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Design, Synthesis and Anti-Bacterial Activity Evaluation of Indole-Based Benzophenone and Their Derivatives

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Abstract: Indole and benzophenone moiety are of significant interest to investigators because they are found in many natural products and pharmacologically active compounds. They represent versatile synthetic building blocks. The benzophenone and indole scaffolds are special structures in medicinal chemistry because these compounds are found in several biologically active natural products, compounds containing indole and benzophenone exhibit anticancer, antiinflammatory, antimicrobial, and antiviral activities. In this study, derivatives of 2-(diphenyl methylene) hydrazine, containing both indole and benzophenone moieties were successfully synthesized. The structural elucidation of the synthesized compounds were done using spectroscopic techniques like IR, ^{1}HNMR, and ^{13}CNMR. The synthesized target compounds were investigated for their in vitro antibacterial activity against two bacterial strains; *staphylococcus aureus (S. auras)*, and *Escherichia coli (E. coli)* using the disc diffusion method. All synthesized target compounds showed no significant activity against S*taphylococcus aureus (S. aureus)* but exhibited moderate activity against *Escherichia coli (E. coli).* Among all the synthesized compounds, 2-*(diphenyl methylene)-1-((1-tosyl-1H-indol-3-yl) methylene) hydrazine* (BHT) (**7b**) showed a good inhibition at a concentration of 50 µg/mL with a zone of inhibition of 21.7 mm against *Escherichia coli (E.coli)* which was comparable with standard drug Ceftriaxone with the zone of inhibition of 26 mm. Thus, this compound could be considered as a lead molecule to design and develop novel antibacterial drugs.

Keywords: Anti-bacterial, Benzophenone, indole, synthesis.

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1. INTRODUCTION

The steady increase in bacterial infections is becoming the major cause of high morbidity and mortality globally, especially in developing countries; this is due to the development of antibacterial and antifungal drug resistance (1). Because of the development of antibiotic resistance and the emergence of new microbial diseases, there is an urgent requirement to develop new antimicrobial agents for the treatment of microbial infections (2).

Heterocyclic compounds represent an important class of biological molecules (3). They are considered as a class of compounds having a great effect in the treatments of various diseases; compounds containing N and O are very active and important compounds in the preparation of drugs. Heterocyclic compounds containing nitrogen have been known to possess a very important role in the field of medicinal chemistry (4). The indole ring system represents one of the most abundant and important heterocycle in the nature (5). Indole and other heterocyclic compounds containing indole moiety have proven to be versatile intermediates for the synthesis of a wide range of bioactive drugs. Amongst the various N-heterocycles, indole motifs have received significant attention due to their presence in proteins, amino acids, bioactive alkaloids, and drugs (6). Indole ring exists in several naturally occurring alkaloids (7). Its derivatives have exhibited a wide range of biological activities (8). In addition, it was reported that various 3-substituted indoles were used as starting materials for the synthesis of several alkaloids, pharmaceuticals, and perfumes (9,10). Compounds bearing an indole nucleus have considerable importance in the development of diverse bioactive compounds; such compounds have been reported to have various biological activities including antimicrobial (11-13),

anticancer (14,15), antiviral (16,17), anti-inflammatory (16-19), etc.

Natural and synthetic benzophenone derivatives have also known for their diverse biological activities. Several compounds belonging to this class of compounds have shown a wide range of biological activity, such as antimicrobial (20, 21), anticancer (22, 23), and anti-inflammatory (24, 25).

A combination of two or more different pharmacophores in a single molecular entity is a new strategy to develop new compounds having higher biological activity, therefore, the combination of indole and benzophenone moieties might provide new effective drugs against multidrug-resistant microbial infections (26).

Inspired by the above facts, we report herein the synthesis of new hybrid compounds combining indole and benzophenone; we hereby successfully report the synthesis and in vitro evaluation of their antibacterial activities against two bacterial strains, namely *Staphylococcus aureus* and *Escherichia coli.*

2. EXPERIMENTAL SECTION

2.1. Materials and Methods

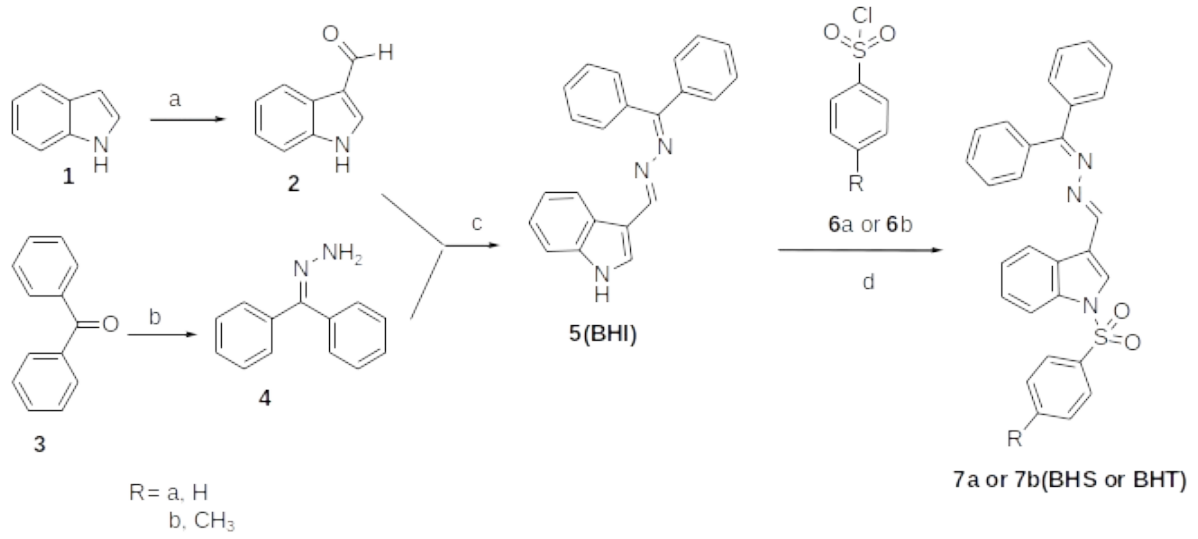
Nuclear Magnetic Resonance (NMR) analysis was recorded on a Bruker Avance 400 MHz spectrometer with tetramethylsilane as internal standard, $CDCl_3$ and DMSO-d_6 as solvent. Infrared (KBr pellet) spectrum was recorded on a Perkin-Elmer BX infrared spectrometer in the range 400-4000 cm^{-1}, Thin Layer Chromatography (TLC) was done using silica gel 60 F254 (type 60) pre-coated aluminum sheets, Electronic Melting Point apparatus were used (for determination of melting points of the synthesized compounds), the spots of the final compounds were visualized by irradiation with UV light at (254 nm and 365 nm) using an HP-UV/Visible lamp. Column chromatography was performed on silica gel (230-240 mesh). All the spectral analyses were carried out at the Department of Chemistry, Addis Ababa University, Ethiopia.

The chemicals used during the experiment were Benzophenone, indole, $POCl_3$, DMF, potassium carbonate (K_2CO_3), Acetone, Sodium hydroxide (NaOH), dichloromethane, glacial acetic acid, ethanol, ethyl acetate, n-hexane, and chloroform. All of them were analytical grade reagent and were used without further purification.

2.2. Chemistry

2.2.1. General procedures for the synthesis of target compounds

Indole (**1**) was used as starting material to synthesize the target compounds, which was reacted with phosphorus oxychloride ($POCl_3$) in the presence of DMF to form compound **2** by using a modified version of Vilsmeier Haack formylation reaction; on another root of reaction, benzophenone (**3**) reacted with hydrazine hydrate to form compound **4**. Then compound **2** and compound **4** were reacted together in ethanol using glacial acetic acid as a catalyst to form compound **5** as an intermediate compound, Finally, the target compounds (**7a** and **7b**) were obtained through substitution of the intermediate (**5**) with sulfonyl derivatives (**6a**) and (**6b**) using potassium carbonate as a mild base catalyst as shown in Scheme 1.



Scheme 1: Reagents and Conditions: a) $POCl_3$, NaOH (aq), DMF, reflux at 60 °C, (b) ethanol, glacial acetic acid, reflux at 90 °C for 6 h. (c) Ethanol, glacial acetic acid, reflux at 90°C for 12 h (d), acetone, K_2CO_3, RT for 24 h.

2.3. Syntheses of the Intermediates and the Target Compounds

2.3.1. Synthesis of 1H-indole-3-carbaldehyde (2)

To dimethyl formamide (DMF) (5 mL, 4.45 mmol) cooled at 0 °C, phosphorous oxychloride (1.75 mL; 10.3 mmol) was added dropwise and the mixture was stirred for 35 minutes then a solution of indole (1) (1 g, 8.5 mmol) in 5 mL of DMF was added dropwise to the reaction mixture and stirred for 2 h at room temperature, followed by the addition of

an aqueous solution of NaOH (15 mL); then the mixture was refluxed at 60 ºC. For 2 h. The progress of the reaction was monitored by using TLC in the appropriate solvent 70:30 (n-hexane and ethyl acetate, v:v). When the reaction was completed, the reaction mixture was placed on an ice bath and the precipitate was extracted with ethyl acetate and washed with 30 mL of water. Then the collected organic layer was dried by using anhydrous sodium sulfate and concentrated under reduced pressure using a rotary evaporator. The crude product was further purified by column chromatography using a mixture of hexane ethyl acetate as eluent and concentrated using a rotary evaporator to give *1H*-indole -3-carboxaldehyde (**2**), yielding 90.49%.

2.3.2. Synthesis of 1-(diphenyl methylene) hydrazine (**4**)
To the solution of benzophenone (1 gram, 5.49 mmol) in 15 mL of ethanol, (3-5 drops) of glacial acetic acid was added and stirred at room temperature for 2-5 minutes. Then hydrazine hydrate (10 mL, 6.59 mmol) was added to the reaction mixture and refluxed at 90 ºC. The progress of the reaction was monitored by using TLC in the appropriate solvent, 90:10 (n-hexane and ethyl acetate, v:v). When the reaction was complete, it was cooled to room temperature and extracted with ethyl acetate, and the extract was washed with 30 mL of water. Then the organic layer was collected and dried by anhydrous sodium sulfate and concentrated under reduced pressure using a rotary evaporator. The crude product was further purified by column chromatography using a mixture of hexane:ethyl acetate as eluent to give 1-(diphenyl methylene) hydrazine (**4**).

2.3.3 Synthesis of 1-((1H-indole-3-yl)-methylene)-2-(diphenyl methylene) hydrazine (BHI) (**5**)
1H-indole -3-carboxaldehyde (0.45 gram; 3.103 mmol) was dissolved in 15 mL of ethanol, and (3-5 drops) of glacial acetic acid was added and stirred at room temperature for 5-10 minutes, then 1-(diphenyl methylene) hydrazine (0.85 gram; 4.35 mmol) was added to the reaction mixture and refluxed at 90 ºC. For 24 h; the completion of the reaction was checked using TLC in the appropriate solvent, 80:20 v:v ratios (n-hexane and ethyl acetate), when the reaction was completed, cooled to room temperature and extracted with ethyl acetate and washed with 30 mL of water. Then the organic layer was collected and dried with anhydrous sodium sulfate and concentrated under reduced pressure using a rotary evaporator. The obtained crude product was further purified by column chromatography using a mixture of hexane:ethyl acetate mixture as eluent and concentrated using a rotary evaporator to give 1-((1H-indole-3-yl)-methylene)-2-(diphenyl methylene) hydrazine (BHI) (**5**).

*2.3.4 Synthesis of 2-(diphenyl methylene)-1-((1-tosyl-1H-indol-3-yl) methylene) hydrazine (BHT) (**7b**)*
1-Tosyl-1H-indole-3-carbaldehyde (0.604 gram, 2.02 mmol) was dissolved in 15 mL of ethanol, and (3-5 drops) of glacial acetic acid was added and stirred at room temperature for 5-10 minutes. Then 1-(diphenyl methylene) hydrazine (0.33 gram; 1.68 mmol) was added to the reaction mixture and refluxed at 90 ºC. The progress of the reaction was monitored by using TLC in the appropriate solvent, 90:10 ratios (n-hexane, and ethyl acetate, v:v). After completion of the reaction, the mixture was extracted with ethyl acetate and washed with 30 mL of water. Then the organic layer was collected and dried using anhydrous sodium sulfate and concentrated using a rotary evaporator. The crude product was further purified by column chromatography using a mixture of hexane ethyl acetate as eluent to give 2-(diphenyl methylene)-1-((1-tosyl-1H-indol-3-yl) methylene) hydrazine compound (**7b**)(BHT).

2.3.5 *Synthesis of 2-(diphenyl methylene)-1-((benzenesulfonyl-1H-indol-3yl-) methylene) hydrazine* (BHS)(**7a**)
1-Benzene sulfonyl-1H-indole-3-carbaldehyde (0.69 gram, 2.44 mmol) was dissolved in 15 mL of ethanol, and (3-5 drops) of glacial acetic acid was added and stirred at room temperature for 5-10 minutes. Then 1-(diphenyl methylene) hydrazine (0.4 gram, 2.04 mmol) was added to the reaction mixture and refluxed at 90 ºC. For 24 h, the progress of the reaction was checked using TLC in the appropriate solvent 90:10 v:v ratio (n-hexane and ethyl acetate) of the solvent mixture. When the reaction was completed, cooled and extracted with ethyl acetate and washed with 30 mL of water. Then the organic layer was collected and dried by anhydrous sodium sulfate and concentrated under reduced pressure using a rotary evaporator. The crude product was further purified by column chromatography using a mixture of hexane and ethyl acetate as eluent to give the target compound (**7a**).

3. RESULTS AND DISCUSSION

3.1 Anti-Bacterial Activity Studies
The anti-bacterial activities of the synthesized target compounds were evaluated against two bacterial strains such as *Escherichia coli* (*E.coli*) and *Staphylococcus aureus* (*S. Aureus)*, and sensitivity testing was conducted by means of disc diffusion method using Ceftriaxone (30 µg/disc) as a standard drug.

3.1.1 Culture media and disk preparation
For quality control of the antibacterial activities, control strains of Escherichia coli (*E. coli*) and Staphylococcus aureus (*S. aureus*) from the American Type Culture Collection (ATCCs) were used. Antibiotic discs were punched out of Whatman filter paper and prepared at a diameter of 6 mm.

3.1.2 Preparation of chemical solution and media for the anti-bacterial activity
Solution for antibacterial activities was prepared as stated by Hoda et al. with minor modification to concentration. Briefly, 50 µg/mL and 25 µg/mL of each chemical was dissolved in 30 µg/mL dimethyl sulfoxide (DMSO) and mixed to form a homogenous solution. A fixed volume of 50 µg/L

and 25 µg/mL of solution were added to previously sterilized Whatman filter paper disks using a sterile micropipette.

For quality control purpose, strains were aseptically inoculated on a sterile nutrient agar plate and then incubated for 48 hours at 37 °C. 5 mL nutrient broth bacterial cultures were prepared by picking 3-5 colonies to form 0.5 McFarland standard. The culture suspension was then inoculated on sterile Muller Hinton agar plate using sterile cotton swab in three directions to get a uniform inoculum. Then a disk with a control Ceftriaxone and solution impregnated disks were placed on the culture plate and incubated for 48 hours at 37 °C. Each disk was labeled with its unique ID number on the back of the Petri dish. The anti-bacterial activity was evaluated for the zone of inhibition around the disk.

3.1.3. Anti-bacterial activity

Antibacterial activity of all the synthesized compounds were evaluated against one gram-negative bacterial strain i.e. *Escherichia coli* and gram-positive *Staphylococcus aureus*. DMSO was used as a solvent control and Ceftriaxone as a positive control. Sensitivity testing was done by disc diffusion method and the diameter of zones of inhibition was measured in millimeters, documented (Table 1) and compared with the control.

Table 1: Zones of inhibition of synthesized compounds and the reference.

Compounds	Concentration (µg /mL)	Zone of inhibition (mm)	
		Gram +ve *S. aureus*	Gram –ve *E. Coli*
BHS (**7a**)	50	6.1	20.3
	25	6.1	14.5
BHT (**7b**)	50	13	21.7
	25	7.1	6.2
BHI (**5**)	25	6.1	12.1
	50	6.2	6.2
Ceftriaxone (+ve control)	30	30	26

Ceftriaxone is positive control prepared from 30 µg /mL in DMSO as solvent. The impregnated disc in samples, as well as positive control, is containing 6 mm in size. In this study, those with a zone of diameter greater than 6 mm (>6 mm) have anti-bacterial activity since the diameter of the disc is 6 mm.

3.2. Characterization

3.2.1. 1-((1H-indole-3-yl)-methylene)-2-(diphenyl methylene) hydrazine (BHI) (**5**)

White solid, yield 72.5%, melting point: 280-282 ^{o}C; IR (KBr, cm^{-1}): 3179.78 (N-H secondary amine) 3055.11 (aromatic C-H), 2921.26, 2853.19 (aliphatic C-H), 1600.04(C=N); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 11.74(1H,s N-H), 8.85(1H,s, H-8), 7.93(2H, d, J=2.9Hz, Ar-H), 7.69(1H,s, H-2), 7.59(2H,d, J =8.0Hz,Ar-H), 7.40 (2H, m, Ar-H), 7.13 (2H, m, Ar-H), 6.90(2H,t, J=7.5Hz, Ar-H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.4, 138.3, 137.5, 121.8, 112.2, 156.9, 133.3, 133.4, 129.7, 128.8, 128.7, 128.6, 128.3, 123.1, 122.6, 121.0, 112.4

3.2.2. 2-(diphenyl methylene)-1-((1-tosyl-1H-indol-3-yl) methylene) hydrazine (BHT) (**7b**)

Blue solid, yield 82.3%, melting point: 262-264 ^{o}C; IR (KBr, cm^{-1}): 3100 to 3000 (Aromatic C-H), 1561.16 (C=N- imine), 1656.38, 1561.16 (C=C stretch), 1313.57 (asymmetric stretch S (=O)), 1174.38 (symmetric stretch S(=O)), 684.92 (S-C stretch); ^{1}H-NMR (DMSO-d_6, 400MHz): δ 10.10 (2H, d, J=3.1Hz, Ar-H), 8.92 (2H,d, J=3.3 Hz, Ar-H), 8.15 (1H, s, N=CH), 8.13 (2H, d, *J*=3.7 Hz, Ar-H), 7.75 (2H, t, *J*=7.7Hz, Ar-H), 7.66 (2H, d, J=8.3 Hz, Ar-H), 7.98 (3H, m, Ar-H), 7.43 (4H, t, J=7.1Hz, Ar-H), 7.69 (1H, s, H-2), 2.50 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.5, 133.4, 135.5, 130.4, 126.6 133.1, 130.4, 130.0, 129.4,129.3, 129,0, 128.8, 128.5, 128.5, 40.6.

3.2.3. 2-(Diphenyl methylene)-1-((benzenesulfonyl-1H-indol-3yl-)methylene) hydrazine (BHS)(**7a**)

Blue solid, yield 79.9%, melting point: 244-246 ^{o}C; IR (KBr, cm^{-1}): 3024.46 (aromatic C-H stretch), 1659.85 (-C=N stretch), 1561.27 (aromatic C=C stretch), 1313.67 (Asymmetric S (=O) 2 stretch), 1174.03 (symmetric S (=O) 2 stretch), 684.89 (-S-C stretch); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.76(2H,d, J=8.0Hz, Ar-H), 7.72 (4H, m, Ar-H), 7.68 (2H, m, Ar-H), 7.50 (2H,d, J=2.8Hz,Ar-H), 7.47(4H, dt, J=8.6Hz,Ar-H), 7.37(2H,d, J=7.2Hz, Ar-H), 7.29(1H,s, -N=CH), 7.41(1H,s, indole, H-2); ^{13}CNMR (DMSO-d_6, 100 MHz): δ 159.5, 135.5, 133.1, 130.4,129.4, 128.5, 133.2, 130.4, 130.1, 129.4, 129.3, 129.0, 128.8, 128.

4. CONCLUSION

In the present study, derivatives of 2-(diphenylmethylene) hydrazine, containing both indole and benzophenone moieties were successfully synthesized. The indole-based benzophenone and its derivatives were biologically active molecules with various activities. The chemical structures of all the synthesized compounds were elucidated by spectroscopic techniques such as IR, ^{1}HNMR and ^{13}CNMR. All the newly synthesized compounds were evaluated for in vitro antibacterial activity by the disc diffusion method and its zone of inhibition was determined

against two different bacterial strains. All the synthesized compounds were mostly active against E.coli and least active against *S. aureus* bacterial strains. Among the synthesized compounds; *2-(diphenyl methylene)-1-((1-tosyl-1H-indol-3-yl) methylene) hydrazine* (**7b**) (BHT) shows better activities with 21.7mm zone of inhibition at concentration of 50 µg/mL against *E.coli* which is comparable to the standard drug ceftriaxone with a zone of inhibition of 26 mm and BHI shows the least activity against *E. coli* at a concentration of 25 µg/mL. Generally, N-substituted derivatives show better activities.

5. CONFLICT OF INTEREST

There are no conflicts of interest.

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