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Synthesis and biological activity of some heterocyclic compounds contains N-benzylidene heterocycle and beta-lactam moiety

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Abstract*—A number of N-benzylidene heterocycle derivatives have been synthesized and their antibacterial activities tested. The new chemical structures synthesized compounds were verified on the basis of spectral and elemental methods of analyses.the antimicrobial activity of the compounds was done by disc diffusion method*

We synthesized two different types of compounds, a combination of compounds based on the structure of isatin and other compounds based on the structure of thiazole. Synthesis of thiazole was performed using green chemistry method and a three-step reaction was used in the synthesis of isatin compounds. We used the Stoell-Becker method to synthesize compounds based on the isatin structure.

The synthesized product was characterized by its physical properties, melting point, TLC and then subjected to the in vitro antibacterial activities against gram-positive and gram-negative strains of microbes

Keywords*— *Antibacterial activity, Green chemistry , isatin , thiazole , N-benzylidene heterocycle

I. INTRODUCTION

Green chemistry is called the environmentally friendly chemistry in which it seeks to use as far as possible methods that introduce the least harm to the environment[1]. Green chemistry focuses on the design of processes that reduce the consumption and production of hazardous chemicals. This part of the science of chemistry focuses on technologies that reduce the consumption of minerals and reduce the production of contamination.[2,3,4,5,6].

Green solvents usually come from renewable and natural sources. [7.8] Recently, juice is used as a catalyst for the synthesis of compounds that have medicinal properties [9] Juice is a great solvent because it is both available and non-toxic and safe. Lemon is a good alternative to the catalyst in the open-flame reaction. [10,11] A Schiff base is a compound with the structure OF R2C=NR' (R' ≠ H) [12]. The formation of carbon-nitrogen double bond is important in the organic synthesis. Schiff bases can be synthesized from an amine and a carbonyl compound [13,14]. Schiff bases compounds are known as organic chemicals due to significant biological activity such as anticancer [15], antitumor [16], anti-inflammatory agents [17], antibacterial [18], antibiotics [19], antimicrobial [20], anticonvulsant activity [21]. Isatin (Indolin-2,3-dione) derivatives are reported to show variety of biological activities like antibacterial [22]. Isatin is one of the most important heterocyclic compounds. For example, Schiff bases of isatin are used for their pharmaceutical properties[23]. Isatin (1H-indole-2,3-dione) was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo by nitric and chromic acids[24]. Substituted isatins are also found in plants, for example the melosatin alkaloids [25].

II. EXPERIMENTAL

2.1 Material and Methods

All chemical materials from Merck and Aldrich Company and used without further purification. The IR spectrum was taken with a Shimidzo 300 spectrometer using potassium bromide pellets. 1HNMR (nuclear magnetic resonance) the spectrum of compound was recorded on a Brucker AMX 250 MHz spectrometer in the DMSO solvent using tetramethyl silan as an internal reference. Melting points of compounds were measured with an electro thermal melting point apparatus and were not corrected. The molar conductance of the complexes in DMSO (1×10-3 M solution) was performed at 25 °C using Oakton ECTestr 11 dual-range, conductivity tester. The progress of the reactions was monitored by thin-layer chromatography (TLC) on silica gel Polygram precoated TLC sheets.

2.2 Preparation of catalyst

In the synthesis of our thiazole derivatives, we used lemon catalyzer as a green catalyst. The method of

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obtaining this catalyst was to wash the fresh lemon first with water, then we cut the lemons with a knife and physically lemon juice We extracted the lemons from the filter and then reacted with the fluid under the filter as a catalyst.

2.3 General procedure for synthesis of Thiazole compounds

A mixture of the selected benzaldehyde (0.1mmol) and 2-Aminobenzothiazole (0.1 mmol) and catalyst juice (lemon juice) (8ml) were added and stirred at 65 °C for the 8 hour. The reaction progress was studied by TLC. The products were dried and recrystallized in hot alcohol to obtain the pure product. The product was characterized by melting point, 1H NMR, IR.

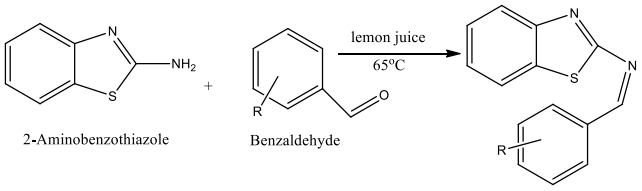

Fig. 1: Synthesis of Thiazole compounds

2.4 synthesis of compound and analytical and spectral data of products

2.4.1 4-((benzo thiazol-2-ylimino)methyl)phenol (a_1)
ivory solide. Yield 75%, mp 240-242 0C.
FTIR (vmax, KBr):1687 (C=N), 3392 ($CH_{aromatic}$), 2170 (OH)3451, (CH_{ar}) 3116, (C=C), 907 cm^{-1}
1HNMR: (DMSO): δ=9.29 ppm (s,1H, HC=N), 9.76 ppm (s,1H, OH), 6.9-7.8 ppm (m,10H, Haromatic)

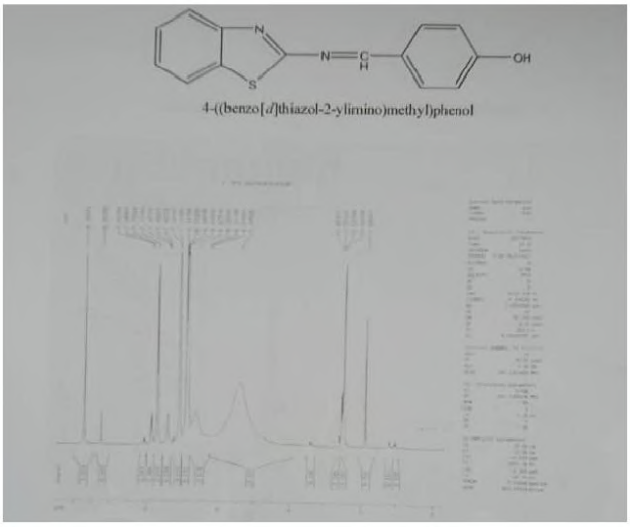

Fig. 2: 1H NMR spectra of 4-((benzo thiazol-2-ylimino)methyl)phenol

4-((benzo thiazol-2-ylimino)methyl)-N,N-dimethylaniline (a_2)
yellow solid. Yield 70%, mp 206-208 0C.
F TIR (vmax, KBr):1660 (C=N) ,1468 (C=C) ,1334 (CN) cm^{-1}
1HNMR: (DMSO): δ=8.08 ppm (s,1H, HC=N), 2.85ppm (s,6H, N(CH_3)), ,7.02-8.05ppm(m,8H,H aromatic)
13CNMR(DMSO):
δ=32.68,34.27,41.84,77.23,77.49,77.74,114.04,114.87,117.47,118.34,124.14,125.29,127.38,128.82,129.15,129.8,131.94,137.63,148.14,158.24,164.08ppm

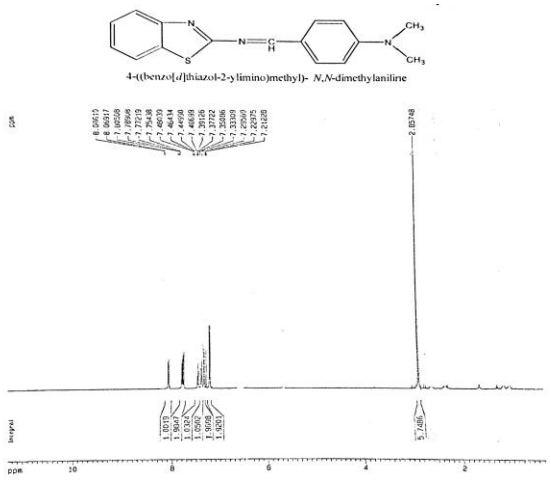

Fig. 3: 1H NMR spectra of 4-((benzo thiazol-2-ylimino)methyl)-N,N- dimethylaniline

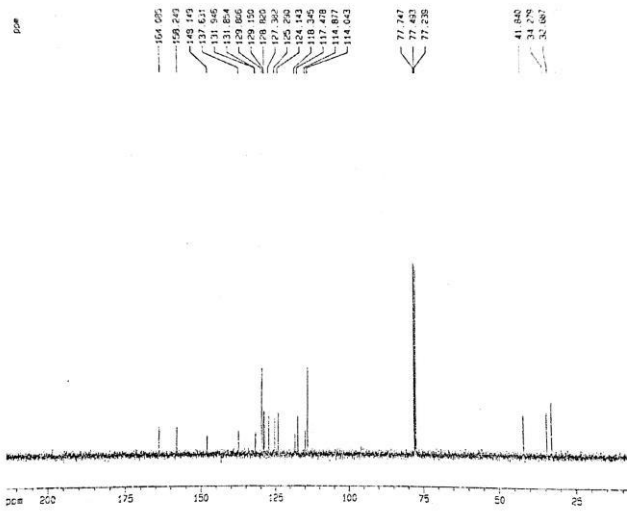

Fig. 4: 13CNMR spectra of 4-((benzo thiazol-2-ylimino)methyl)-N,N- dimethylaniline

N-(benzo thiazol-2-yl)-1-(furan-2yl)methanimine (a_3)
black solide. Yield 75%, mp 163-1165 0C. FTIR (vmax, KBr):3333 (NH_2) ,3172(CHaromatic) , 1738(C=C) ,1637(C=N), 1351(C-N) cm^{-1}
1HNMR:(DMSO): δ=8.36ppm(s,1H, HC=N),6.79ppm ,6.00-8.00ppm (m,8H, Haromatic)

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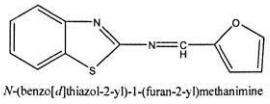
8.37ppm (s,1H, Haromatic),8.92ppm (s,1H, C=NH), 12.04 ppm (s,1H, SH).



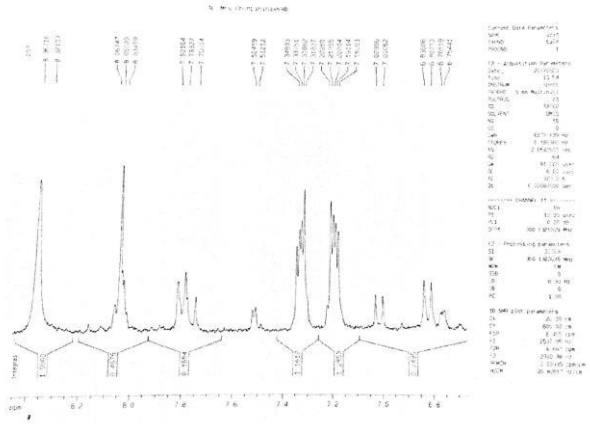


Fig. 5: 1H NMR spectra of N-(benzo thiazol-2-yl)-1-(furan-2yl)methanimine (a_3)

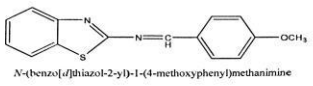
N-(benzo thiazol-2-yl)-1-(4-methoxyphenyl)methanimine (a_4)

Dark yellow. Yield 80%, mp 180-185 0C.

FTIR (vmax, KBr):1727 (C=N),1125(C-O), 2852 (SH),1401 (C=C), 1609 (C=N),1513 (OCH_3),1463 (OCH_3), cm^{-1}

1HNMR(DMSO) : δ=8.05 ppm (s,1H,HC=N),2.23(s,1H,OCH_3),7.00-8.03(m,9H,Haromatic)

13CNMR(DMSO): It represents 15 carbons



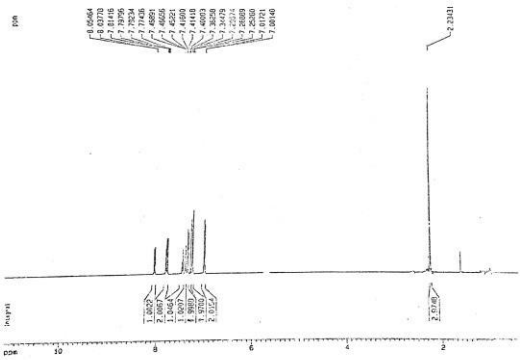


Fig. 6: 1H NMR spectra of N-(benzo thiazol-2-yl)-1-(4-methoxyphenyl)methanimine

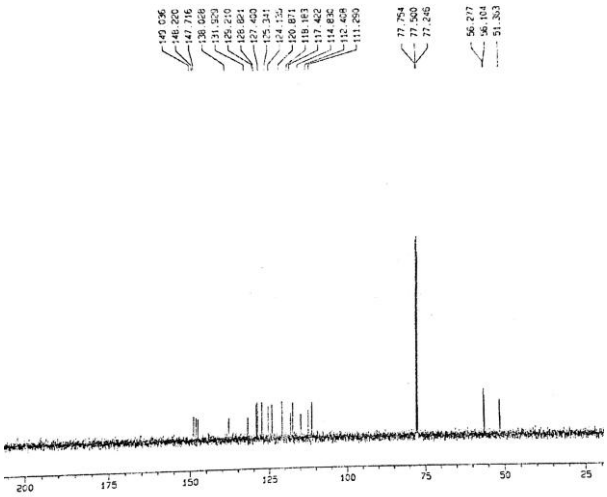


Fig. 7: 13C NMR spectra of N-(benzo thiazol-2-yl)-1-(4-methoxyphenyl)methanimine

2.5 General procedure for synthesis of Isatin compounds

In this reaction, we dissolved (.1 mmol)2, 4 di-nitrophenylhydrazine in a solvent of ethanol(20ml) in the presence of sulfuric acid, and then added various benzaldehyde(.1mmol) to the reaction medium, resulting in orange-colored precipitation(3).(.1mmol) product No. 3 was dissolved in dichloromethane solvent. Then, dissolve the (.15 mmol)oxalyl chloride in dichloromethane and add the solution No. 3 as droplet to oxalic chloride in dichloromethane and place in reflux conditions for 4 hours. Finally, add a further amount of (.3 mmol)AlCl3 to the reaction medium and place it in the reflux conditions for one night, then add the water and ice to the reaction. The progress of the reaction was monitored by TLC. The product was dried and recrystallized from hot alcohol to obtain the pure product. The product was characterized by melting point, 1H NMR, IR.

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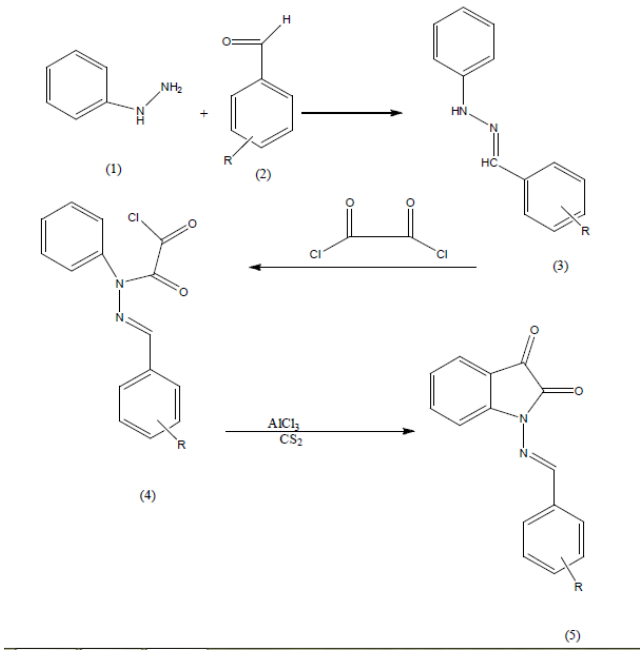

Fig. 8: Synthesis of Isatin compounds

2.6 synthesis of compound and analytical and spectral data of products

2.6.1 (E)-1-(benzylideneamino)-5,7-dinitroindoline-2,3-dione (b_1)

red solide. Yield 68%, mp 159-163 0C.

FT-IR (vmax , KBr) : 3101.63 (C-H) , 1728.66 (C=O) , 1619.83 (C=N) ,

1331.11 (NO2)

1H – NMR (DMSO) : 8.87 (S , 1H , H between to NO2) , 8.72 (S, 1H , H Near

NO2) , 8.34 (S ,1H , CH=N) 7.81-7.82 (d , 2H ,CH- Ar) 7.49 (m , 3H , CH –

Ar)

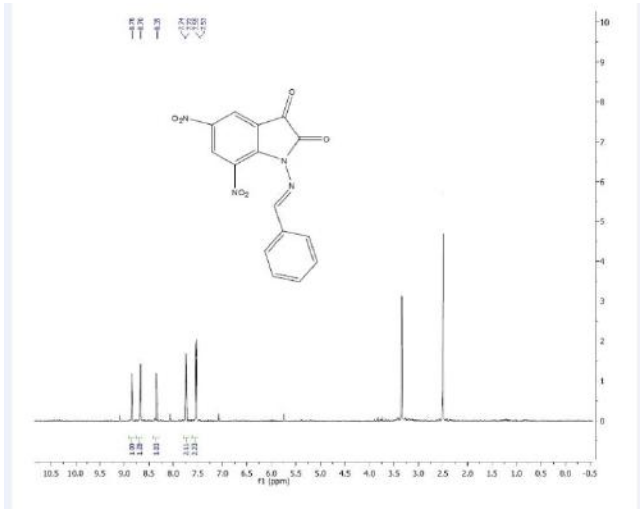

Fig.9: 1H NMR spectra of (E)-1-(benzylideneamino)-5,7-dinitroindoline-2,3-dione (b_1)

(E)-1-(benzylideneamino)indoline-2,3-dione (b_2)

Red solid. Yield 65%, mp 179-181 0C.

FT-IR (vmax , KBr) : 2811.45 (C-H) , 1727.44 and 1747.66 (pair C=O),

1615.36 (C=N) , 1400-1600 (Ar)

1H-NMR (CDCl3,

400 MHz): δ 9.69 (s, 1H, HC=N), 7.80 (d, J=7.6 Hz, 2H, indoline ring), 7.59–7.66 (m, 2H, phenyl), 7.43 (d, J=6.8 Hz,

4H, phenyl), 7.15 (t, J=15.2 Hz, 1H, indoline ring).

(E)-1-((4-methoxybenzylidene)amino)-5,7-dinitroindoline-2,3-dione (b_3)

Red solide. Yield 75%, mp 168-170 0C. FT-IR (vmax , KBr) : 1705.47 and 1684.97 (pair C=O) ,

1334.68 (NO2) , 1273.54 (C-O), 1625.49 (C=N) , 1400-1600 (Ar)

1H – NMR (DMSO) : 3.82 (S , 3H ,OCH3) , 7.03-7.05 (d , 2H , CH-Ar) ,7.72-

7.74 (d , 2H , CH – Ar) 8.33 (S, 1H ,CH=N) 8.88 (S , 1H , between NO2) 8.74

(S, 1H , near NO2)

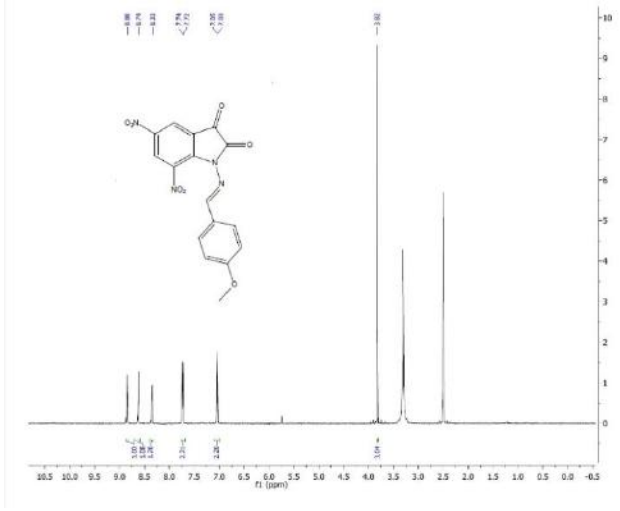

Fig. 10: 1H NMR spectra of 1-((4-methoxybenzylidene)amino)-5,7-dinitroindoline-2,3-dione (b_3)

(E)-1-((4-methylbenzylidene)amino)-5,7-dinitroindoline-2,3-dione (b_4)

Dark red solide. Yield 72%, mp 193-195 0C.

FT-IR (vmax , KBr) : 3089.30 (C-H) , 2922.00 (C-H) , 1719.92 (pair C=O) ,

1613 (C=N) 1325.98 (NO2)

1H – NMR (DMSO) : 2.82 (S , 3H , CH3) , 7.31-7.33 (d , 2 H , CH- Ar) , 7.75-

7.77 (d , 2H , CH- Ar) , 8.41 (S, 1H , CH=N) , 8.72 (S , 1H , near NO2) , 8.82

(S , 1H , between NO2)

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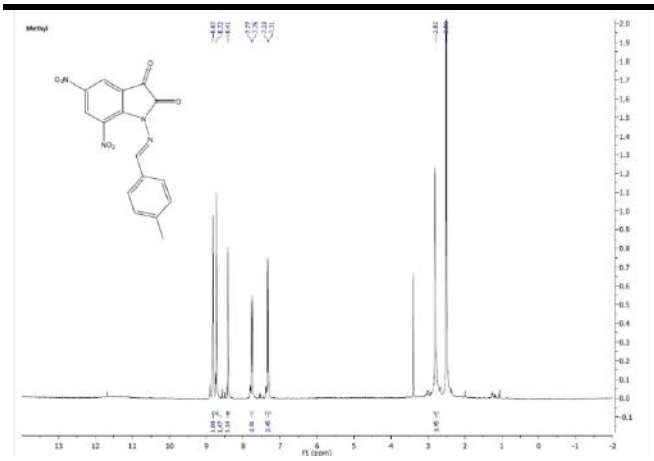

Fig. 11: 1H NMR spectra of (E)-1-((4-methylbenzylidene)amino)-5,7-dinitroindoline-2,3-dione (b_4)

(E)-1-((4-chlorobenzylidene)amino)-5,7-dinitroindoline-2,3-dione (b_5)

Red solide. Yield 68%, mp 182-185 0C. FT-IR (vmax , KBr) : 3090.71 (C-H) , 1710.64 and 1689.55 (pair C=O) 1613.09 (C=N) , 1402.52 and 1585.25 (NO2) , 1613.09 (C=N) , 1400-1600
(CH-Ar)
1H – NMR (DMSO) : 7.53-7.55 (d , 2 H , CH- Ar), 7.72-7.74 (d , 2H , CH- Ar) ,
8.35 (S, 1H , CH=N) , 8.70 (S , 1H , H near NO2), 8.78 (S , 1H , between NO2)

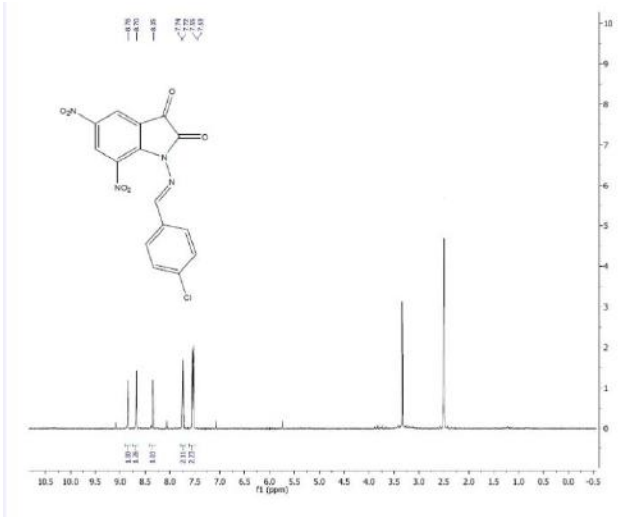

Fig. 12: 1H NMR spectra of (E)-1-((4-chlorobenzylidene)amino)-5,7-dinitroindoline-2,3-dione (b_5)

2.7 In vitro antibacterial activity

Bacillus subtilisin (ATCC: 6633) and Staphylococcus aureus (ATCC: 6838) as gram-positive bacteria Escherichia coli (ATCC: 25922), Serratia marcescens (ATCC: 13880) as gram-negative bacteria. We used these two classes of bacteria to test the antibacterial activity of our compounds.

Microorganisms were cultured onto Muller Hinton Agar (MHA) plate and incubated for 18-24 h at 35 °C. The density of bacteria cultures required for the test was adjusted to 0.5 McFarland (1. 5 ×108 CFU/ml) (CFU = Colony Forming Unit). The antibacterial activity of the synthesized compounds were determined with two methods: minimum inhibitory concentration (MIC) of antibiotic for that bacteria and the disc diffusion methods. The test was repeated three times to increase precision.

2.7.1- Disc diffusion method

The disk diffusion method Is a method by which the antibacterial activity of the compounds is measured. The compounds (0. 04 g) were dissolved in 2 mL DMSO. A bacterial culture (which has been adjusted to 0. 5 McFarland) was used to lawn Hinton agar plates using a sterile swab. The discs had been impregnated with synthesized compounds were placed on the Muller-Hinton agar surface. Tetracycline and cephradine were used as standards for antibacterial measurements. As expected, DMSO did not show any antibacterial activity. After incubation for 18-24 h at 35 °C, The extent of non-growth of each substance was measured in millimeters. the disk diffusion method values are presented in Table 1.

Table. 1: Inhibition zone of Compounds against bacterial strains

	G (+)		
G (-)			
Compounds	B.sabtilis	S.aureus	
E.coli	S.marcescen		
A1	12	N.A	
14	10		
A2	10	15	
16	13		
A3	N.A	10	
N.A	14		
A4	15	12	
13	10		
B1	16	15	
11	N.A		
B2	N.A	13	
15	14		

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B3	10	21	12	9
B4	N.A	N.A	10	N.A
Tetracycline	10	21	12	9
Polymixin	10	N.A	12	N.A
DMSO	0	0	0	0

2.7.2-Minimal Inhibitory Concentration (MIC) method

In microbiology, the minimum inhibitory concentration (MIC) is the lowest concentration of a chemical which prevents the visible growth of a bacterium. MIC is the lowest concentration of the antimicrobial compound, which inhibits the visible growth of a microorganism after overnight incubation. In this method, the various concentrations of synthesized compounds were made from 2000 to 1. 95µg/ml in a sterile tube. A 1 ml sterile Muller Hinton Broth (MHB) was poured in each sterile tube followed by addition of 1 ml test compound in tube 1. Two-fold serial dilutions were carried out from all the tubes and excess broth (1ml) was discarded from the last tube. To each tube 0. 1 ml of the standard microorganism (1. 5 ×108 CFU/ml) was added. Turbidity was observed after incubating the inoculated tubes at 35 °C for 24 h. the MIC values are presented in Table 2.

Table. 2: Minimal Inhibitory Concentration, µg/ml of Compounds against bacterial strains.

	G(+)	G(+)	G(-)	G(-)
Compounds	B.sabtilis	S.aureus	E.coli	S.marcescen
A1	250	500	1000	17.5
A2	16.72	125	60.5	16.72
A3	15.62	125	15.62	15.62
A4	1000	1000	17.5	17.5
B1	17.5	1000	125	15.62
B2	250	500	1000	16.72
B3	16.5	125	500	17.5
B4	1000	500	125	17.5

III. CONCLUSION

In this study concentrates on the importance of fruit juice in organic transformations with biocatalyst exclusivity and Synthesis of Isatin based structures as an active biological structure.The avail of fruit juice in organic synthesis is based on acidic properties, enzymatic activity, benign environmental nature, cheap material, and commercial usability. The benefit of synthesizing structures based on the isatin structure is that since isatin is one of the Indole derivatives and the Indole nucleus is present in many biological structures, then Isatin derivatives can have high biological properties.

The catalyst based activity is consisting of the benefit of fruit juices in various organic transformations including the formation of C-C and C-N bonds in different synthetically organic compounds that researched before. We can Forecast that in next years the chemistry of natural catalysts will continue to attract remarkable research activity. It can also be expected that in the coming years more new compounds will be synthesized based on the structure of the Isatin sciences, which can be attributed to the biological properties of these compounds.

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