

Green Protocole for the Synthesis and Antimicrobial Activity of Chalcone Derivatives of Indole Nucleus

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(Received November 15, 2021)

Abstract: Synthesis of (E)-1-phenyl-3-(2-phenyl-1*H*-indol-3-yl)prop-2-en-1-one(5a-h) was prepared by the condensation reaction of different 3-Formyl-2-phenylindole derivatives (2a-e) and substituted acetophenons in quantitative yield by applying green synthetic methods as microwave irradiation using KSF catalysts under solvent-free mild reaction conditions with high product yields. The structures of the synthesized compounds were characterized on the basis of elemental analysis, IR, ¹HNMR, ¹³C NMR, and mass spectral data. The synthesized compounds were screened for antibacterial activity. Most of the tested compounds belonging to the (E)-1-phenyl-3-(2-phenyl-1*H*-indol-3-yl)prop-2-en-1-one series exhibited promising activities.

Keywords: Indole, Acetophenone, Microwave irradiation, Antibacterial activity.

1. Introduction

Heterocycle contributes an indispensable role in chemistry due to their wide range of applications in the field of drug design, material science, agrochemicals, photochemistry, and dyes and so on¹⁻⁴. Indoles are probably the most extensively dispersed heterocyclic compounds in nature having medicinal importance. Tryptophan 2-amino-3-(3'-indolyl)propionic acid,) is a naturally occurring essential amino acid and a constituent of most proteins, it also serves as a biosynthetic precursor for a wide variety of tryptamine-indoles. The indole skeleton is one of the most attractive

frameworks with a wide range of biological and pharmacological activities including anticancer⁵, antirheumatoid⁶, anti HIV⁷, anti-inflammatory⁸, anti-diabetic⁹, antihistaminic¹⁰, anticonvulsant¹¹, AT1 Antagonists¹², antihypertensive¹², antioxidant¹³ and antimicrobial¹⁴, Phenyl group at 2-position of indole moiety enhance biological activities like antimicrobial, monoamine oxidase inhibition¹⁵. The derivatives of 2-phenyl indoles exhibits have shown potent CNS depressant activity¹⁶, metastatic activity¹⁷ and antimicrobial¹⁸ activity.

Microwave irradiation is an established, convenient synthetic method. This technique has been applied to a variety of reactions resulting in a reduction of reaction time, higher yield, greater selectivity, and lesser product contamination¹⁹. Montmorillonite KSF showed catalytic activity for this condensation reaction and has many advantages over catalysts like NaOH, KOH such as easy to handle, low cost, and elimination of metal waste. Keeping in view these observations and continuation of our studies towards the synthesis of a variety of bioactive heterocycles²⁰, herein we have designed various strategies to synthesize some noble indolyl chalcone derivatives. In order to make a comparative study and assessed the efficiency of these synthetic routes, we have used conventional and solvent-free methods (microwave irradiation) to get the target molecule. All the synthesized compounds screened for antimicrobial activity.

2. Materials and Methods

Chemistry: Melting points of all the synthesized compounds are determined in open capillary tubes and are uncorrected. The IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin Elmer- 557 model. Reactions are monitored by thin-layer chromatography (TLC) using silica gel-G as adsorbent, and the spots were visualized using UV light and iodine. ¹H NMR and ¹³C NMR spectra were recorded on BRUKER AVANCE II 400-MHz NMR Spectrometer using tetramethylsilane (TMS) as an internal standard and DMSO- d_6 /CDCl₃ as a solvent. The mass spectral data were obtained on a JEOLD-300 spectrometer. Microwave-assisted reactions were carried out in a domestic MW oven (LG MS-194A) operating at 2450 MHz.

General Method (i): Conventional synthesis of (5a-h) Synthesis of (E)-1-phenyl-3-(2-phenyl-1*H*-indol-3-yl)prop-2-en-1-one (5a): A mixture of 2-Phenyl-1*H*-indole-3-carbaldehyde (0.22 g, 1 mmol) and acetophenone (0.2 ml, 1 mmol) in anhydrous ethanol (25 ml) was refluxed in the presence

of piperidine (0.8 ml) for 20 h. The reaction mixture poured into ice water, neutralized with acetic acid to get solid compound which was filtered and recrystallized from ethanol to obtain pure compound. Yield 76%; dark brown solid; mp 170-172 °C; the compounds (5a-h) also synthesized by the above method. Physical and analytical data of these compounds (5a-h) shown in (Table-1).

General Method (ii): Microwave-Assisted Solvent-free synthesis of (5a-h): The reaction was carried out in a domestic microwave (800 W, 2450 MHz). A mixture of 2-Phenyl-1*H*-indole-3-carbaldehyde (0.22 g, 1 mmol) and acetophenone (0.2 ml, 1 mmol), and montmorillonite KSF (0.4 g) were mixed thoroughly in a pestle mortar. This mixture was then transferred into a conical flask (100 cm³) and irradiated with microwaves for 5-11 min. After completion of the reaction (indicated by TLC), ethanol was added and the mixture was filtered, The filtrate was concentrate and then the crude product so obtained was recrystallized from ethanol to obtain pure compound (5a-h). The catalyst left as the residue was washed 2-3 times with ethanol and dried in vacuum for reuse. The compounds of the series (5a-h) also synthesized by the above method. Result and conditions of the synthesis of (E)-1-phenyl-3-(2-phenyl-1*H*-indol-3-yl)prop-2-en-1-ones (5a-h) shown in (Table-2)

Table 1. Physical and analytical data of (E)-1-phenyl-3-(2-phenyl-1*H*-indol-3-yl)prop-2-en-1-ones (5a-h)

Compound	R	R ¹	Molecular Formula	Molecular Weight	Melting point (°C)	Elem. Analysis (Cal. /Found)		
						C	H	N
5a	H	H	C ₂₃ H ₁₇ NO	323.39	170-172	85.42/85.41	5.30/5.29	4.33/4.32
5b	F	H	C ₂₃ H ₁₆ FN O	341.32	205-207	80.92/80.91	4.72/4.71	4.10/4.09
5c	Br	H	C ₂₃ H ₁₆ Br NO	402.28	206-208	68.67/68.66	4.01/4.00	3.48/3.47
5d	Cl	H	C ₂₃ H ₁₆ Cl NO	357.83	193-195	77.20/77.19	4.61/4.60	3.91/3.90
5e	CH ₃	H	C ₂₄ H ₁₉ NO	337.41	222-224	85.43/85.41	5.68/5.66	4.15/4.13
5f	CH ₃	Cl	C ₂₄ H ₁₈ Cl NO	371.86	247-249	77.52/77.51	4.88/4.86	3.77/3.75
5g	Cl	F	C ₂₃ H ₁₅ ClF NO	375.82	203-205	73.50/73.49	4.02/4.00	3.73/3.72
5h	Br	F	C ₂₃ H ₁₅ BrF NO	420.27	211-213	65.73/65.72	3.60/3.58	3.33/3.32

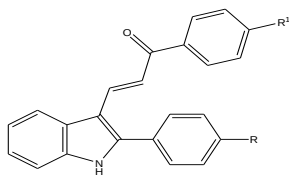
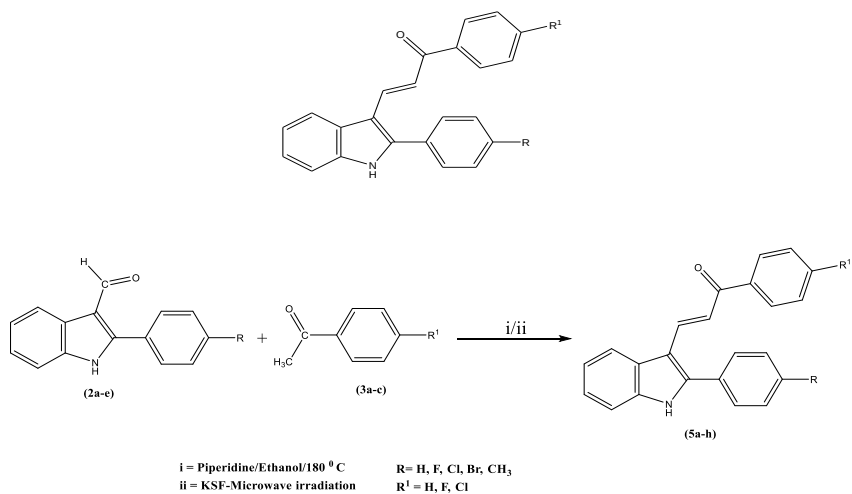


Table 2. Result and conditions of the synthesis of (E)-1-phenyl-3-(2-phenyl-1*H*-indol-3-yl)prop-2-en-1-ones (5a-h)

Compound	% Yield Time required				Temp. ($^{\circ}\text{C}$)
	ii	iii	ii (min.)	iii (min.)	
5a	82.1	68.2	5	30	70
5b	89.3	78.5	7	30	60
5c	82.3	75.6	8	40	50
5d	90.1	67.5	11	45	65
5e	84.5	77.6	9	30	60
5f	84.4	65.0	6	50	75
5g	78.5	70.5	5	30	55
5h	83.0	71.3	8	40	60



Scheme 1. Schematic representation for the synthesis of (E)-1-phenyl-3-(2-phenyl-1*H*-indol-3-yl)prop-2-en-1-ones

3. Result and Discussions

Synthesis: 2-Phenylindole derivatives were obtained by the method of Joshi et al.,^{were} subjected to formylation with phosphorous oxychloride and dimethylformamide under Vilsmeier-Haack Formylation reaction. We carried out Claisen-Schmidt condensation reaction between 3-Formyl-2-phenylindole derivatives (2a-e) and various substituted acetophenones (3a-c) catalyzed by piperidine to get indolyl chalcones (5a-h) Scheme-1. All synthesized compounds were characterized by IR, ^1H NMR, ^{13}C NMR, and mass spectroscopic data.

In the IR spectra of 2-Phenyl-1*H*-indole-3-carbaldehyde derivatives (2a-e), the N-H stretching band is shifted towards lower wave number $3410\text{--}3350\text{ cm}^{-1}$ due to the presence of carbonyl group at position 3 of the indole ring, the carbonyl absorption band is observed downfield between $1620\text{--}1605\text{ cm}^{-1}$ due to conjugation of the carbonyl group with indole ring. In ^1H NMR spectra of 2-Phenyl-1*H*-indole-3-carbaldehyde derivatives, the N-H resonance signal is observed in the region of $\delta\ 10.1\text{--}11.2\text{ ppm}$ as a broad singlet. Aromatic protons are observed as multiplet from $\delta\ 7.1\text{--}7.9\text{ ppm}$. Singlet due to $-\text{CHO}$ proton appears in the region $\delta\ 9.0\text{--}10\text{ ppm}$.

In the IR spectra of (E)-1-phenyl-3-(2-phenyl-1*H*-indol-3-yl)prop-2-en-1-ones (5a-h), the N-H absorption appears as a broad band $3380\text{--}3200\text{ cm}^{-1}$. Characteristic absorption due to carbonyl group appears in the range of $1620\text{--}1605\text{ cm}^{-1}$. The downfield shift is due to conjugation of the carbonyl group with the olefinic double bond and aryl groups, which results in the delocalization of electrons of carbonyl group giving ionic resonance structures. The olefinic double bond ($\text{C}=\text{C}$) appears between the range of $1605\text{--}1595\text{ cm}^{-1}$. The ^1H NMR spectra of (E)-1-phenyl-3-(2-phenyl-1*H*-indol-3-yl)prop-2-en-1-ones (5a-h) exhibit a complex splitting pattern. The two olefinic protons constitute an AB system and appear as a pair of doublet, the downfield doublet in the region $\delta\ 7.30\text{--}7.43\text{ ppm}$ due to ($\text{CH}=\text{CH}$) proton and the doublet in the region $\delta\ 6.97\text{--}7.01\text{ ppm}$ due to ($\text{CO}-\text{CH}$) proton. Aromatic proton appears as a complex multiplet in the region $\delta\ 6.70\text{--}7.60\text{ ppm}$. N-H resonance signal appears as a broad singlet from $\delta\ 10.9\text{--}10.2\text{ ppm}$.

4. Spectral Data of Compounds

(E)-1-phenyl-3-(2-phenyl-1H-indol-3-yl)prop-2-en-1-one (5a): IR (KBr) $\nu_{\max}$ in cm^{-1} : 3408, 2920, 2850, 1685, 1280; ^1H NMR ($\text{DMSO-d}_6 + \text{CDCl}_3$) in δ (ppm): 10.04 (s, 1H, indole NH), 7.32 (d, 2H, $\text{CH}=\text{CH}-$), 6.9-8.0 (m, 14H, Ar-H); ^{13}C NMR ($\text{DMSO-d}_6 + \text{CDCl}_3$) in δ (ppm): 182.3 (C=O), 137.3, 136.9, 132.1, 131.3, 129.0, 122.2, 120.5, 119.9, and 111.3; ESI-MS 324.39[M + 1] $^+$.

(E)-3-(2-(4-fluorophenyl)-1H-indol-3-yl)-1-phenylprop-2-en-1-one (5b): IR (KBr) $\nu_{\max}$ in cm^{-1} : 3409, 2918, 2847, 1682, 1281; ^1H NMR ($\text{DMSO-d}_6 + \text{CDCl}_3$) in δ (ppm): 10.04 (s, 1H, indole NH), 7.22 (d, 2H, $\text{CH}=\text{CH}-$), 6.8-8.1 (m, 13H, Ar-H); ^{13}C NMR ($\text{DMSO-d}_6 + \text{CDCl}_3$) in δ (ppm): 184.3 (C=O), 137.5, 136.6, 132.4, 131.5, 129.2, 126.4, 122.7, 120.6, and 111.8; ESI-MS 342.32[M + 1] $^+$.

(E)-3-(2-(4-bromophenyl)-1H-indol-3-yl)-1-phenylprop-2-en-1-one (5c): IR (KBr) $\nu_{\max}$ in cm^{-1} : 3306, 2924, 2854, 1667, 1272; ^1H NMR ($\text{DMSO-d}_6 + \text{CDCl}_3$) in δ (ppm): 11.04 (s, 1H, indole NH), 7.82 (d, 2H, $\text{CH}=\text{CH}-$), 6.6-8.7 (m, 13H, Ar-H); ^{13}C NMR ($\text{DMSO-d}_6 + \text{CDCl}_3$) in δ (ppm): 184.8 (C=O), 147.5, 146.6, 142.4, 138.5, 132.2, 131.4, 130.7, 126.6, 112.4 and 104.8; ESI-MS 403.28[M + 1] $^+$.

(E)-3-(2-(4-chlorophenyl)-1H-indol-3-yl)-1-phenylprop-2-en-1-one (5d): IR (KBr) $\nu_{\max}$ in cm^{-1} : 3419, 2908, 2857, 1681, 1282; ^1H NMR ($\text{DMSO-d}_6 + \text{CDCl}_3$) in δ (ppm): 11.24 (s, 1H, indole NH), 6.82 (d, 2H, $\text{CH}=\text{CH}-$), 6.8-8.6 (m, 13H, Ar-H); ^{13}C NMR ($\text{DMSO-d}_6 + \text{CDCl}_3$) in δ (ppm): 183.1 (C=O), 145.5, 142.6, 141.4, 138.6, 132.6, 132.4, 130.2, 124.2, 113.2 and 111.8; ESI-MS 358.83[M + 1] $^+$.

(E)-1-phenyl-3-(2-(p-tolyl)-1H-indol-3-yl)prop-2-en-1-one (5e): IR (KBr) $\nu_{\max}$ in cm^{-1} : 3408, 2938, 2837, 1672, 1282; ^1H NMR ($\text{DMSO-d}_6 + \text{CDCl}_3$) in δ (ppm): 10.34 (s, 1H, indole NH), 7.23 (d, 2H, $\text{CH}=\text{CH}-$), 6.7-8.3 (m, 13H, Ar-H), 2.3 (s, 3H, CH_3); ^{13}C NMR ($\text{DMSO-d}_6 + \text{CDCl}_3$) in δ (ppm): 184.0 (C=O), 153.5, 136.6, 132.4, 130.5, 129.2, 126.2, 122.8, 120.3, 111.8 and 22.3; ESI-MS 338.83[M + 1] $^+$.

(E)-1-(4-chlorophenyl)-3-(2-(p-tolyl)-1H-indol-3-yl)prop-2-en-1-one (5f): IR (KBr) $\nu_{\max}$ in cm^{-1} : 3387, 2989, 2835, 1671, 1284; ^1H NMR ($\text{DMSO-d}_6 + \text{CDCl}_3$) in δ (ppm): 10.35 (s, 1H, indole NH), 7.06 (d, 2H, $\text{CH}=\text{CH}-$), 6.8-8.2 (m, 12H, Ar-H), 2.2 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6

+ CDCl_3) in (ppm) : 182.0 (C=O), 156.5, 146.6, 136.4, 133.5, 129.1, 126.6, 122.3, 119.7, 110.8 and 23.3; ESI-MS 372.86[M + 1]⁺.

(E)-3-(2-(4-chlorophenyl)-1H-indol-3-yl)-1-(4-fluorophenyl)prop-2-en-1-one (5g): IR (KBr) ν_{max} in cm^{-1} : 3418, 2907, 2847, 1682, 1287; ^1H NMR (DMSO-d_6 + CDCl_3) in δ (ppm) : 11.78 (s, 1H, indole NH), 6.81 (d, 2H, CH=CH-), 6.6-8.62 (m, 12H, Ar-H); ^{13}C NMR (DMSO-d_6 + CDCl_3) in δ (ppm) : 183.0 (C=O), 145.2, 141.6, 141.3, 137.6, 131.6, 131.0, 130.1, 123.2, 113.1 and 110.8; ESI-MS 376.82[M + 1]⁺.

(E)-3-(2-(4-bromophenyl)-1H-indol-3-yl)-1-(4-fluorophenyl)prop-2-en-1-one (5h): IR (KBr) ν_{max} in cm^{-1} : 3406, 2912, 2870, 1681, 1282; ^1H NMR (DMSO-d_6 + CDCl_3) in δ (ppm) : 10.78 (s, 1H, indole NH), 6.80 (d, 2H, CH=CH-), 6.8-8.9 (m, 12H, Ar-H); ^{13}C NMR (DMSO-d_6 + CDCl_3) in δ (ppm) : 185.2 (C=O), 155.6, 141.2, 140.1, 133.8, 132.6, 131.6, 130.2, 123.4, 111.1 and 109.7; ESI-MS 421.27[M + 1]⁺.

5. Antibacterial Studies

The newly synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus* (ATCC 29213) and *Escherichia coli* (ATCC 25922) by Kirby-Bauer well diffusion method with reference to Streptomycin. The investigation of antibacterial screening data revealed that all the tested compounds (5a-h) showed moderate to good bacteria activity. Compound 5e and 5f showed more potent antibacterial activity with zone of inhibition more than 22 mm, it may be due to the presence of methyl and methoxy groups in the indole moiety. The bacterial zones of inhibition values are summarized in (Table 3). The bar graph representation zone of inhibition (mm)^a of compounds (5a-h) against tested bacterial strains is shown in fig. 1.

Table 3. Zone of inhibition (mm)^a of compounds (5a-h) against tested bacterial strains

Entry	Compound	Bacterial strains	
		<i>S. aureus</i> (ATCC 29213)	<i>Escherichia coli</i> (ATCC 25922)
1	5a	17.2 ± 0.6	16.4 ± 0.3
2	5b	18.2 ± 0.4	16.8 ± 0.6
3	5c	19.4 ± 0.5	18.3 ± 0.2
4	5d	18.9 ± 0.3	17.7 ± 0.4
5	5e	21.3 ± 0.3	22.0 ± 0.2
6	5f	22.1 ± 0.4	22.1 ± 0.5

7	5g	20.0 ± 0.2	19.4 ± 0.8
8	5h	20.7 ± 0.4	20.4 ± 0.5
9	Standard	27.5 ± 0.6	24.4 ± 0.3
Streptomycin was used as a standard ^a 50 μ l/ml of the compound in each well			

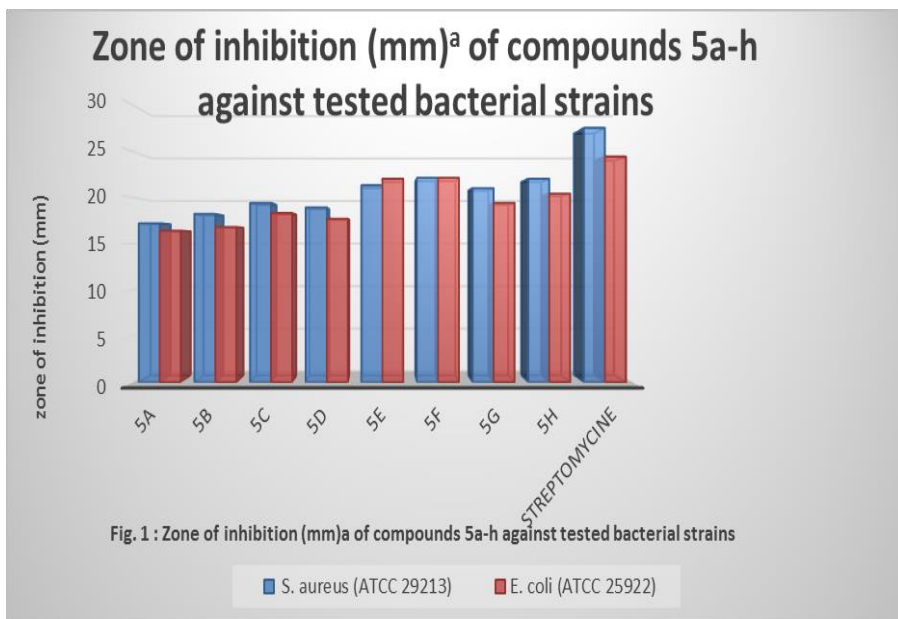


Figure 1. Zone of inhibition (mm) of compounds 5a-h against tested bacterial strains

6. Conclusion

In conclusion, we have designed, synthesized, and characterized a new series of (E)-1-phenyl-3-(2-phenyl-1*H*-indol-3-yl)prop-2-en-1-ones (5a-h) by various simple, efficient, solvent-free greener methods. The synthesized compounds screened antibacterial analysis. Some of the synthesized compounds viz., - (5e) and (5f) having -CH₃ substituted at indole moiety exhibits as more prominent for all screening analysis. Consequently, there is a good scope to develop a synthetic less harmful antibacterial drug.

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