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Synthesis, characterization and antimicrobial evaluation of some new N-(2,4-dichlorobenzyl)-indolylchalcones

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ABSTRACT

Series of new 1-{N-(2,4-dichlorobenzyl)indolyl)}-1-phenylpropanones were synthesized. The intermediate 1H-indolyl-1-phenylpropenones were synthesized by the reaction of 3-acetyl indole with appropriate benzaldehyde in the presence of aqueous sodium hydroxide solution 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.

Keywords: Indolylchalcones, Antibacterial activity, Antifungal activity.

INTRODUCTION

The indole nucleus is an important structure in numerous natural or synthetic alkaloids [1] and in medicinal chemistry [2]. The diversity of the structures encountered, as well as their biological and pharmacological [3] relevance, have motivated research aimed at the development of new economical, efficient and selective synthetic strategies, particularly for the synthesis of substituted indole rings [4-5]. The substituted indoles have been referred to as privileged structures since they are capable of binding to many receptors with high affinity [6]. Therefore, the synthesis and selective functionalization of indoles have been the focus of active research [7–9].

Chalcones (1,3-diaryl-2-propen-1-ones) with an enone system between two aromatic rings constitute an important class of natural products which serve as precursors for the preparation of various flavonoids and exhibit interesting pharmacological activities [10,11]. Natural and synthetic chalcones have shown broad spectrum of biological activities such as anti-inflammatory [12], antituberculosis [13], antifungal [14], antimalarial [15], antileish-manicidal [16] and anticancer [17-21]. Recently indolyl chalcones and N-substituted indolyl chalcones gained considerable interest due to antitumor [22], anticancer [23] and cellular cytotoxicities [24].

Based on the above observations and earlier investigations, here we are reporting the synthesis of various 1-{N-(2,4-dichlorobenzyl)indolyl)}-3-phenylpropanones and 1-{N-(2,4-dichlorobenzyl)indolyl)}-1-phenylpropanones and evaluation of their antibacterial and antifungal activity.

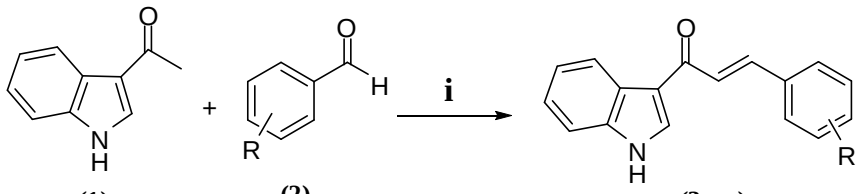
EXPERIMENTAL SECTION

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. ^{1}H NMR and ^{13}C NMR spectra ($CDCl_3$) were recorded on a Brucker Avance 400 MHz spectrometer using tetramethylsilane (TMS, $\delta = 0$ ppm) as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer.

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

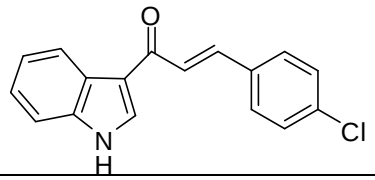
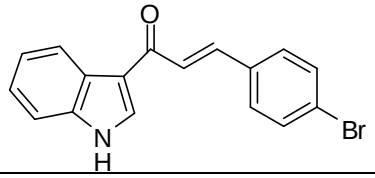
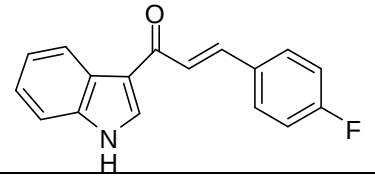
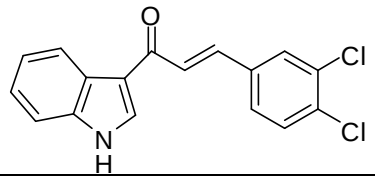
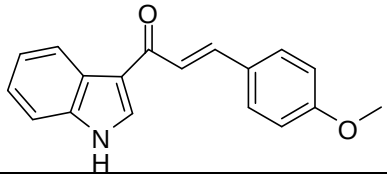
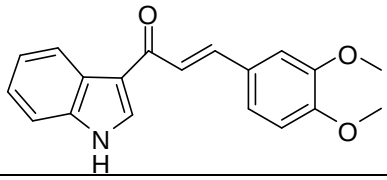
3-acetylindole (1) (0.04mol) was dissolved in ethanol (30 mL) and unsubstituted benzaldehyde (2) (0.04 mole) was added to it. Then, solution of NaOH (5 mL 25%) was added and reaction mixture was refluxed for 12 h. After completion of reaction (monitored by TLC, 12 h), the reaction mixture was poured into crushed ice and neutralized with dil. HCl. 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).

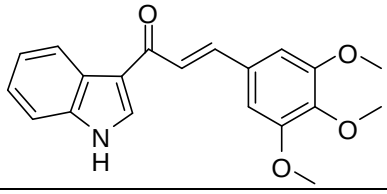


(1) **(2)** **(3a-g)**

Scheme 1. i) NaOH, ethanol, reflux, 15 h

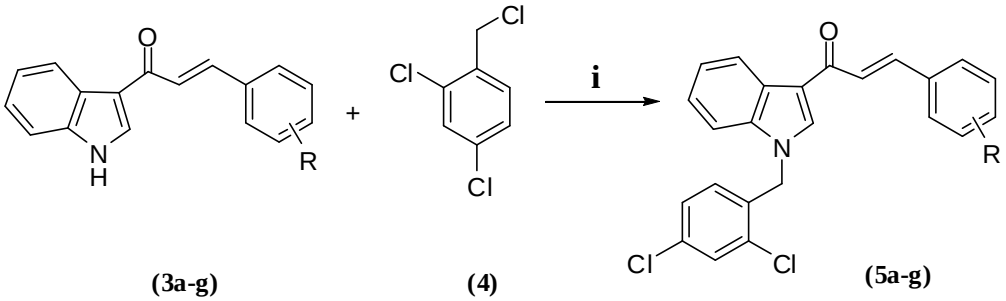
Table1 : Synthesis of 1*H*-indolyl-1-phenylpropenones (3a-g)

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 synthesis1-{N-(2,4-dichlorobenzyl)indolyl)}-1-phenylpropanones(5a-g)

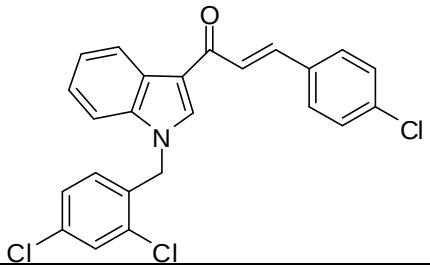
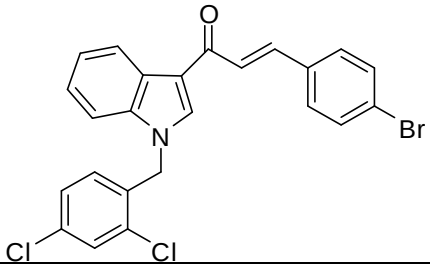
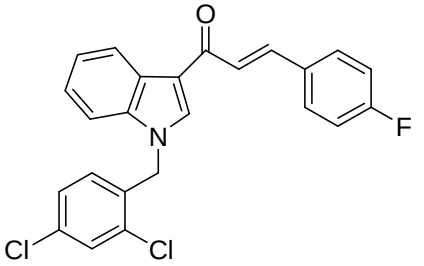
A mixture of 1*H*-indolyl-1-phenylpropenones (3a-g) (0.03), 2,4-dichlorobenzyl chloride (4), K_2CO_3 (0.5 g) and dimethylformamide (10 mL) was stirred vigorously and refluxed for 2 h. After completion of reaction as monitored by TLC, the reaction mixture was cooled, and poured onto crushed ice. The precipitated solid was filtered off, washed with water, dried and recrystallized from ethanol to give (5a-g) Table-2.

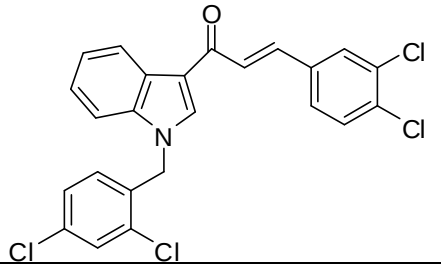
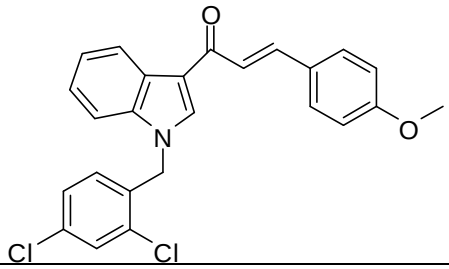
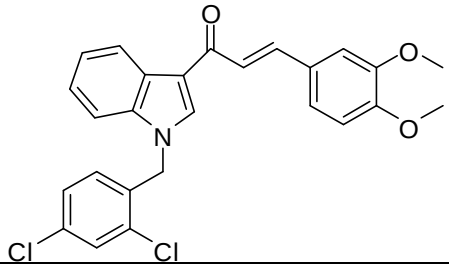
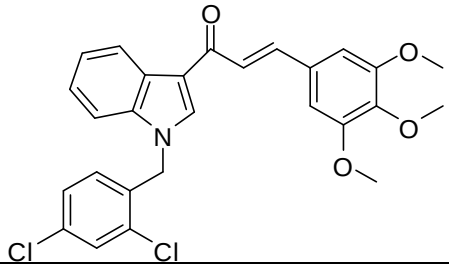


(3a-g) **(4)** **(5a-g)**

Scheme 2. i) DMF, K_2CO_3 rt, 4 h

Table 2 : Synthesis1-{N-(2,4-dichlorobenzyl)indolyl)}-1-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	

Spectral data of selected compounds:

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

Yellow solid; IR (KBr, cm^{-1}): 3060, 2866, 1,898, 1641, 1573, 1476, 1374, 1073;, ^1H NMR ($CDCl_3$,400MHz) (δ, ppm): 8.16 (d, 1H, ben-H), 7.58 (d, 1H, –CH=CH–), 7.46 (d, 1H, –CH=CH–), 7.42 (d, 2H, ben-H), 7.03–7.14 (m, 6H, ben-H), 6.90 (d1, 2H, benH), 6.85 (d,1H, ben-H), 5.25 (s, 2H, CH_2) 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, 67.80; H, 3.91; N, 3.43.

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

Yellow solid; IR (KBr, cm^{-1}): 3065, 2855, 1898, 1650, 1140, 1560, 1476, 1350, 1030;, ^1H NMR ($CDCl_3$,400MHz)(δ, ppm): 3.99 (s, 3H OCH_3), 8.10 (d, 1H, ben-H), 7.50 (d, 1H, –CH=CH–), 7.34 (d, 1H, –CH=CH–), 7.48 (d, 2H, ben-H), 7.10–7.15 (m, 6H, ben-H), 6.90 (d, 2H, benH), 6.85 (d,1H, ben-H), 5.25 (s, 2H, CH_2) MS (ESI, m/z): 436.1 [M^+ + 1]. Anal. Calcd for $C_{25}H_{19}C_{l2}NO_2$: C, 68.82; H, 4.39; Cl, 16.25; N, 3.21; O, 7.33. Found: C, 68.80; H, 4.30; N, 3.35.

Biological activity

The antimicrobial activities of the synthesized 1-{N-(2,4-dichlorobenzyl)indolyl)}-1-phenylpropanones (5a-g) were determined by disc diffusion method [25]. 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 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)}-1-phenylpropanones (5a-g)

Sr. No.	Zone of inhibition (mm)			
	P. vulgaris	*S.aureus*	*Alternaria*	*C. lunata*
5a	7.63±0.15	8.05±0.25	5.05±0.23	5.01±0.31
5b	6.86±0.23	5.95±0.10	7.12±0.11	10.30±0.20
5c	9.92±0.06	10.02±0.05	6.24±0.06	9.17±0.11
5d	13.55±0.05	11.13±0.23	8.02±0.11	10.10±0.32
5e	12.06±0.25	13.78±0.15	13.28±0.20	8.10±0.13
5f	11.10±0.28	8.90±0.30	12.25±0.11	13.50±0.15
5g	9.16±0.25	7.86±0.22	10.86±0.18	11.00±0.10
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.

RESULTS AND DISCUSSION

The intermediate 1*H*-indolyl-1-phenylpropenones were synthesized by the reaction of 3-acetyl indole with appropriate benzaldehyde in the presence of aqueous sodium hydroxide solution 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 mass 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.

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 5f found to be active against *P. vulgaris.* Compounds 5d and 5e were found to be active against *S. aureus*. In comparison with standard antifungal nystatine, compounds 5e, and 5f, were found to be active against *Alternaria* and compounds 5f, 5g were found to be active against *C. lunata*. Compound 5e showed highest antibacterial activity were as compound 5f showed highest antifungal activity.

CONCLUSION

In conclusion, we have synthesized series of new 1-{N-(2,4-dichlorobenzyl)indolyl)}-1-phenylpropanones from intermediate 1*H*-indolyl-1-phenylpropenones. The structures of the newly synthesized N-substituted indolyl chalcones were confirmed by FT-IR, ^{1}H and ^{13}C 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.

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