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One pot synthesis of 3-substituted indole derivatives and their antimicrobial activity

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Abstract: In this study, we describe the creation of a straightforward and incredibly effective protocol for synthesizing new 3-Substituted indole derivatives. This multicomponent action involved Indole, Acetylacetone, and active aldehyde derivatives in ethanol as solvent followed by acetonitrile as a base. We want to go through current developments in organic synthesis methodology for multicomponent reactions that produce substituted indole derivatives with a more environmentally friendly base catalytic condition, as well as the applications that go along with them. The synthesized indole derivatives were tested for their ability to suppress the growth of microorganisms. In addition, proteins and nucleic acids have a great affinity for indoles, hindering DNA replication, preventing protein synthesis, and promoting cellular metabolism. FT-IR, ^{1}H-NMR, and MS characterize the synthesized indole derivatives.

Keywords: One-pot multicomponent reaction; Base catalyst; Indole derivatives; Biological activity; protocol.

1. Introduction

In recent years, many people have worked in heterocyclic chemistry because Heterocyclic compounds have a wide range of applications. They are used in agrochemical, pharmacological, and other biological activities [1]. N, O, and S-containing elements are classified under the heterocyclic compound. Some examples are pyrrole, indole, furan, thiophene, etc. [2]. These compounds show different types of reactivity in organic synthesis. Indole and its derivatives are a significant class of N-containing heterocyclic compounds because of the reactivity of nitrogen atom [3]. The indole molecule is flexible and reactive, showing nucleophilic and electrophilic reactions on the third position of the pyrrole ring [4]. Electrophilic addition at the 3-position is more stable as it has a three-resonating structure, and there is no positive charge on nitrogen atom [5]. Indole shows different reactions such as protonation, nitration, sulfonation, acylation and halogenations, and base (NaOH, CH_3CN, NEt_3, and $NH(CH_2)_5$) catalyzed reactions [6]. The base has two types: homogenous base [7] and heterogenous base [8]. Homogenous bases [9], such as KOH, NaOH, and sodium-potassium methoxide, serve as effective catalysts, and heterogeneous bases are alkaline earth metal oxides [10] such as MgO, CaO SrO, zeolites, and KNO_3 loaded on Al_2O_3.

The base is usually a suitable proton acceptor and plays a vital role in the organic synthesis reaction. Homogenous bases are readily soluble in methanol and ethanol for synthesis. Base catalyst processes are more advantageous than acid-catalyzed reactions [11] because base-catalyzed transformations are at a higher speed for transesterification, decrease reaction temperature and pressure with less base volume, and have high conversion efficiency [12]. In addition, they are readily available at low cost and increase the reactivity of reaction intermediate [13]. The reaction in which more than two components are mixed in one pot from the desired compound is called a one-pot multicomponent reaction [14]. These reactions are beneficial because of less solvent waste [15], less time, and less environmental impact compared to a step-by-step reaction [16]. A. Strecker reported the first MCR in 1850, using a multicomponent approach to synthesize α-amino acids [17]. After that, several reports evolved MCRs, including the total synthesis of biologically active natural products and drug molecules [18]. We have seen many one-pot multicomponent reactions of indole and its derivatives [19]. which show biological activities [20], namely antidiabetic [21,22], anticancer [23], antimicrobial [24], anti-HIV [25], antiviral [26], anti-inflammatory [27], antioxidant [28,29], anticholinesterase [30], antitubercular [31], and antimalarial [32] antifungal [33] activities, etc. We sought to create a new series of 3-substituted indole

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derivatives with side chains of various architectures in light of the crucial biological features of the indole ring, as these derivatives might have intriguing and practical antibacterial activity [34]. Most of the time, medicinal chemists use indole derivatives [35].

2. Material and methods

2.1. Chemical and reagents

Chemicals were bought from Himedia and Sigma-Aldrich. An open capillary tube melting point device was used to calculate each melting point. ^{1}HNMR was done by a Bruker 500 MHz instrument. Spectrometers employing tetramethylsilane (TMS) as an internal reference standard and deuterated dimethyl sulfoxide (DMSO-D_6) as the solvent On a Bruker 37 tensor, FTIR spectra of the synthesized chemicals were done. TLC plates were used for monitoring the reaction and were purchased from Merck.

2.2. Methodology

Scheme-1

Take 100 mL round bottom flask, add Aldehyde (2) (0.046g/mol), and Acetylacetone (3) (0.051g/mol) in ethanol solvent; after 15 minutes at 60°C temperature, indole (1) (0.058g/mol) was mixed in solution with continue heating, and condensation was done for 3 to 6 h. During the reaction, TLC was done in 15 minutes time intervals. After the reaction, separate the compound with ethyl acetate and water in a separating funnel. We get two layers: the organic layer containing desired product separate the organic layer from water, then filter the compound neutralized with acid and recrystallized from ethanol; after recrystallization, the compound produced is 3-((1H-indol-3-yl)(phenyl)methyl)pentane-2,4-dione(4) indole derivative.

Scheme-2

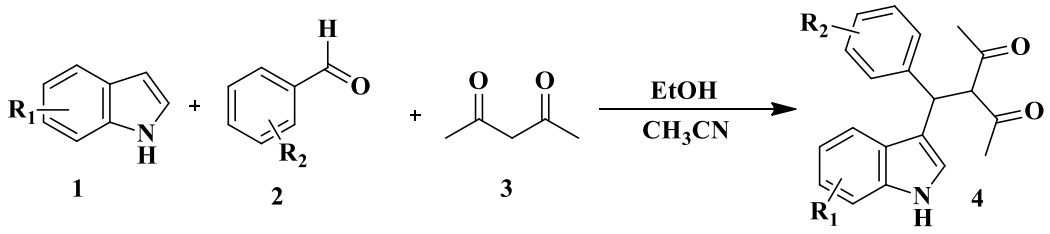
The solution of substituted Benzaldehyde (5) (0.275g/mol) and Acetone (6) (1mL) in ethanol (2.5mL) was added in 5% aqueous Sodium hydroxide (NaOH) (5mL). After being agitated for 1.5 hours at room temperature, the reaction mixture was diluted with water (20mL) and then chilled to 0°C. After the reaction, 2N hydrochloric acid was used to neutralize the diluted solution. Ethyl acetate was used to extract the products after the solvent was evaporated with a rotatory evaporator. A yellowish solid was produced when the substance underwent silica gel column chromatography purification. One-pot multi component reaction for the synthesis of indole derivatives has been done by (E)-4-(2-hydroxy phenyl)but-3-en-2-one(7) (synthesized in the first step) (0.05g/mol), Oxindole(8) (0.019g/mol), Sodium ethoxide (0.171g/mol) and DCM (10mL) as a solvent and stirred at room temperature for 1hr to produce 1-(6-methyl-6,11-dihydrochromeno[2,3-b]indol-11-yl) propane-2-one(9).

2.3. In vitro antimicrobial evaluation of Indole derivatives

The antimicrobial activities of the synthesized derivatives of indole (**1a, 1b, 1c, 1d, 1e, 2a, and 2b**) were measured by disc diffusion standard protocol as reported (Perez et al., 1990). The bacterial strains, Gram-negative, i.e., *Escherichia coli* (DH5α, Invitrogen) and Gram-positive *Micrococcus luteus* (Microbial Type Culture Centre (MTCC), Chandigarh), were used in the experiments in comparison to Rifampicin as a standard antibacterial agent. On Mueller-Hinton agar (MHA) plates, 100 µL of the bacteria's overnight cultures were spread out with an adjustment of 0.5 McFarland. DMSO was used as a solvent and as a control. At a concentration of 10 micrograms/mL, the Indole compounds were evaluated. The plate inhibition zones were measured by millimeters and compared to a reference standard after incubating at 37°C for 24 hours. In addition, the indoles minimal inhibitory concentration (MIC) was ascertained using the microdilution broth method. Graph 1 reports the findings of antimicrobial screening investigations.

3. Experimental section

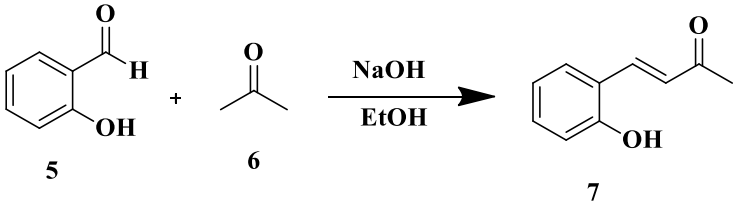
Indole (1) (0.058g/mol), aldehyde (2) (0.046g/mol), and Acetylacetone (3) (0.051g/mol) were taken in an equimolar amount in the presence of base methyl cyanide and mixed in a round bottom flask of ethanol as a solvent heated at 60^{0}C the temperature for 3 h in between, TLC was done to check the progress of the reaction. After the reaction, the compound was separated, and different indole derivatives were synthesized and characterized by NMR, Mass, and antimicrobial activity. Synthesized derivatives as shown in Table 1.



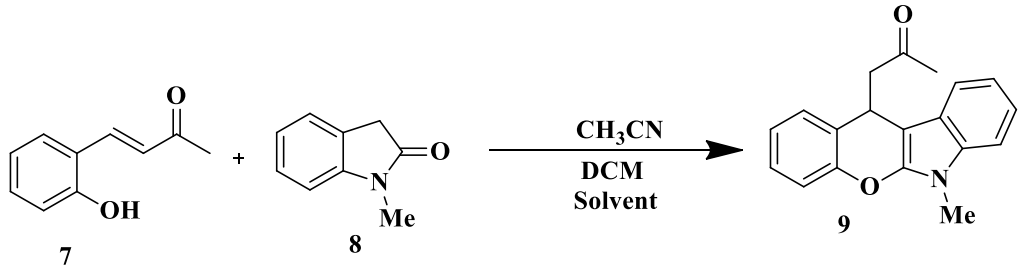
3-((1*H*-indol-3-yl)(phenyl)methyl)pentane-2,4-dione

Scheme 1. Schematic route for the synthesis of indole derivative

I Step



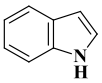
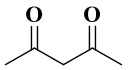
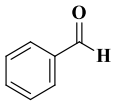
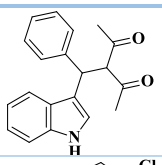
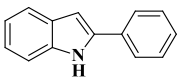
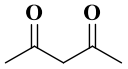
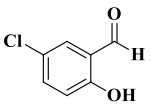
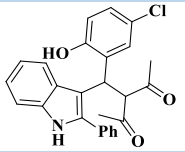
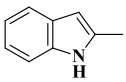
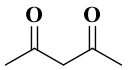
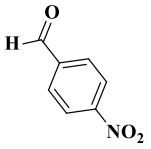
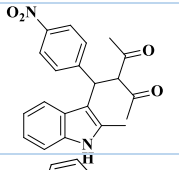
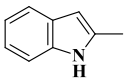
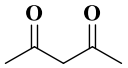
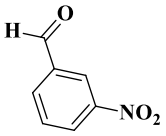
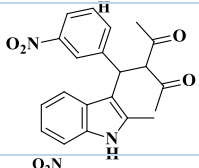
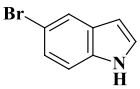
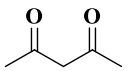
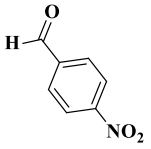
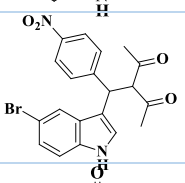
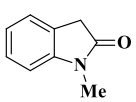
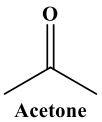
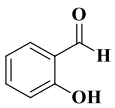
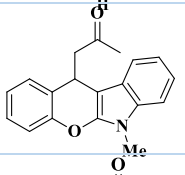
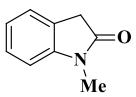
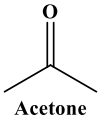
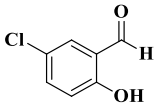
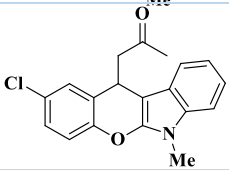
II Step



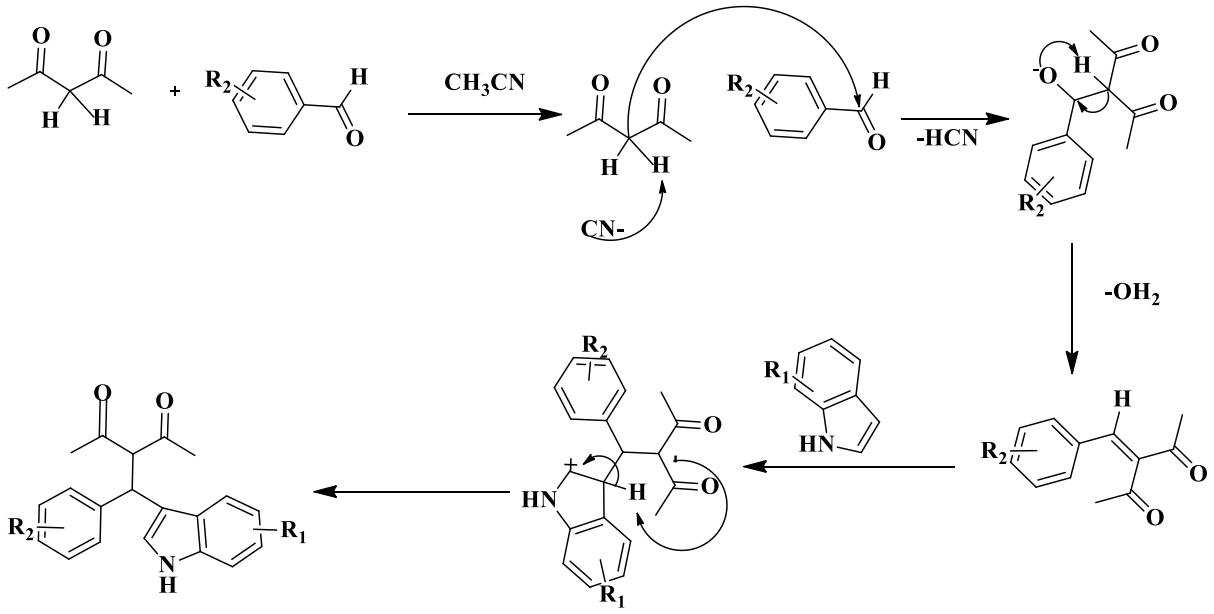
1-(6-methyl-6,11-dihydrochromeno[2,3-*b*]indol-11-yl)propan-2-one

Scheme-2. Schematic route for the synthesis of Oxindole derivative

Table 1. Different derivatives of indole.

Entry	Indole	Acetylacetone	Substituted-aldehyde	Products
1a				
1b				
1c				
1d				
1e				
2a				
2b				

3.1. Proposed mechanism for Synthesis of 3-((1H-indol-3-yl)(phenyl)methyl)pentane-2,4-dione using Base as a catalyst



3.2. Spectral data of compounds

3-((1H-indol-3-yl)(phenyl)methyl)pentane-2,4-dione (1a)

Dark brown color solid.

m.p. 268-272 °C;

IR (KBr) ($v_{max,}$ cm^{-1}): 3404.58, 1442.12, 1326.92, 1089.93, 737.48, 587.12.

^{1}H NMR (500 MHz, DMSO d_6) δH (ppm): 1.8-2.4 (s, 6H, Me), 3.3-4.9 (d, 2H, CH), 7.2-7.3 (m, 5H, Ar-H), 6.7(m, 2H, ArH) 7.8-7.9(m, 2H, ArH), 7.2 (s, 1H), 10.60 (s, 1H, NH).

MS: (m/z) (%) 304.10(100%).
Exact Mass: 305.14 Elemental Analysis: C, 78.66; H, 6.27; N, 4.59; O, 10.48 Found to be C, 78.60; H, 6.35; N, 4.63; O, 10.40.

3-((5-chloro-2hyroxyphenyl) (2-phenyl-1H-indol-3-yl) methyl) pentane-2,4-dione (1b)

Light brown color solid.

m.p. 272-276 °C;

IR (KBr) ($v_{max,}$ cm^{-1}): 3737.88, 1696.78, 1543.74, 1439.94, 1065.85, 906.70, 737.20, 681.33.

^{1}H NMR (500 MHz, DMSO d_6) δH (ppm):1.7-2.4 (s, 6H, Me), 3.3-4.9 (d, 2H, CH), 7.4 (m, 5H, ArH), 6.8-7.4 (m, 5H, ArH), 7.8 (s, 1H, ArH), 9.8 (s, 1H, OH), 11.49 (s, 1H, NH).

MS: (m/z) (%) 429.31(100%).
Exact Mass: 431.13 Elemental Analysis: C, 72.30; H, 5.13; Cl, 8.21; N, 3.24; O, 11.11 Found to be C, 72.10; H, 5.33; Cl, 8.17; N, 3.24; O, 11.15.

3-((2-methyl-1H-indol-3-yl)(4-nitrophenyl) methyl) pentane-2,4-dione (1c)

Brown color solid.

m.p. 266-270 °C;

IR (KBr) ($v_{max,}$ cm^{-1}): 3380.49, 2921.30, 1592.60, 1514.78, 1459.58, 1330.98, 1003.09, 842.58, 739.89, 587.28, 543.82.

1H NMR (500 MHz, DMSO d_6) δH (ppm): 1.6-2.4 (s, 9H, Me), 3.2-4.9 (d, 2H, CH), 7.2-8.3 (m, 4H, ArH), 6.3-7.6 (m, 4H, ArH), 11.22 (s, 1H, NH).
MS: (m/z) (%) 358.34(100%).
Exact Mass: 364.14 Elemental Analysis: C, 69.38; H, 5.53; N, 7.53; O, 17.56 Found to be C, 69.31; H, 5.53; N, 7.60; O, 17.56

3-((2-methyl-1H-indol-3-yl)(3-nitrophenyl) methyl) pentane-2,4-dione (1d)

Light brown color solid.

m.p. 275-278 °C;

IR (KBr) ($v_{max,}$ cm^{-1}): 2306.59, 1523.75, 1343.62, 1177.72, 735.82**.**

^{1}H NMR (500 MHz, DMSO d_6) δH (ppm): 2.0-2.4 (s, 9H, Me), 3.4-4.6 (d, 2H, CH), 7.5-8.6 (m, 4H, ArH), 6.7-7.9 (m, 4H, ArH), 11.12 (s, 1H, NH).

MS: (m/z) (%) 377.23(100%).
Exact Mass: 364.14 Elemental Analysis: C, 69.38; H, 5.53; N, 7.69; O, 17.56 found to be C, 69.31; H, 5.53; N, 7.60; O, 17.56.

3-((5-bromo-1H-indol-3-yl)(4-nitrophenyl)methyl)pentane-2,4-dione (1e)

Red-brown color, solid.

m.p. 280-283 °C;

IR (KBr) ($v_{max,}$ cm^{-1}): 3644.73, 3179.01, 1844.67, 1692.96, 1510.71, 1434.70, 1203.09, 793.25, 589.04.

^{1}H NMR (500 MHz, DMSO d_6) δH (ppm): 2.0-2.4 (s, 6H, Me), 3.5-4.9 (d, 2H, CH), 7.1 (s, 1H, ArH),

7.3-7.5 (m, 3H, ArH), 7.4-8.1 (m, 4H, ArH), 10.12 (s, 1H, NH).

MS: (m/z) (%) 429.19(100%).
Exact Mass: 428.04 Elemental Analysis: C, 55.96; H, 3.99; Br, 18.61; N, 6.53; O, 14.91 Found to be C, 55.86; H, 3.90; Br, 18.70; N, 6.63; O, 14.91.

1-(6-methyl-6,11-dihydrochromeno[2,3-b]indol-11-yl)propan-2-one (2a)

Light green color, solid

m.p. 278-280 °C;

IR (KBr) ($\nu_{max,}$ cm^{-1}): 3730.38, 3617.22, 1550.47, 1247.31, 968.58, 746.26, 547.88.

^{1}H NMR (500 MHz, DMSO d_6) δH (ppm): 2.0-2.4 (s, 3H Me), 2.4-3.3 (d, 2H, CH_2), 5.0 (s, 3H, N-Me), 6.6-8.0 (m, 8H, Ar-H).

MS: (m/z) (%) 291.13(100%).
Exact Mass: 291.13 Elemental Analysis: C, 78.33; H, 5.88; N, 4.81; O, 10.98 Found to be C, 78.30; H, 5.91; N, 4.90; O, 10.90.

1-(2-chloro-6-methyl-6, 11-dihydrochromeno[2,3-b] indol-11-yl) propan-2-one (2b)

Green color, solid.

m.p. 280-282 °C;

IR (KBr) ($\nu_{max,}$ cm^{-1}): 3349.91, 1552.60, 1403.18, 743.25, 542.01.

^{1}H NMR (500 MHz, DMSO d_6) δH (ppm): 1.6-2.3 (s, 3H Me), 2.4-3.3 (d, 2H, CH_2), 4.9 (s, 3H, N-Me), 6.6-8.0 (m, 7H, Ar-H).

MS: (m/z) (%) 325.09(100%).
Exact Mass: 325.09 Elemental Analysis: C, 70.05; H, 4.95; Cl, 10.88; N, 4.30; O, 9.82 Found to be C, 70.15; H, 4.85; Cl, 10.88; N, 4.38; O, 9.90.

4. Results and Discussion

In this research, a base catalyst-based one-pot multicomponent condensation approach for synthesizing indole derivatives (**1a–2b**) was designed. Both (Scheme 1) and (Scheme 2) were used. The indole derivatives (**1a–1e**) were created using the Base catalyst to condense 1H-indole-3-carbaldehyde, aldehyde, CH_3CN, and substituted aldehyde in a single pot. After looking into other organic bases, such as piperidine, DBU, and Et_3N, we produced the matching indole derivatives with yields of 90, 70, and 80%, respectively. Finally, we utilized a variety of solvents in our studies (CH_3OH, dioxane, MeOH, and acetone), and the yields did not indicate any preference. These findings suggested that employing CH_3CN as a base at reflux would be the ideal synthesis condition. A good base is needed for the intermediate's subsequent reaction to neutralize the proton and produce carbanion. As a result, we chose to screen various base catalysts and solvents (Table 2). FTIR, 1HNMR, and mass spectrometric analyses were used to identify the produced compounds (**1a-2b**). These indole compounds were produced with fast reaction times with excellent yields. The structures of novel compounds were displayed in Tables 1 and 2, together with yield percentage and reaction duration. Due to indole N-H stretching, all molecules absorb 3450–3386 cm^{-1} in FT–IR spectra. The 1673–1611 cm^{-1} absorption is caused by the aromatic C–N function.

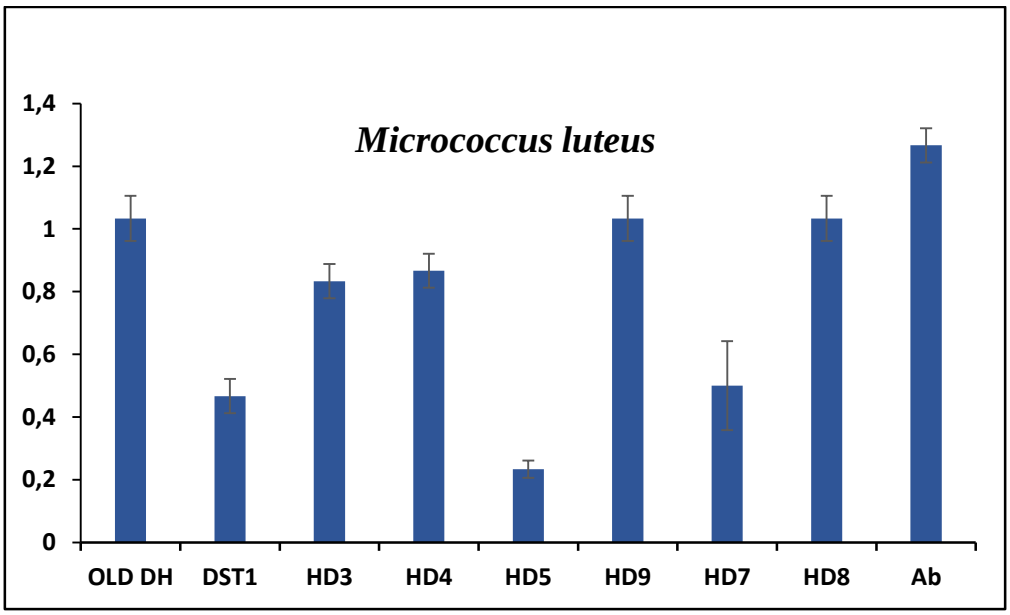
The O-H group is responsible for the absorption of 3688–3644 cm^{-1} (str.) (**1a-2b**). Due to the N-H proton of indole, all the compounds showed a singlet between δ = 12.463 and 10.135 ppm in the ^{1}H NMR spectra. Due to all compounds aromatic benzene ring protons, the multiple was seen δ = 7.627 to 7.159 ppm. Due to the hydroxy protons in (**1a-2b)**, a singlet was seen δ = 14.956 to 8.840 ppm. Molecular ion peaks that matched the molecular formula could be seen in the mass spectra.

Table 2. Optimization of reaction conditions for scheme-1 and scheme-2.

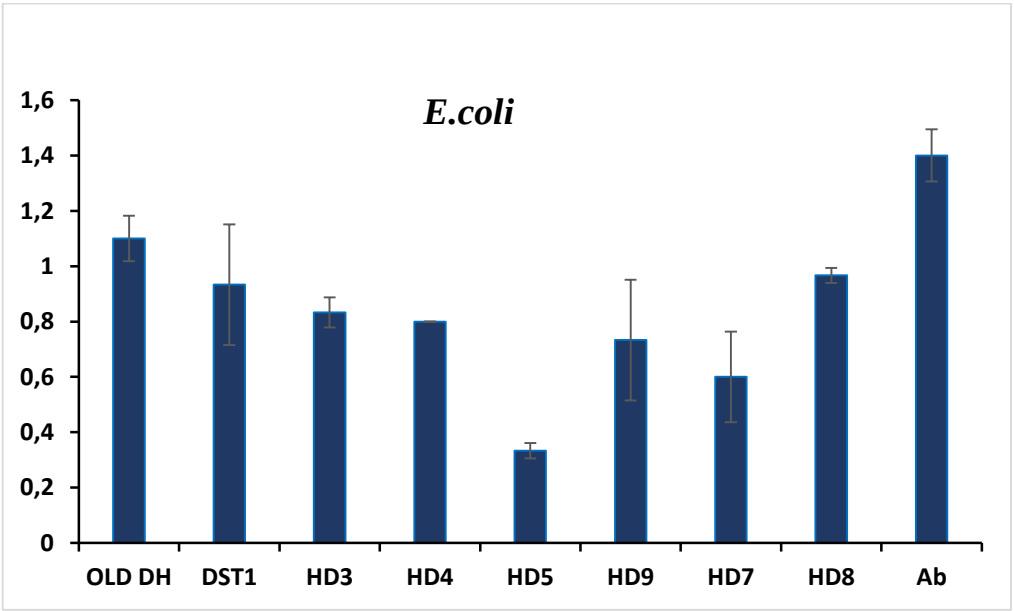
Sr. No.	Solvent	Base	Time(h)	Yield (%)
1.	EtOH	CH_3CN	3	90
2.	1,4 Dioxane	CH_3CN	3	70
3.	MeOH	CH_3CN	6	60
4.	1,4 Dioxane	NEt_3	6	72
5.	EtOH	NEt_3	3	60
6.	MeOH	NEt_3	3	80
7.	EtOH	$NH(CH_2)_5$	3	60
8.	1,4 Dioxane	$NH(CH_2)_5$	5	75
9.	MeOH	$NH(CH_2)_5$	3	60
10.	Acetone	CH_3CN	6	80

4.1. Antimicrobial study of synthesized derivatives
Following the measurement in the zone of inhibition for the two bacterial strains, a disc diffusion assay on MH Agar was used to assess the antibacterial activity of the indole derivatives. The synthetic indole compounds' antibacterial activity against the chosen microorganism at a concentration of 10 micrograms/mL is depicted in graphs 1 and 2. As a control substance, DMSO has no zone of inhibition. The Indole derivatives exhibited antibacterial activity even at a lesser concentration (10 µg). Escherichia coli (Gram-negative) and Micrococcus luteus (Gram-positive) were used to test the antibacterial activity of all eight produced compounds. According to the data shown in graphs (1 and 2), the derivatives **2a, 1e, 1d**, and **1a** were more active against Gram-positive and Gram-negative bacteria than Rifampicin. Compared to Rifampicin, 1a, 2b, and 1b showed moderate effectiveness against E. coli and Micrococcus luteus. Compared to an antibiotic agent, all the remaining evaluated compounds had poor action (**1b** and **1c**) against Micrococcus luteus and **1e** and **1c** against E. coli (Rifampicin). Because proteins and nucleic acids have a strong affinity for indoles, DNA replication is inhibited, which stalls protein synthesis and furthers cellular metabolism.

Some coding; (**2a- OLD DH, 2b- DST-1, 1a-HD3, 1a*-HD4 1b-HD5, 1c-HD7, 1d-HD8, 1e-HD9**).



Graph -1. Antimicrobial activity of 3-substituted Indole on Micrococcus luteus bacteria



Graph-2. Antimicrobial activity of 3-substituted Indole on E. coli bacteria

5. Conclusion

In conclusion, our research has revealed a base-catalyzed synthesis of highly functionalized Indole

derivatives that is automatically efficient and requires less time and effort. The yield was good, and the reaction conditions were benign. The one pot, as mentioned earlier, multicomponent reactions point to a great potential for the synthesis of compounds that are advantageous to biological. They are both environmentally beneficial and are not harmful to human health. Base-catalyzed indole derivatives may be used to guide future efforts to build a library of indole derivatives with potential medical applications.

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