Synthesis, Characterization and Biological Activity of new Indole Schiff Bases, Derived from 2-(5-Bromo-3,3-Dimethyl- 1,3-Dihydro-Indol-2-Ylidene)-Malonaldehyde with Substituted Aniline

Hawraa Hussein Khudhayer[1], Fadhil Lafta Faraj[2]
[1, 2] Department of Chemistry, College of Sciences, University of Diyala/Iraq
E-mail: hawraahk950@gmail.com

Abstract
New Schiff Bases have been synthesized by reaction of 2-(5-bromo-3,3-dimethyl-1,3-dihydro-indol-2-ylidene)-malonaldehyde with substituted aniline. The chemical purity structures of the new synthesized compounds was observed by TLC and the chemical structures were characterized by FT-IR, 1H, NMR. New compounds were screened for their antibacterial activity against E. coli and S. aureus by the agar well diffusion method, which revealed different results.
Keywords: Synthesis, Schiff bases, Malonoaldehyde, Substituted anilines, Biological activity.

1. Introduction

A heterocyclic compound is a cyclic compound in which one or more of the ring atoms is an atom other than carbon. A ring atom that is not carbon is called a heteroatom. The name comes from the Greek word heteros, which means "different." The most common heteroatoms found in heterocyclic compounds are N, O, and S. [1] Heterocyclic compounds have a wide range of many applications, but are of particular interest in medicinal chemistry and industrial application. [2,3] Indole is an aromatic heterocyclic organic compound and it is a white solid compound at room temperature. The indole chemical formula is C_8H_7N. It has a bicyclic structure, consisting of a benzene ring and a pyrrole nucleus are fused in 2,3 positions of the pyrrole ring Figure 1 [4]

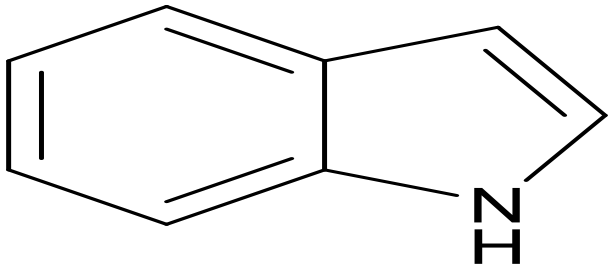

Figure (1): the chemical structures of indole ring

An azomethine group is a functional group that contains a carbon nitrogen double bond with the nitrogen atom linked to an aryl or alkyl group but not hydrogen. Stabilized Schiff bases are usually synthesized from the condensation of aromatic primary amines and active carbonyl group of aromatic aldehydes and ketones. [5] Schiff bases were first reported by Hugo Schiff in 1864. [6] The indole Schiff bases were known as a significant class of heterocyclic organic compounds which have wide applications in many fields for examples Anti-inflammatory activity [7], Antimicrobial activity, [8] antibacterial, antifungal, antitumor activity [9] and Antioxidant. [10]

2. Experimental

Chemistry part

1.1. Materials and Methods

All chemicals and solvents used during synthesis compounds were purchased from a number of different companies such as Merck, BDH, Sigma Aldrich and Fulka. They were used as obtained without further purification. The purity of the synthesized compounds was checked it by TLC sheet and the chemical structures were characterized by FT-IR, 1H-NMR .The melting points of compounds were determined on GallenKamp(MFB-600) melting point apparatus and are uncorrected. FT-IR spectra of compounds were recorded PERKIN ELMER SPEACTUM-65 within the range [4000-400] using KBr Disc in the Chemistry Department /Diyala University. The ^{1}H-NMR spectra was recorded by Bruker 400 MHz spectrophotometer with TMS as internal standard and deuterated DMSO was used as a solvent.

1.2.Synthesis Methods

Synthesis of 2-(-5-bromo-3,3-dimethylindolin-2-ylidene)-3-((4-methoxyphenyl)imino)propanal As illustrated in Figure. 2.

A solution of (0.15 g, 0.5 mmol) 2-(5-bromo-3,3-dimethylindolin-2-ylidene)malonaldehyde was dissolved in ethanol 15 ml and (0.062 g, 0.5 mmol) of 4-methoxyaniline was dissolved in ethanol 10ml and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 °C for 16hrs. A solvent was reduced to one quarter; yellow precipitate was formed, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. The purity of this compound was determined by using TLC with pre-coated silica gel, which gave one spot. IR data in (cm^{-1}): 2976υ (CH aromatic), 2724υ(CH aldehyde, 1669 υ (CH=O), 1515υ (C=C), 1925υ (CHN), 1346υ (CH3), 1259υ (C-N), 818 υ (C-Br) and 778 υ(C-H bending). 1HNMR (500MHz,DMSO,δppm). 13.97(s, 1H,

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NH), 9.40 (s,1H,HCO), 8.58(s,1H,HCN), 7.02-7.66 (7H,Ar-H), and1.60 (s,6H, 2x CH3) 3.80 (s, 3H OCH_3).

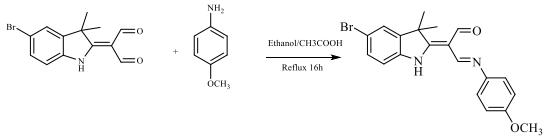


Figure (2) synthetic pathway of 2-(-5-bromo-3,3-dimethylindolin-2-ylidene)-3-((4-methoxyphenyl)imino)propanal

Synthesis of 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((4-bromophenyl)imino)propanal As illustrated in Figure. 3.

A solution of (0.15 g, 0.5 mmol) 2-(5-bromo-3,3-dimethylindolin-2-ylidene)malonaldehyde was dissolved in ethanol 15 ml and (0.087 g, 0.5 mmol) of 4-bromoaniline was dissolved in ethanol 10ml and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 °C for 16hrs. A solvent was reduced to one quarter; yellow precipitate was formed, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. The purity of this compound was determined by using TLC with pre-coated silica gel, which gave one spot. IR data in (cm-1): 2960υ (CH aromatic), 2724υ(CH aldehyde, 1669 υ (CH=O), 1582υ (C=C), 1925υ (CHN), 1334υ (CH3), 1231υ (C-N), 814 υ (C-Br) and 767 υ(C-H bending). 1HNMR (500MHz,DMSO,δppm). 13.95 (s, 1H, NH), 9.44 (s,1H,HCO), 8.68 (s,1H,HCN), 7.47-7.75 (7H,Ar-H), and1.60 (s,6H, 2x CH3) .

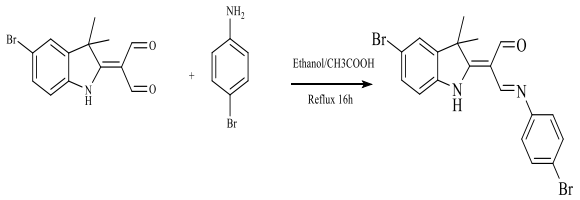


Figure (3) synthetic pathway of 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((4-bromophenyl)imino)propanal

Synthesis of 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2,4-dichlorophenyl)imino)propanal As illustrated in Figure. 4.

A solution of (0.1 g, 0.33 mmol) 2-(5-bromo-3,3-dimethylindolin-2-ylidene)malonaldehyde was dissolved in ethanol 15 ml and (0.05 g, 0.33 mmol) of 2,4-chloroaniline was dissolved in ethanol 10ml and then 10 drops of glacial acetic acid was added into the mixture. The mixture was refluxed in a water bath at 78 °C for 5hrs. A solvent was reduced to one quarter; yellow precipitate was formed, filtered off, recrystyled by ethanol to afford pure yellow precipitate and dried in oven. The purity of this compound was determined by using TLC with pre-coated silica gel, which gave one spot. IR data in (cm-1): 2960υ (CH aromatic), 2724υ(CH aldehyde, 1669 υ (CH=O), 1586υ (C=C), 1925υ (CHN), 1330υ (CH3), 1227υ (C-N), 818 υ (C-Br) and 767 υ(C-H bending). 1HNMR (500MHz,DMSO,δppm). 13.98 (s, 1H, NH), 9.44 (s,1H,HCO), 8.68 (s,1H,HCN), 7.48-7.69 (6H,Ar-H), and1.61 (s,6H, 2x CH3) .

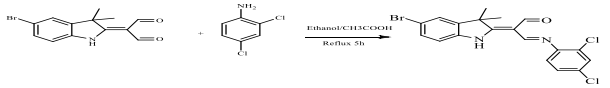


Figure (4) synthetic pathway of 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2,4-dichlorophenyl)imino)propanal

Biological part

Material and Methods

Staphylococcus aureus was cultured and identified on Blood agar and Mannitol salt agar. Escherichia coli isolate was cultured and identified on MacCkonky agar and Eosin Methylene blue.

MacFarland turbidity standard

The preparing solution from the company (Biomeriex) was used in calibrating the number of bacterial cells, as it gives an approximate number of cells 1.5 x 108 cells/ml.

Muller Hinton agar

This medium was prepared by dissolving 38 gm in 1L of distillated water and sterilized by autoclave at 121 °C and under pressure 15 pounds for 15 minutes cooled and poured into sterile dishes and kept in the refrigerator until use.

Determination the Antimicrobial activity of synthesized compounds by agar well diffusion method

1- A number of bacteria colonies were transported by loop to prepare the suspended bacteria and put it in tubes contain brain heart infusion broth to activate the bacteria. The tubes were incubated for (18 - 24) h at 37 °C. The suspended bacteria was compared to the standard MacFarland solution (1.5 x 108) cells/ml. After that the bacteria suspended was spread by Sterile Swab, it was spread on the plates containing Muller Hinton agar and then left the plate for a while to dry.

2- A holes were made with a diameter of 5 mm in the culture media by using sterilized a cork borer

3- 100 µl of the material were added to each hole individually by micropipette. After then, incubate the dishes at 37 °C for 24 h.

4-The effectiveness of each concentration was determined by measuring the diameter of the inhibition zone around each hole.

3. Results and Discussion

1. Chemistry results

The new synthesized compounds were subjected to TLC; spectral studies like HNMR, and FTIR, and their results are discussed below. The physical properties such as the percentage yield and melting point of the compounds (1, 2 and 3) are represented in Table No.1

Table (1): Physical properties of the synthesized compounds (1-3)

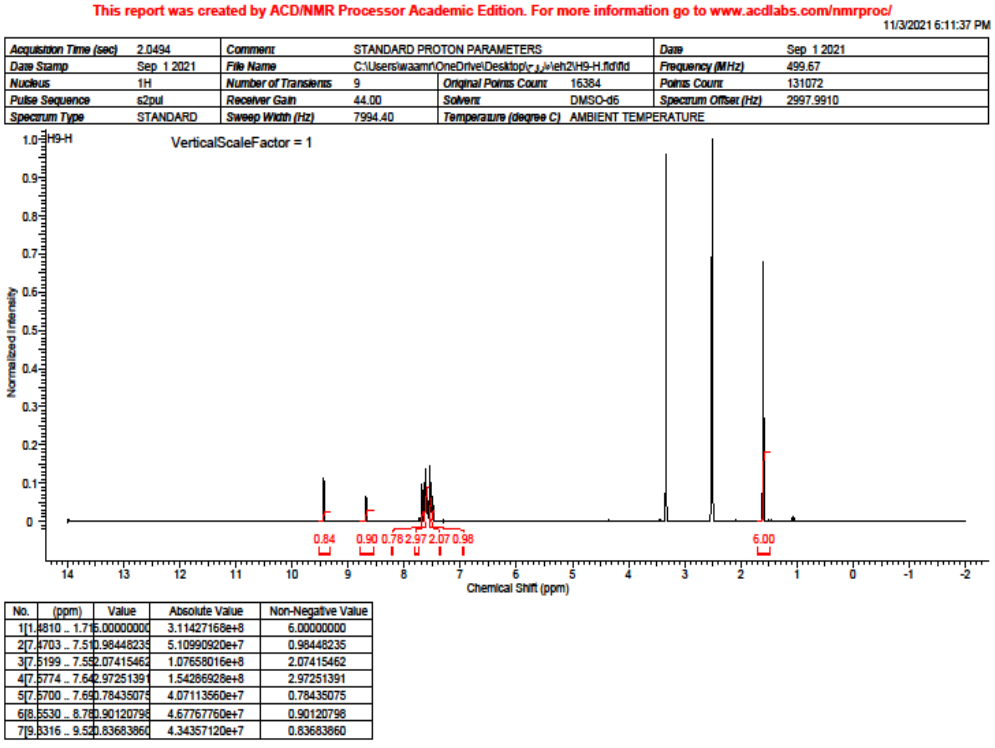
Compound No.	Molecular formula	Percentage Yield	Melting Point °C
1	$C_{20}H_{19}BrN_2O_2$	76%	152-155 °C
2	$C_{19}H_{16}Br_2N_2O$	70%	166-168 °C
3	$C_{19}H_{15}BrCl_2N_2O$	79%	177-179 °C

IR Study

The IR results of the synthesized compounds were shown bsorption bands in the 4,000 - 400 cm-1 range, especially the new functional group (azomethine group CH=N) at 1625 cm-1, 1621 cm-1 and 1586 cm-1 for synthesized compounds (1, 2 and 3) respectively . which approved to formation the accuracy chemical structure of synthesized compounds. Also strong absorption band at 1669 cm-1, 1669 cm-1,1669 cm-1 for compounds(1, 2and 3) respectively which were belonged to (C=O)of the carbonyl group . As well as stretching frequency at 1515 and 1582 cm-1 for compounds (1 and 2) respectively, 1586 cm-1 for compounds (3) were referred to (C=C) group [11,12]. at the same time the synthesized compounds were appeared an absorption bands at 1259 cm-1 , 1231 cm-1 and 1227 cm-1 which attributed to (C-N) groups [13] of synthesized compounds (1, 2 and 3) respectively [14]. Finally, absorption band at 1346 cm-1 and 1330 cm-1 for compounds (1 and 3) respectively and 1334 cm-1 for compounds (2) were appointed to (CH3) group . All these main absorption bands are approved the chemical structures of the synthesized compounds (1, 2 and 3).

NMR Study

1H-NMR,spectra were reported in DMSO (dimethyl sulfoxide) with chemical shifts in ppm and using TMS (tetramethylsilane) as standard.The 1H-NMR results for compound (3) Fig. (6) shown single signals at 13.98 ppm was belonged to proton of (NH) of indole ring . A singlet signal at 9.44 ppm was referred to proton atom of carbonyl group (C=O). As well as, single signal at 8.68 ppm was attributed to proton of Schiff base group (CH=N) Signals were appeared in the region between (7.69-7.48) ppm were assigned to protons of aromatic ring for (3) compound . Finally peak at 1.61 ppm was belonged to six protons of two methyl groups. 1H NMR results of other compounds (1 and 2) are discussed and listed in table (2).



No.	(ppm)	Value	Absolute Value	Non-Negative Value
1	[1.4810 .. 1.715	6.00000000	3.11427168e+8	6.00000000
2	[7.4703 .. 7.519	0.98448235	5.10990920e+7	0.98448235
3	[7.5199 .. 7.552	2.07415462	1.07658016e+8	2.07415462
4	[7.5774 .. 7.642	2.97251391	1.54286928e+8	2.97251391
5	[7.5700 .. 7.695	0.78435075	4.07113560e+7	0.78435075
6	[8.5530 .. 8.780	0.90120798	4.67767760e+7	0.90120798
7	[9.8316 .. 9.523	0.83683860	4.34357120e+7	0.83683860

Figure (5): 1H NMR spectrum of 2-(5-bromo-3,3-dimethylindolin-2-ylidene)-3-((2,4-dichlorophenyl)imino)propanal

Table. (2): The chemical shift in ppm to1H NMR results of compounds (1-3)

Compound No.	NH-	C=O	CH=N-	Ar-H	para OCH3	2xCH3
1	13.97	9.40	8.58	7.66-7.05	3.80	1.60
2	13.95	9.44	8.68	7.47-7.75	-	1.60
3	13.98	9.44	8.68	7.69-7.48	-	1.61

Biological results

The antibacterial activity of newly compounds was examined by using the agar well diffusion method on Muller Hinton agar medium with MacFarland turbidity as a standard solution. The zones of inhibition exhibited by the tested compounds were measured in (mm), as shown in Figure 9. The results are reported in Table 5. According to the screening results, the compounds (4,6) have no inhibitory

action against both E. coli and S. aureus bacteria, whereas the compound (4) has mild/moderate activity.

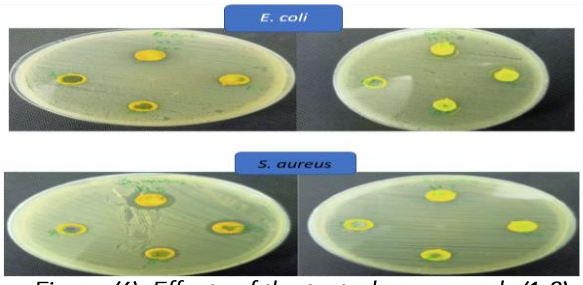


Figure (6): Effects of the tested compounds (1-2) against

Saureus and E. coli.

Table (2): Antibacterial activity of compounds (1,2).

Microorganism Tested materials	S. aureus				E. coli			
	25%	50%	75%	100%	25 %	50 %	75 %	100%
Comp. 1	10mm	13mm	14mm	15mm	R	R	R	12mm
Comp. 2	R	R	R	R	R	R	R	R

4. Conclusion

The newly compounds (1-3) have been synthesized by reaction of 2-(3, 3-dimethyl-5-bromo indolin-2-ylidene) malonaldehyde with various aromatic primary amines, substituted anilines. The chemical structure of the obtained compounds have been characterized and approved by TLC, FT-IR, 1H-NMR techniques. The new synthesized compounds were screened for their antibacterial activity, which revealed different results.

5. Acknowledgment

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