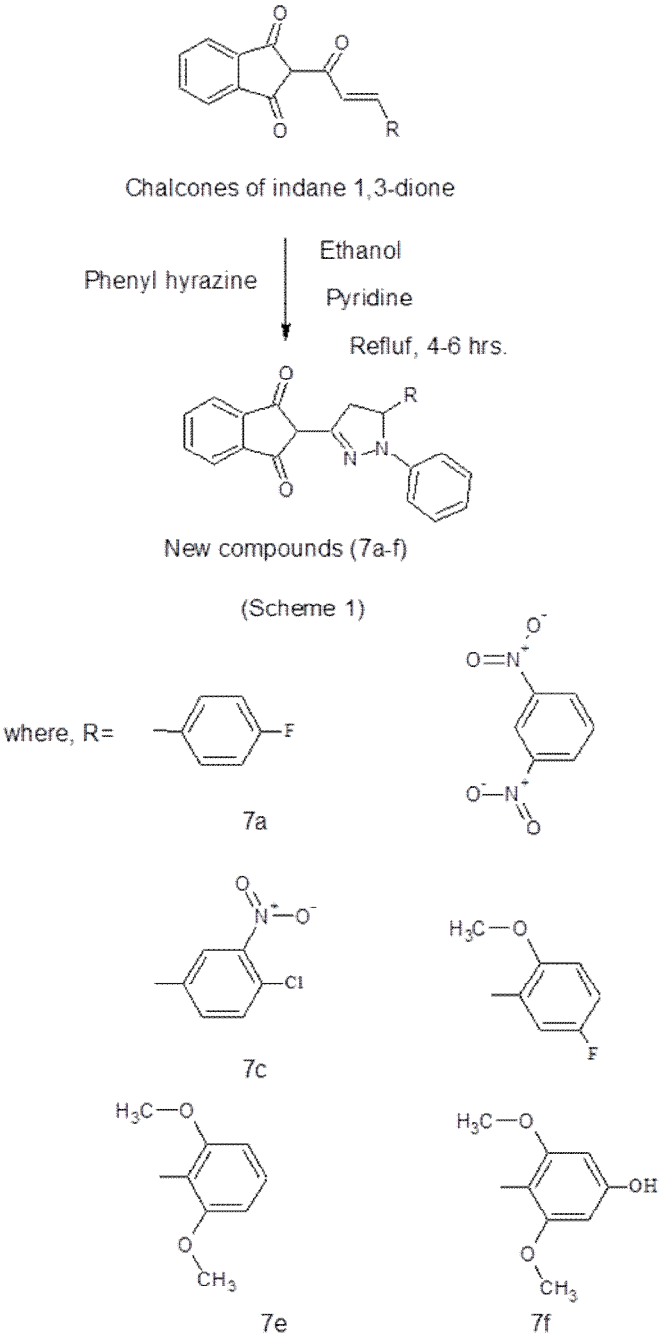
Antimicrobial Activity:

The newly synthesized compounds were screened for their antibacterial activity against two gram positive bacteria viz. *S. aureus, B. subtilis* and two gram negative bacteria viz. *K. pneumoniae, S. aeruginosa* and antifungal activity against *C. albicans and A. niger* using serial tube dilution technique. In this technique, the tubes of broth medium (brain Heart infusion broth) containing graded doses of compounds were inoculated with test organisms. After suitable incubation, growth occurred in those tubes, where the concentration of compound was below the inhibitory level and the culture becomes turbid. No growth was noticed above the inhibitory level and the tubes remained clear. The broth medium was purchased from HI media Laboratories Ltd., Mumbai, India. Preparation of medium, subculture and incubation was done as per the standard procedure. Ciprofloxacin and fluconazole was used as standard for the comparison of antibacterial and antifungal activity respectively and the results are represented in **table 1**.

Anti-tubercular activity:

The newly synthesized compounds were also screened for their anti - tubercular activity [13] against *M. tuberculosis* using microplate Alamar Blue Assay(MABA) [14, 15] by serial dilution method which was carried out at microbiology laboratories of Maratha Mandal's NGH Institute of Dental Sciences, Belgaum, India.

The compounds were screened at 100-0.8 g/ml concentration against *M. tuberculosis* (H37 RV Strain) ATCC No27294 in middle brook7H9 broth medium to determine MIC. Pyrazinamide and streptomycin were used as reference drugs for the comparison of activity. Preparation of inoculum, subculture and incubation was done as per the standard procedure. The MIC was defined as the lowest drug concentration which prevented the colour change from blue to pink. And the results are represented in **table 2**.



SCHEME 1

Table 1: Antimicrobial Activity of the compounds (7a-f)

Compound Code	MIC in µg/ml					
	S. aureus	B. subtilis	K. pneumoniae	S. aeruginosa	C. albicans	A. niger
7a	25	25	12.5	50	12.5	12.5
7b	12.5	25	12.5	25	12.5	12.5
7c	25	12.5	12.5	25	12.5	12.5
7d	12.5	25	12.5	25	12.5	25
7e	25	12.5	12.5	50	25	25
7f	12.5	12.5	6.25	12.5	12.5	12.5
Ciprofloxacin	02	02	01	04	--	--
Fluconazole	--	--	--	--	16	18

Results

All compounds of our study were screened for their antibacterial, antifungal and antitubercular activities against the species of organisms mentioned in the above sections. The compounds 7a,7b and 7c are more active against fungi comparing to compounds 7d,7e and 7f. All the compounds are active against one gram positive and one gram negative bacteria, but compound 7f was most active against almost all organisms of bacteria, fungi and *M. tuberculosis* comparing to other compounds because of presence of hydroxyl group at para position of benzene ring. Overall the activity results of all the compounds tested were significant and satisfactory.

Table 2: Antitubercular Activity of the compounds (7a-f)

Compound Code	MIC in µg/ml
7a	12.5
7b	12.5
7c	12.5
7d	12.5
7e	12.5
7f	6.25
Pyrazinamide	3.125
Ciprofloxacin	3.125
Streptomycin	6.25

Discussion

A new series of phenyl pyrazoline derivatives from chalcones of indane-1,3-dione have been synthesized and evaluated for their antimicrobial and antitubercular activities. The structures of all the newly synthesized compounds are confirmed by various spectral and elemental analysis. All the compounds exhibited significant activities against all the strains used to study. So, it can be concluded that these classes of compounds certainly hold great promise towards good active leads in medicinal chemistry.

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