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Synthesis, Characterization and Antibacterial Activity of Indole Based-Chalcone Derivatives

Salah Hamza, Dagne Addisu and Yenealem wagew*

Department of chemistry, Hawassa university natural and computational science, Ethiopia

***Corresponding author:** Yenealem wagew, Department of chemistry, Hawassa university natural and computational science, Ethiopia, **E-mail**: yenealemwagew@gmali.com*

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ABSTRACT

Indole-based chalcone derivatives were synthesized via the reaction of indole and 5-bromo-indole with phosphoursoxychloride in the present of DMF to form formayl indole using Vilsmeyer Haack formylation reaction and the intermediate compound were formed by using condensation reaction. Finally cyclization reaction to get the target compound. The structure of all the synthesized compounds were elucidated by spectral analysis using IR, 1H NMR, and 13C NMR, spectrometer, The synthesized compounds were also evaluated for their antibacterial activities against three bacterial strains using agar well diffusion method and their antibacterial activity were screened for against gram positive bacteria staphylococcus aureus and gram-negative bacteria Klebsiella pneumonia, and Escherichia coli bacterial species. The synthesized chalcone 3-(4,5-dihydro-1,3-diphenyl-1H-pyrazol-5-yl)- 1Hindole was found to be good inhibiting the growth of Staphylococcus auraes (S. auraes) and Klebsiella pneumonia (k.pnemonia) bacteria strain at the concentration of 10µg/ml shows good antibacterial activity with zone of inhibition 16µg/ml and 25µg/ml with compared to the standard drug gentamicin at the concentration of 10µg/ml with zone of inhibition 21µg/ml and 29µg/ml respectively, against most bacteria strains Compared to the standard drug. Therefore, this compound could be a good starting point to develop new compounds for treating these pathogenic diseases.

Keywords: Spectroscopy techniques; Antibacterial; Chalcone; Indole

INTRODUCTION

Chalcones have a simple chemistry which enables a multiplicity of substitutions with easy synthesis. Currently, a variety of methods and schemes are available for the synthesis of chalcone and its derivatives. In each of these methods, the most important part is condensation of two aromatic systems (with nucleophilic and electrophilic groups) to yield the chalcone scaffold.

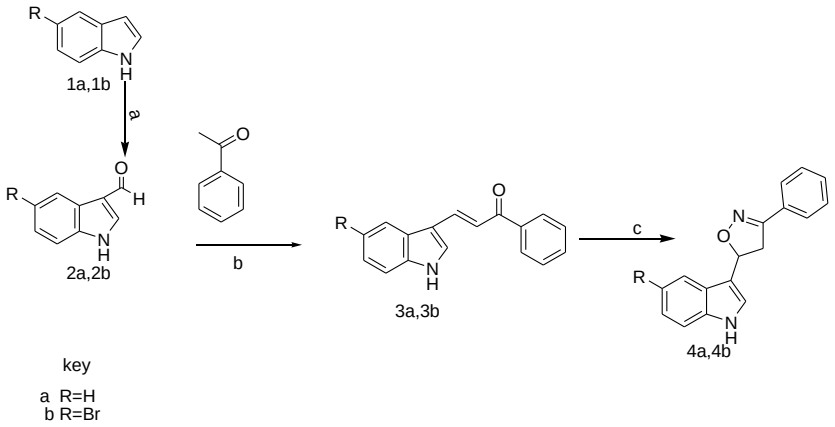
Since the introduction of penicillin in the 1940s, antibiotics have a history of success in controlling mortality due to infectious diseases [1] the emergence and spread of antimicrobial resistance has become one of the most serious public health concerns across the world. Thus developments of novel antimicrobial drugs are becoming an urgent need.

The indole structure is found in many organic compounds like the amino acid tryptophann in alkaloids, and in pigments and an important class of heterocycles not only because they are among the most ubiquitous compounds in nature, but also because they have a wide range of biological activities. Hence, it is not surprising that indoles act as lead compounds and are key building blocks in numerous pharmaceuticals [2]. Indole nucleus is one of the most important alkaloid molecule found extensively in biological system and it has become an important structural component in many synthetic pharmaceuticals [3-5]. Indoles have been intensely investigation in both academia and industry owing to their wide range of biological activity.

The indole framework is a medicinally relevant scaffold and has become widely identified as a privileged structure or pharmacophore [6]. The indole scaffold is present in thousands of isolated natural products and also medicinal (synthetic) compounds with diverse therapeutic activity.

The structural diversity and biological importance of nitrogen containing heterocycles have made them attractive targets for synthesis over many years. Indole derivatives are biologically important chemicals with a wide range of therapeutic properties antifungal [7], antiviral [8], antimalarial

[9], have been reported to be associated with the indolic nucleus. Chalcones were first isolated from flavonoid biosynthesis in plants [10] and since then many studies have focused on structural modifications of the chalcone scaffold and the variety of its biological activities [11]. Chalcones consist of two aromatic rings connected by an a,b-unsaturated carbonyl group. It has been shown that the removal of a,b-unsaturated carbonyl system could hinder their biological activities [12] . In the present investigation, the synthesis of the title compounds was achieved from the simple synthetic rout (scheme 1).



Scheme 1: reagent and conditions :(a) $POCl_3$,NaOH,DMF ,reflux at 60°c,(b) KOH, Ethanol, reflux 100°C for 24hrs ,(c) K_2CO_3, $NH_2OH.HCl$, Ethanol and reflux at 100°C

EXPERIMENTAL SECTION

Materials and methods

All reagents and solvents were pure & analytical grade purchased from commercial sources and were used without further purification; Melting points of all synthesized compounds were determined in open capillary tubes using a Gallenkamp melting point apparatus with thermometer (0°C to 350°C), and were uncorrected; Infrared Red (KBr pellet) spectrum was recorded on Perk-Elmer BX infrared spectrometer in the range 4000-400 cm^{-1}. Nuclear Magnetic Resonance (NMR) analyses were performed on a Bruker avance 400MHz/100MHz spectrometer with tetramethyl silane as internal standard and DMSO-*d*6 /$CDCl_3$ as solvents; the progress of the reaction was monitored by TLC silica gel plates; the purification of the products was performed using column chromatography using silica gel (100-200 mesh); Thin layer chromatography was performed using pre-coated aluminum plates, coated with silica gel GF254. Developed plates were visualized under UV lamp (254 nm). All the spectral analyses were carried out at the Department of Chemistry, Addis Ababa University, Ethiopia.

Chemistry

The target compounds were synthesized starting from the reaction indole with phosphorus oxy chloride in the present of DMF to form indole-3-carboxaldehyed, which react with acetophenone in the present of potassium hydroxide in ethanol for the formation of 3-(1H-indol-3-yl)-1-phenylprop-2-en-1-one as intermediate compound (3) finally cyclization reaction with hydroxyl amine or phenyl hydrazine gave the target compounds as shown scheme 1 below.

Synthesis and characterization

General procedure for the synthesis of 1H-indole-3-carboxaldehyde/5-bromo 1H-indole-3-carboxaldehyde (2a,b)

To a solution of indoles/ 5-bromoindole (1a /1b) (42.6 mmol) in dry DMF (187.4 mmol) in an ice-salt bath, $POCl_3$ (47.1 mmol) was subsequently added with stirring over a period of 30 min. After completion of addition, the temperature was raised to 40ºC, the syrup was stirred for 1.5 h at same temperature. At the end of the reaction (as indicated by TLC) 25gms crushed ice was added to the reaction mixture. The obtained solution was transferred into 250 mL RB flask, NaOH (470 mmol) dissolved in 50 mL water was added with constant stirring and the resultant suspension was heated rapidly to the boiling point and allowed to cool to room temperature, The mixture was allowed to stand in refrigerator overnight. The precipitate was filtered off, washed thrice with 100 mL water, yielding 1H-indole-3-carboxaldehyd/ 5-bromo-1H-indole-3-carboxaldehyd (2a/b).

Synthesis of 3-(1H-indol-3-yl)-1-phenylprop-2-en-1-one

Acetophenone (0.3g, 2.5mmol) was dissolved in 10ml of ethanol and potassium hydroxide (0.1g, 1.78mmol) was added and stirred at room temperature for 20 minutes, then indole-3-carboxaldehyde (0.3g, 2mmol) was added in the reaction mixture and refluxed at 100°C for 24 hrs., after completion of the reaction (monitored by TLC) the reaction mixture was cooled and extracted with ethyl acetate and washed with water, the organic layer was collected and dried over anhydrous sodium sulfate and concentrated using rotary evaporator. The product was further purified by column chromatography.

Synthesis of 3-(4,5-dihydro-3-phenylisoxazol-5-yl)-1H-indole

3-(1H-indol-3-yl)-1-phenylprop-2-en-1-one (3a) (200mg,0.81mmole) was dissolved 10 ml of ethanol, and stirred for 20minutes in the presence of potassium carbonate and hydroxylamine hydrochloride 0.79mg,(0.97mmole)was added and reflux for 9hr at 100°C . The reaction progress was checked by using TLC. The product was extracted by ethyl acetate and absorbed by anhydrous sodium sulfate then concentrated using Rotary

Vapor to get the 3-(4,5-dihydro-3-phenylisoxazol-5-yl)-1H-indole. The product was purified by using column chromatography with (90:10 ratio of n-hexane and ethyl acetate). Then the purified solution of the compound was concentrated using rotary evaporator.

Synthesis of 3-(5-bromo-1H-indol-3-yl)-1-phenylprop-2-en-1-one

Acetophenone (0.33g, 2.756mmole) was dissolved in 10ml of ethanol and potassium hydroxide(0.385g,6.89mole) was added and stirred at room temperature for 20 minutes and 5-bromoindole -3-carboxyaldhyde (0.2g,8.9mole) was added in the reaction mixture and refluxed at 100°c.The reaction was continued for 24-27hrs to yield 3-(5-bromo-1H-indol-3-yl)-1-phenylprop-2-en-1-one.The progress of the reaction was monitored by using TLC in appropriate solvent 70:30 ratio (n-hexane and ethyl acetate) respectively. After completion of the reaction the mixture was extracted with ethyl acetate and washed with water. Then the organic layer was collected and dried by anhydrous sodium sulfate and concentrated using rotary evaporator. The product was further purified by column chromatography with (70:30 ratio of n-hexane and ethyl acetate) and concentrated using rotary evaporator to give 3-(5-bromo-1H-indol-3-yl)-1-phenylprop-2-en-1-one.

Synthesis of-5-bromo-3-(4, 5-dihydro-3-phenylisoxazol-5-yl)-1H-indole

3-(5-bromo-1H-indol-3-yl)-1-phenylprop-2-en-1-one (200mg,0.62mole) was dissolved 10 ml of ethanol, and stirred for 20minutes in the presence of potassium carbonate .Then hydroxylamine hydrochloride(67.9mg,0.97mole) was added and reflux for 9hr at 100°C and the reaction progress was monitored by using TLC. The product was extracted with ethyl acetate and absorbed by anhydrous sodium sulfate. Then concentrated using Rotary Vapor to get 5-bromo- 3-(4,5-dihydro-3-phenylisoxazol-5-yl)-1H-indole. The product was purified by using column chromatography with (90:10 ratio of n-hexane and ethyl acetate). Then the purified solution of the compound was concentrated using rotary evaporator.

RESULT AND DISCUSSION OF SYNTHESIS COMPOUND

Characterization of compound 3-(1H-indol-3-yl)-1-phenylprop-2-en-1-one

Yellow solid; yield 70%; Mp: 180°c ,^{1}HNMR (DMSO-d6, 400MHz):δ 11.92(1H,s,NH),8.19(1H,s,H-2),7.55(5H,m,phenayl ring including H-10 and H-11) ,7.31(4H,s, in indole ring).

^{13}C NMR (DMSO-d6): δ 189.4, 112.9, 123.2, 137.9, 138.9, 113.2, 115.91, 120.8, 121.6, 125.6, 128.5, 129.1, 132.83, 133.6 and 139.5 and IR (KBr, cm−1) Vmax = singlet broad band at about 3343cm^{-1}indicating the presence of N-H stretch of secondary amine. Strong absorption bands at 2989.9cm^{-1}showed the presence of aromatic sp^{2}C-Hstretch.A stretching at1760.1cm^{-1} show the carbonyl group and Strong bands at1647.9cm^{-1}show the presence of aromatic C=C- ring stretching and the stretching 1458.3 shows the presence of aliphatic carbon to carbon double bond .
Note that: C-14' and C-14 is symmetry the have the same chemical shift similar carbon c-15 and 15'.

Characterization of compound 3-(4,5-dihydro-1,3-diphenyl-1H-pyrazol-5-yl)-1Hindole

White solid, yield 57%, m.p170°C Rf valve 0.51 in hexane and ethyl acetate (90:10).

The ^{1}HNMR spectrum (DMSO-d6, 400MHz). δ 11.2 (1H,s,NH), 7.76(2H,d, H-14&14'J=3.6Hz), 7.51 (3H,m,phenyl ring OR H-15,15'&16), 7.14(4H,s,H5-H8), 6.85(1H s,H-2), 6.00(m, 1H, H-10) , 3.50-3.56(dd,1H,H-11J=20) and 3.67-3.76(,dd,1H,H-11J=20).and ^{13}C NMR (DMSO-d6): 124.6, 114.2, 125.8, 119.3, 122.0 ,119.5 ,112.3, 130.3, 77.6 , 40.6 , 156.9 , 137.3 , 129.3, 127.0 and 130.2 . The IR (KBr pellet) spectrum (*v* in cm^{-1}) shows broad bands spectrum at 3398.34cm^{-1} indicating the presence of N-H stretch of secondary amine. The absorption bands at about 3000cm^{-1} showed the presence of aromatic sp^{2} C-H stretch. The absorption bands at about 2923cm^{-1}to 28854cm^{-1} showed that presence ofsp^{3} C-H asymmetric and symmetric stretch. Strong bands at 1458.08 and 1620 shows the presence of C=N and C=C ring stretching and 1377cm^{-1}the presence of (C-O-N) stretching.

Characterization of compound 3-(5-Bromo-1H-indol-3-yl)-1-phenylprop-2-en-1-one

3-(5-Bromo-1H-indol-3-yl)-1-phenylprop-2-en-1-one :Was obtained as yellow solid, yield 70 %, m.p 175°c Rf value 0.40 in hexane and ethyl acetate with 70:30 solvent system .

^{1}HNMR spectrum($CDCl_3$, 400MHz δ_H in ppm) : the strong singlet peak at 9.49 ppm was assigned to (1H,s,NH).signals at δ8.15 (1H,s,H-2), 8.08(1H,d,H-10, J=2.4Hz), 7.64(2H,d,H-14&14' J=16.2Hz), 7.60(1H,d,H-11, J=6.4), 7.53(3H,m, phenyl ring),7.50(1H,s,H-5) ,7.43(1H,d,H-7, J=13Hz), and 7.33(1H,d,H-8,J=9.6Hz) are shown. Thus, the1H-NMR spectrum showed a total9-proton such as 6-aromatic, 1-amine and 2-hydrogen are located =CH-Ar(H-10)and CO-CH(H-11).

The ^{13}C-NMR spectrum (CDCL3, 400MHz, δ_C in ppm): δ: 130.9, 113.9, 127.1, 118.4, 115.1, 123.3, 113.4, 135.9, 138.3, 126.5, 191.2, 138.8, 128.7, 128.4 and 132.5. The IR (KBr pellet) spectrum information (*v* in cm^{-1}): shows singlet broad bands at about 3343cm^{-1} indicating the presence of N-H stretch of secondary amine. Absorption bands at 2989.9cm^{-1} showed the presence of aromatic sp^{2}C-H stretch. The absorption band at 1760.1cm^{-1} shows the presence of carbonyl group. Strong absorption bands at 1647.9cm^{-1}show the presence of aromatic C=C- ring stretching, the stretching at 1450.3 shows the presence of aliphatic carbon to carbon double bond and the absorption band at 737.5cm^{-1} shows the presence of and C-Br stretching.

Characterization of compound 5-bromo-3-(4,5-dihydro-3-phenylisoxazol -5-yl)-1H-indole

5-bromo-3-(4, 5-dihydro-3-phenylisoxazol-5-yl)-1H-indole was obtained that white solid, yield 75%,m.p 164^{0}c Rf valve 0.49 in(90:10) hexane and ethyl acetate .

The ^{1}HNMR spectrum ($CDCl_3$, 400MHz). Chemical shift valve δ 9.0 (1H,s,NH), 8.39(2H,d, H-14&14'J=4.4Hz),7.31(3H,m,phenyl ring OR H-15,15'&16J=5.2Hz), 7.79(1H,d,H-8, J=3.1Hz),7.49 (1H,s, H-5), 7.51(1H,d,H-7 J=4.2Hz), 6.70 (1H,s,H-2), 6.00 (1H,m,H-10) ,3.72-3.80(1H,dd,H-11 J=10Hz)and 3.42-3.60(1H, dd,H-11 J=10Hz).

The ^{13}C-NMR spectrum ($CDCl_3$, 400MHz, δ_C in ppm): The chemical shift valve δ: 125.5, 114.9, 126.9, 121.8, 113.4, 123.7, 113.0, 135.4, 77.3, 40.9, 156.9, 129.6, 128.8, 126.8 and 130.3. The IR (KBr pellet) spectrum (ν in cm^{-1}). Shows broad bands at about 3398.34cm^{-1} indicating the presence of N-H stretch of secondary amine. The absorption bands at about 3182.33cm^{-1} showed the presence of aromatic-sp^2C-H stretch. The absorption bands at about 2923cm^{-1} to 2854cm^{-1}showed the presence of sp^3C-H symmetry and asymmetry stretch. Strong bands at 1462 and 1377 shows the presence of Ar-C=C and C=N ring stretching and 722cm^{-1} shows the presence of and C-Br stretching.

CONCLUSION

This study is a few attempts to synthesize chalcone from acetophenone with indole and its derivatives as starting material. The chalcone motif is present in an extensive range of biologically active molecules with various activities. The chemical structures of all synthesized compounds were elucidated by spectroscopic techniques such as IR, 1H-NMR and 13C-NMR.All the newly synthesized compounds were evaluated in vitro for antibacterial activity by the disc diffusion method and its zone of inhibition was determined against three different bacterial strains. The synthesized compounds were also evaluated for their antibacterial activities against three bacterial strains using agar well diffusion method and their antibacterial activity were screened for against gram positive bacteria *staphylococcus aureus* and gram-negative bacteria *Klebsiella pneumonia*, and *Escherichia coli* bacterial species. Among the synthesized chalcone 3-(4,5-dihydro-1,3-diphenyl-1H-pyrazol-5-yl)-1Hindole was found to be good inhibiting the growth of *Staphylococcus auraes (S. auraes) and Klebsiella pneumonia (k.pnemonia)* bacteria strain at the concentration of 10µg/ml shows good antibacterial activity with zone of inhibition 16mm and 25mm with compared to the standard drug gentamicin at the concentration of 10µg/ml with zone of inhibition 21mm and 29mm respectively Therefore, this compound could be a good starting point to develop new compounds for treating these pathogenic diseases.

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