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Synthesis And Antimicrobial Evaluation Of Some New N-(2,4 Dichlorobenzyl)-Indolylchalcones From 1H-indolyl-3 phenylpropenones

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Abs tract:-*Series of new 1-{N-(2,4-dichlorobenzyl)indolyl)}-3-phenylpropanones were synthesized. The intermediate 1H-indolyl-3-phenylpropenones were synthesized by the reaction of indole-3-carboxaldehyde with appropriate acetophenone in the presence of piperidine under reflux condition. Thus, the prepared intermediate indolyl chalcones has been subsequently treated with 2,4-dichlorobenzyl chloride in the presence of potassium carbonate and DMF as solvent under reflux condition to afford title compounds in good yield. The structures of intermediate and newly synthesized N-(2,4 dichlorobenzyl)- indolylchalcones were confirmed by physical and spectral analysis. All the N-(2,4 dichlorobenzyl)- indolylchalcones were evaluated for antibacterial and antifungal activities. Selected N-(2,4 dichlorobenzyl)- indolylchalcones showed good to excellent antibacterial and antifungal activities with reference to the well-established standards.*

Keyw ords:1H-indolyl-3-phenylpropenones, N-(2,4 dichlorobenzyl)- indolylchalcones, Antibacterial activity, Antifungal activity.

INTRODUCTION

Indole alkaloids have been proved to be medicinally important natural compounds. Indole ring constitutes an important template for drug design such as the classical NSAIDs indomethacin and indoxole. Further indole derivatives have been reported to possess promising biological activities including analgesic (Kameyama T et. al., 1985), antipyretic (Bredt AB and Girey GJ 1982), antifungal (Sridhar SK et. al.; 1999), anti-inflammatory (Kumar A et. al.; 2004; Singh N et al., 2008; Radwan MAA et. al., 2007), anthelmintic (Danilo Davyt et. al., 1998), cardiovascular (Kumar A et. al., 1986), anticonvulsant (El-Gendy Adel A et. al., 1997; Gitto R et. al., 2009), antimicrobial (Trivedi B and Shah VH. 1993; Bhusare SR et. al., 2004) and selective COX-2 inhibitory activities (Guo WHZ et. al., 2003; Kalgutkar AS et. al., 2000; Hu W et. al., 2003; Caron S et. al., 2003). Thus the efficient synthesis of novel substituted indole derivative compounds still represent highly pursued target. The substitution of heterocyclic moiety at the 3- position of indole ring markedly influences the anti-inflammatory activity (Ismail MMF et. al., 1997).

Chalcones (α, β-unsaturated ketones) are important intermediate products in organic synthesis (Ranu BC et. al., 2005; Mukherjiee S et. al., 2001) they also exhibit versatile biological activity (Ram V J et. al., 2000; Xia Y et. al., 2000). Recent studies on biological evaluation of chalcones revealed some to be anti-cancer (Rojas J et. al., 2002), nitric oxide regulation modulatory (Satyanarayana M et. al., 2004) and anti-hyperglycemic agents (Bu X and Li Y 1996). These compounds are usually synthesized by the Claisen–Schmidt condensation of aromatic aldehydes with methyl ketones in the presence of bases such as KOH, (Daskiewicz J B et. al., 1999) LiHDMS (Sebti S et. al., 2002) and calcined NaNO3/ natural phosphates (Iranpoor N and Kazemi F 1998). The acid catalysed methodologies include the use of Zeolites (Narender T and Reddy K R 2007), K3PO4 (Agarwal A et. al., 2005) and BF3–Et2O (Taukerman S V et. al., 1969). The indole derivatives have been widely studied, α, β-unsaturated ketones of chalcone types containing this heterocycle in which products of crotonic condensation of 3-formyl indole derivatives with different acetophenones were described previously in basic media using mostly piperidine as a catalyst (Deb-Das D C and Kumar R B N 1992; Order R B and Lindwal H G 1945; Manna F et. al., 1999; Zahran M et. al., 2001). But the substitution of hydrogen atom present on nitrogen atom of indolyl chalcone ring by benzyl ring is not much more explored. We are presenting in this context synthesis of 1H-indolyl-3-phenylpropenones and their N-benzylation with 2,4-dichlorobenzyl chloride to afford novel N-(2,4 dichlorobenzyl)- indolylchalcones and investigation of their antimicrobial activity.

EXPERIMENTAL SECTION:

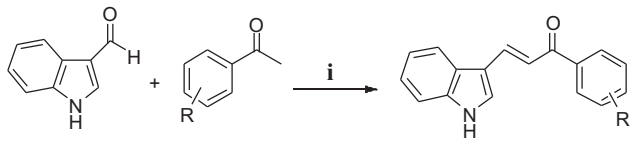
Materials and Methods:

All reagents were obtained from commercial suppliers, Merk Pvt. Ltd., Sd Fine Chemicals Mumbai, Aldrich USA and used without further purification. Melting points were determined in an open glass capillaries and are uncorrected. The purity of compounds was checked by TLC. The IR spectra of all compounds were recorded in KBr on

Shimadzu FT-IR spectrophotometer. 1H NMR and 13C NMR spectra (CDCl3) were recorded on a Brucker Avance 400 MHz spectrometer using tetramethylsilane (TMS, δ= 0 ppm) as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer.

General Procedure for the synthesis of 1H-indolyl-3-phenylpropenones (3a-g)

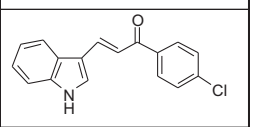
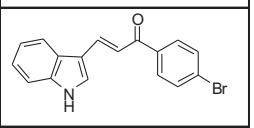
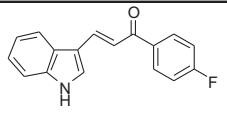
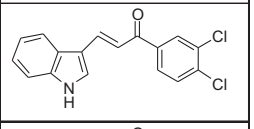
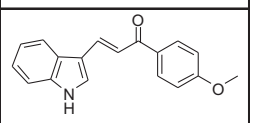
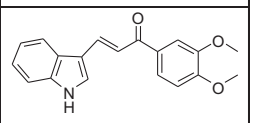
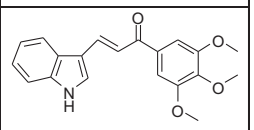
Indole-3-carbaldehyde (1) (0.04mol) was dissolved in ethanol (30 mL) and unsubstituted acetophenone (2) (0.04 mol) was added to it. Then, pipyridine (2-3 mL) was added and reaction mixture was refluxed for 6 h. After completion of reaction (monitored by TLC, 12 h), the reaction mixture was poured into crushed ice and neutralized with acetic acid. The product was precipitated out. It was separated, washed with water and dried. It was purified by recrystallization from ethanol to give 3a. The same general procedure was followed for the compound 3b-g (Table 1).



(1) (2) (3a-g)

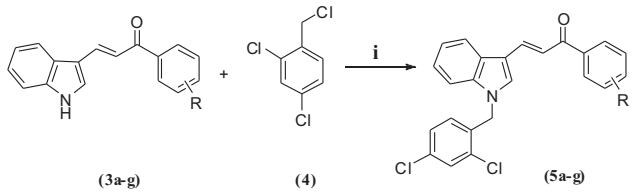
Scheme 1. i) Piperidine, ethanol, re?ux, 12 h.

Table 1 synthesis of 1H-indolyl-3-phenylpropenones (3a-g)

Compound	R	Product
3a	4-chloro	
3b	4-bromo	
3c	4-fluoro	
3d	3,4-dichloro	
3e	4-methoxy	
3f	3,4-dimethoxy	
3g	3,4,5-trimethoxy	

Procedure for the synthesis 1-{N-(2,4-dichlorobenzyl) indolyl)}-3- phenylpropanones (5a-g)

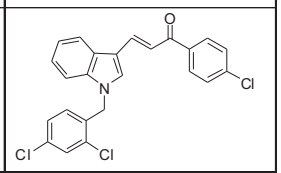
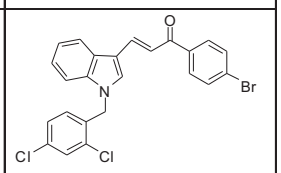
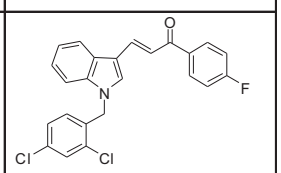
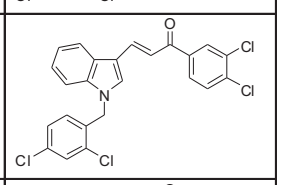
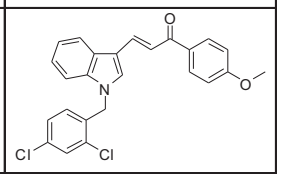
A mixture of 1H-indolyl-3-phenylpropenones (5a-g) (0.03), 2,4-dichlorobenzyl chloride (4), K2CO3 (0.5 g) and dimethylformamide (10 mL) was stirred vigorously and refluxed for 2 h. After completion of reaction as monitored by TLC, the reaction mixture was cooled, and poured onto crushed ice. The precipitated solid was filtered off, washed with water, dried and recrystallized from ethanol (Table 2).

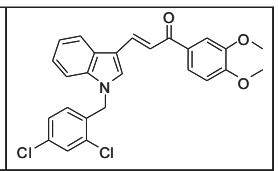
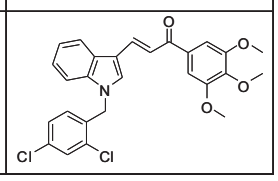


(3a-g) (4) (5a-g)

Scheme 2. i) DMF, K2CO3 rt, 4 h.

Table 2 synthesis 1-{N-(2,4-dichlorobenzyl)indolyl)}-3-phenylpropanones (5a-g)

Compound	R	Product
5a	4-chloro	
5b	4-bromo	
5c	4-fluoro	
5d	3,4-dichloro	
5e	4-methoxy	

5f	3,4-dimethoxy	
5g	3,4,5-trimethoxy	

Biological activity

The antimicrobial activities of the synthesized tri-arm star shaped chalcones V a-j were determined by disc diffusion method (Biljana RD and Niko SR 2010). The compounds were evaluated for antibacterial activity against *Proteus vulgaris, Staphylococcus aureus*. The antifungal activity was evaluated against *Alternaria and Curvularia lunata.* The test compounds 5a-g in measured quantities, were dissolved in dimethyl sulphoxide (DMSO) to get the final concentration 200 µg/m L. The bacterial (24 h) and fungal (48 h) cultures from the slants were diluted with sterile distilled water and mixed thoroughly to prepare a clear homogeneous suspension. These suspensions were spread on solidified agar (NA-nutrient agar for bacteria and PDA-potato dextrose agar for fungi) medium. The filter paper disks prepared by only DMSO (as a negative control) and with solutions of test compounds 5a-g and 9a-g as well as standard compounds (Penicillin and Nystatin as positive control) were carefully placed over the spread cultures and incubated at 37 o C for 24 h for bacteria and at 28-30 o C for 48 h for fungi. After the incubation period, the plates were examined for the zone of inhibition. The diameters for the zone of inhibitions were measured (in mm) including the diameter of the disk also. All determinations were made in triplicate for each of the compound and the average value was taken. The antibacterial and antifungal activity was evaluated against *P. vulgaris, S.aureus, Alternaria, and C. lunata.* The outcomes of mean values and standard deviation are shown in Table 3.

Table 3 Antibacterial and Antifungal activities of synthesized 1-{N-(2,4 dichlorobenzyl)indolyl)}-3-phenylpropanones (5a-g)

Sr.No.	Zone of inhibition (mm)			
	P. vulgaris	*S.aureus*	*Alternaria*	*C. lunata*
5a	8.63±0.13	11.05±0.30	6.05±0.11	7.01±0.61
5b	9.46±0.25	5.95±0.16	7.12±0.11	6.30±0.20
5c	10.92±0.16	9.02±0.15	8.24±0.23	11.17±0.28
5d	13.45±0.11	11.16±0.27	6.08±0.17	8.12±0.33
5e	11.16±0.20	12.02±0.18	12.28±0.25	11.23±0.24
5f	10.10±0.26	7.78±0.37	12.20±0.26	12.23±0.16
5g	14.14±0.11	9.72±0.18	11.68±0.28	11.12±0.23
Penicillin (Std.)	15	15	NA	NA
Nystatin (Std.)	NA	NA	15	15
DMSO -Ve Control	-	-	-	-

P. vulgaris = Proteus vulgaris, S.aureus = Staphylococcus aureus C. lunata = Curvularia lunata; NA = Not Applicable; (-) = No zone of inhibition, Values are means of three replicates, ± Standard deviation.

Spectroscopic data of selected compounds:

(E)-3-(1-(2,4-dichlorobenzyl)-1H-indol-3-yl)-1-(4-fluorophenyl)prop-2-en-1-one (5c)

Yellow solid; IR (KBr, cm^{-1}): 3070, 2865, 1880, 1659, 1580, 1467, 1365, 1073;, ^{1}H NMR ($CDCl_3$,400MHz) (δ, ppm): 8.10 (d, 1H, Ar-H), 7.52 (d, 1H, –CO-CH=CH–), 7.43 (d, 1H, –CH=CH–), 7.47 (d, 2H, Ar-H), 7.08–7.20 (m, 6H, Ar-H), 6.96 (d1, 2H, Ar-H), 6.90 (d,1H, Ar-H), 5.20 (s, 2H, CH2) MS (ESI, m/z): 424.1 [M +1]. Anal. Calcd for $C_{24}H_{16}Cl_2FNO$: C, 67.94; H, 3.80; N, 3.30. Found: C, 67.85; H, 3.76; N, 3.25.

(E)-3-(1-(2,4-dichlorobenzyl)-1H-indol-3-yl)-1-(4-methoxyphenyl)prop-2-en-1-one(5e)

Yellow solid; IR (KBr, cm^{-1}): 3080, 2869, 1890, 1655, 1145, 1576, 1470, 1355, 1038;, 1H NMR ($CDCl_3$,400MHz)(δ, ppm): 3.95 (s, 3H OCH3), 8.13 (d, 1H, Ar-H), 7.55 (d, 1H, –CO-CH=CH–), 7.38 (d, 1H, –CH=CH–), 7.50 (d, 2H, Ar-H), 7.15–7.20 (m, 6H, Ar-H), 6.95 (d, 2H, H), 6.88 (d,1H, Ar-H), 5.30 (s, 2H, CH_2) MS (ESI, m/z): 436.1 [M + 1]. Anal. Calcd for $C_{25}H_{19}Cl_2NO_2$: C, 68.82; H, 4.39; Cl, 16.25; N, 3.21; O, 7.33. Found: C, 68.78; H, 4.33; N, 3.25.

RESULTS AND DISCUSSION:

The intermediate 1*H*-indolyl-3-phenylpropenones were synthesized by the reaction of indole-3-carboxaldehyde with appropriate acetophenone in the presence of piperidine under reflux condition. Thus, the prepared intermediate indolyl chalcones has been subsequently treated with 2,4-dichlorobenzyl chloride in the presence of potassium carbonate and DMF as solvent under reflux condition to afford title compounds in good yield. All

newly synthesized N-substituted chalcones were characterized by FT-IR, ^{1}H, ^{13}C NMR spectroscopy to conform their structures and characterization results are in good agreement with respective structures. Further newly synthesized N-substituted chalcones were evaluated for their antibacterial and antifungal activity.

CONCLUSION:

In conclusion, we have synthesized series of new 1-{N-(2,4-dichlorobenzyl)indolyl)}-3-phenylpropanones from intermediate 1*H*-indolyl-3-phenylpropenones. The structures of the newly synthesized N-substituted indolyl chalcones were confirmed by FT-IR, 1H and 13C NMR spectroscopy and further screened for their antimicrobial activity. The antibacterial and antifungal activity revealed that most of the compounds showed moderate to good activity.

The electron withdrawing and releasing substituent does not show any considerable effect on yield of N-substituted chalcones. In comparison with standard antibacterial penicillin, compounds 5d, 5e and 5g found to be active against *P. vulgaris*. Compounds 5a and 5d were found to be active against S. aureus. In comparison with standard antifungal nystatine, compounds 5e, 5f and 5g were found to be active against *Alternaria* and compounds 5e, 5f were found to be active against C. *lunata.* Compound 5f showed highest antibacterial activity were as compound 5f showed highest antifungal activity.

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