IIETA International Information and Engineering Technology Association
Advancing the World of Information and Engineering

Journal of New Materials for Electrochemical Systems
Vol. 26, No.3, July 2023, pp.227-231
Journal homepage: http://iieta.org/journals/jnmes

Synthesis and Identification of Thiazines-4-on Derived from Sulfamethoxazole, and Testing of some of their Antibacterial Properties

Huda Turki Mahdi [1]and Malath Khalaf Rasheed[2]

1 Chemistry Department-Collage of Education-University of Samarra. Samarra. Iraq.
2 Chemistry Department-Collage of Education-University of Samarra. Samarra. Iraq.

Corresponding email: huudaturky@gmail.com

https://doi.org/10.14447/jnmes.jnmes.v26i3.a10

Received: June 14, 2023
Accepted: July 29, 2023

Keywords:
2-Amino benzothiazol , thiazines, antibacterial, Sulfamethoxazole

ABSTRACT

The 2-Amino benzothiazol (A) was prepared by reacting Sulfamethoxazole with potassium thiocyanate in the presence of bromine as a catalyst. The 2-amino benzothiazol (A) was reacted with benzaldehyde derivatives in the presence of glacial acetic acid as a catalyst and ethanol as a solvent to produce the Schiff base derivatives (H1-H3). This method was also used to manufacture the Schiff base derivatives (H4-H6). Preparation of thiazines derived from Schiff base derivatives (H1-H3) with the appropriate solvent. The study evaluated the efficacy of several compounds against four bacterial strains, namely E. coli, Staphylococcus aureus, Streptococcus pyogenes, and Klebsiella pneumonia. The findings indicated that the tested compounds exhibited varying degrees of effectiveness against the bacteria at different concentrations (0.1, 1, and 10 mg/ml), with some demonstrating good to moderate activity. The standard antibiotic, Fluconazole, was also included in the experiment at a concentration of 5 mg/ml for comparison purp.

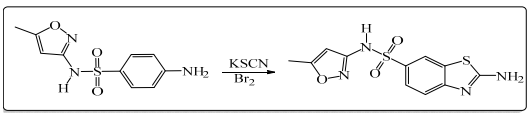
1. INTRODUCTION

Sulfamethoxazole (SMZ or SMX) IUPAC, also known as 4-Amino -N-(5-methylisoxazol-3-yl) benzenesulfonamide, is a broad-spectrum antibiotic. It was first certified in the United States in 1961. It is currently most commonly used in conjunction with trimethoprim (abbreviated SMX-TMP). Sulfamethalazole, sulfisomezole, and sulfamethazole are other names for it. It is used to treat a variety of bacterial infections and is effective against both positive and negative microorganisms [1]. The chemical compound known as 2-aminobenzothiazole has the formula C7H6N2S and is classified as an aromatic phenyl ring fused thiazole ring molecule [2]. In the fields of medical and pharmaceutical chemistry, a number of 2-aminobenzothiazole derivatives play an essential role due to the versatility and breadth of the biological activities that may be performed by these compounds. variations. Various synthetic derivatives of 2-Aminobenzothiazole were demonstrated, exhibiting diverse biological activities and pharmacological variations [3-4] Thiazine is a heterocyclic compound consisting of a six-membered ring containing two heteroatoms, nitrogen (N) and sulfur (S), located at the 1,3 positions within the ring. Thiazines exhibit significant utility in the field of medical and pharmaceutical chemistry, and have demonstrated diverse biological activities [5-6]. A large set of dyes, including methylene blue thiazine, have phenothiazine structures and are employed as dyes, tranquilizers, and insecticides. Thiazine can help you lose some of the additional water weight on your stomach. Thiazine is a pretty basic diuretic supplement that eliminates water and increases vascularity. It is also used in medicine as an anabolic agent [7-8]. The active core of cephalosporins, which are among the most extensively used β-lactum antibiotics, is the 1,3-thiazine nucleus [9-10]. The potential of thiazine to inhibit the growth of tuberculosis and germs, to deactivate HIV (human immunodeficiency virus) in biological fluid, and to serve as an agonist for cannabinoid receptors is a significant property of the compound [11-12].

2. EXPERIMENTAL METHODS

2.1. Preparation of 2-Amino benzothiazol (A)

Dissolved 0.02 mol of Sulfamethoxazole in glacial acetic acid as a solvent with the addition of 0.02 mol potassium thiocyanate in the presence of bromine. After 10 hours of refluxing, the mixture was neutralized with 10% sodium hydroxide, the reaction mixture was allowed to cool, filtered, and the precipitate was collected and recrystallized from ethanol. The process was repeated three times. The chemical compound in question exhibits a molecular formula of C11H10N4O3S2, possesses an orange hue, displays a melting point range of 132-134 oC, and has a yield of 84%. As in the following equation:

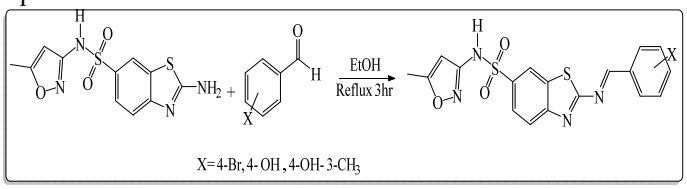


..(1)

Equation of reaction for the preparation 2-Amino benzothiazol (A)

2.2 General method for Preparing of Schiff's Bases

0.0016 mol of 2-Amino benzothiazol (A) was mixed with 0.0016 mol of different benzaldehyde when a catalyst such as glacial acetic acid is present and ethanol as a solvent. The mixture was reflux 3 hrs. Leave the mixture to cool, wash with water, filter and collect the precipitate. Table (1) illustrates some of the physical characteristics of the compounds that have been created (H1-H3), as shown in the following equation:



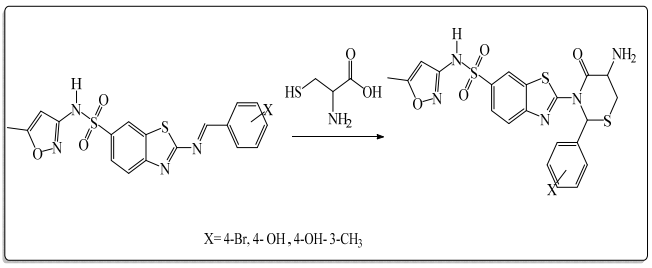
Equation of reaction for the preparation of Schiff's Bases derivatives (H1-H3)

Table 1 Some physical properties of the prepared derivatives (H1-H3).

Comp No.	Molecular Formula	Molecu-lar Weight	Color	M.P °C	Yiel -d%
H_1	C18H13BrN4O3S2	477,35	Dark Yellow	142-144	66
H_2	C18H14N4O4S2	414.45	green	138-140	70
H_3	C19H16N4O4S2	428.48	Yellow -Green	150-152	75

2.3. Preparation of Derivatives of Thiazines (H4-H6)

In the presence of zinc chloride as a catalyst and dioxane as a solvent, 0.001 mol of Schiff's bases (H1-H3) were mixed with 0.001 mol of the amino acid cysteine. The reaction was carried out in the presence of zinc chloride. The mixture was refluxed for 10 hours. Leave the mixture to cool, wash with water, filter and collect the precipitate. Table (2) illustrates some of the physical characteristics of the compounds that have been created (H4-H6), as shown in the following equation:



Equation of reaction for preparing the derivatives of Thiazines (H4-H6)

2.4 Methods of characterization

All the chemicals applied in our study are obtainable from Fluka. And Sigma Aldrich]; The Melting points have been specified by Electro thermal capillary apparatus. Infrared spectra were obtained using ATR technique Shimadzu 8400S, Fourier Transforms Infrared spectros-copy SHIMADZU in the range (400-4000) cm-1. The 1H-NMR spectra were obtained on a Bruker model ultra-shield 400MHz in the laboratories of the University of Science and Technology (Tehran). Using tetra methyl silane (TMS) as internal reference and DMSO-d6 as solvent, Mass spectrum analyses were performed by Agilent Technology MS 5973 device.

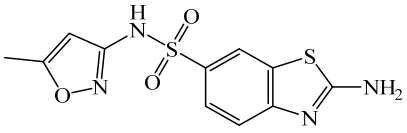
Table 2. Some physical properties of Thiazines (H4-H6)

Comp. No.	Molecular Formula	Molecular Weight	Color	M.P °C	Yield %
H_4	C21H18BrN5O4S3	580,49	Yellow	223-225	32
H_5	C21H19N5O5S3	517,59	Yellow	202-204	28
H_6	C22H21N5O5S3	531,72	Yellow-Dark	225-227	52

3. RESULTS AND DISCUSSION

The infrared spectra of the prepared compound (A1) indicated the appearance of the symmetrical and asymmetrical amine group (-NH2) for 2-Amino benzothiazol (A) at (3361,3467 cm-1). Moreover, the appearance of the (νC-H arom.) at (3072 cm-1). The appearance of absorption bands for (νC-H alip.) at (2975 cm-1). The results were in agreement with the literature [13].

The structural formula of the compound was confirmed by proton 1H-NMR spectroscopy. Singlet signal was seen for compound (A) at [=2.31 ppm (s,3H), CH3]. A Singlet signal appeared at [δ=6.14ppm, (s,1H,] refers to a proton five ring and the singlet signal at [δ=7.07ppm, (s,2H) NH2]. While the multiple signals at [δ=7.86-8.42ppm, (m,3H, CH Arom)] . and Singlet signal appeared at [δ =11.27 ppm, (s,1H,NH)] (14). (figure(1)



The FT-IR spectra were utilized to validate the structures of the Schiff's bases that were synthesized. The spectra demonstrated the absence of the distinctive absorption frequencies of both (C=O) at (1720-1740) cm-1 and (-NH2) at (3300-3500) cm-1 of the aldehyde and the primary amine, respectively. The stretching absorption bands of the azomethine group (C=N) were observed within the spectral range of (1695-1674) cm-1. Furthermore, Table 3 presents the stretching absorption data of the remaining groups in addition to their respective appearances.

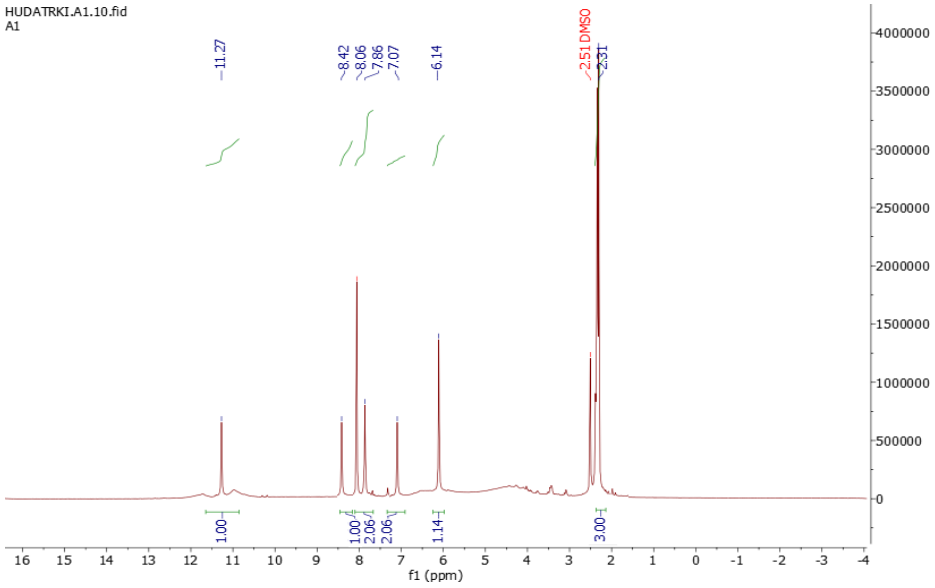


Figure 1 [1]H-NMR spectrum of compound A

Table 3: FT-IR spectrum data of Schiff's Bases derivatives (H1-H3)

IR (KBr) cm^{-1}									
Comp. No.	**NH**	**C-H arom.**	**C-H alip.**	**C=N**	**C=C**		**SO2**		**Others**
							Asym	**Sym**	
H1	3357	3078	2995	1695	1589	1465	1338	1265	C-Br 597
H2	3357	3020	2927	1674	1598	1458	1338	1217	OH 3418
H3	3360	3087	2966	1674	1598	1463	1332	1267	OH 3427

Table 4. Chemical Shift δ ppm of (H_1-H_3).

Comp No.	**Alkyl groups**	**Five ring**	**CH=N**	**Ar-H**	**NH**	**others**
H1	3H s 2.31	1H s 6.14	1 H s 9.09	7H m 7.76-8.39	1H s 11.27	…….
H2	3H s 2.19	1H s 6.15	1 H s 9.15	7H m 6.95-8.41	1H s 11.48	OH 1Hs 9.78
H3	6H s 2.13, 2.31	1H s 6.15	1 H s 9.03	6H m 6.98-8.46	1H s 11.34	OH 1Hs 9.77

The confirmation of synthesized compound structures is achieved through the utilization of [1]HNMR spectra. The figure2 is presented below.
The 1H NMR spectra of the molecule H3, as well as Table 4's chemical shift in ppm of the transition from H1 to H3.

The prepared of Thiazines (H4-H6) were characterized by FTIR. The spectra showed that the stretch vibration absorption bands of (C=N) in Schiff's Bases were no longer present. The spectral data presented in Table 5 indicates the presence of absorption bands corresponding to the amine group (N-H) within the wavenumber range of 3477-3413 cm-1. Additionally, the appearance of absorption bands associated with vC-Harom within the range of 3031-3029 cm is also observed.

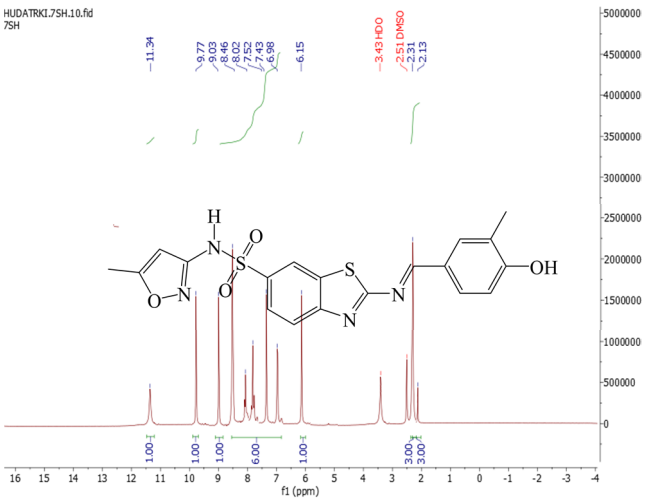


Figure 2 ^{1}H-NMR spectrum of compound H3

Table 5: FT-IR spectrum data of Thiazines (H4-H6)

IR (KBr) cm^{-1}										
Comp. No	NH2		NH	C-H arom.	C-H alip.	C=O lactam	C=C		C-S	Others
H 4	3477	3417	3230	3029	2916	1618	1587	1488	675	C-Br 540
H 5	3477	3413	3232	3031	2930	1618	1589	1488	675	OH 3548
H 6	3471	3415	3210	3028	2918	1618	1587	1488	675	OH 3548

The confirmation of synthesized compound structures is achieved through the utilization of ^{1}HNMR spectra. The figure4 is presented below.

The ^{1}H NMR spectra of the molecule H5, as well as Table 6's chemical shift in ppm of the transition from H5 to H6.

Table 6. Chemical Shift δ ppm of (H_5-H_6).

Comp. No.	Alkyl groups	Thiazines ring	Five ring	Ar-H	NH 2	NH	Others
H5	3H s 3.32	4H s,m 3.06-5.91	1H s 6.04	7H m 6.71-8.43	2H s 8.80	1H s 11.34	OH 1Hs 9.06
H6	6H s 2.32, 2.09	4H s, m 2.93-5.88	1H s 6.15	6H m 7.06-8.46	2H s 8.83	1H s 11.28	OH 1Hs 9.78

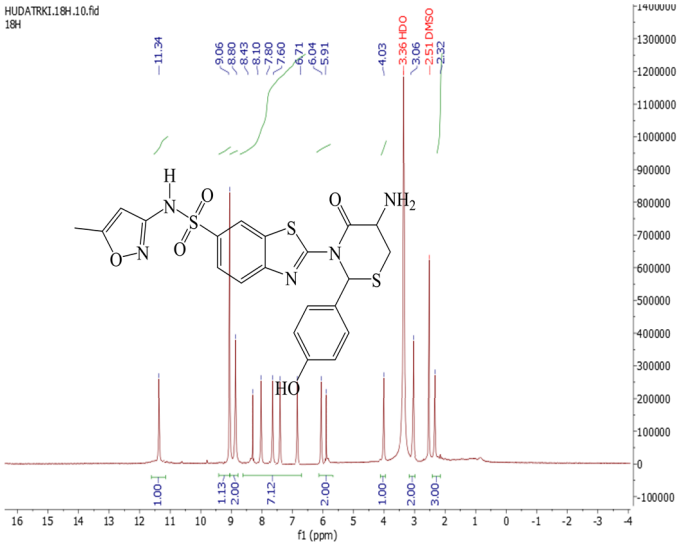


Figure 3. ^{1}H-NMR spectrum of compound H5

The mass spectrum of the molecule (H4) was recorded, and it displayed a major peak at m/z + = 467 along with a relative abundance (12%) owing to the molecular weight of the compound (C18H18N4O5S3), as shown in Figure (4). Scheme 1 presented partial segments of H4 compound.

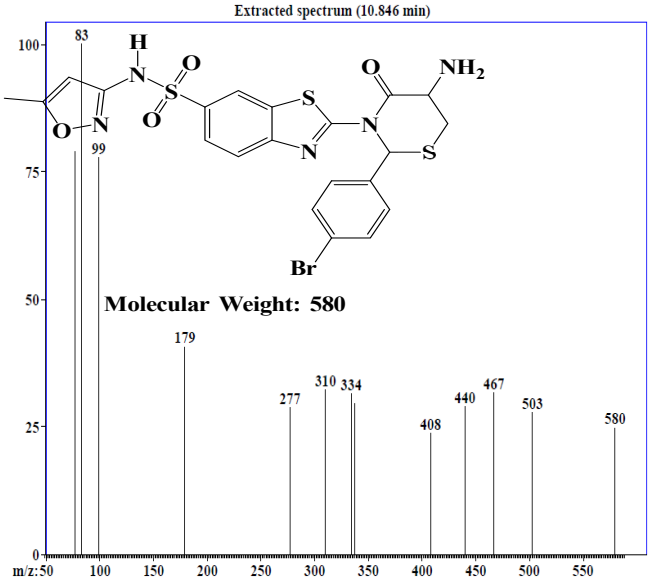
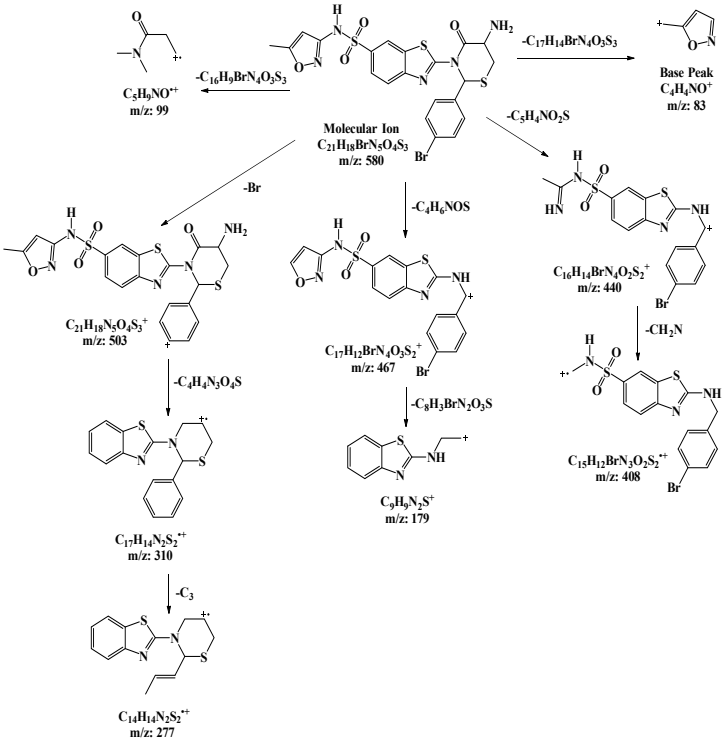


Figure 4. Mass spectrum of compound H4



Scheme (1) Fragments of compound H4

Assessment of the biological efficacy of certain synthesized compounds [15]. E. coli, Staphylococcus aureus, Streptococcus pyogenes, and Klebsiella pneumonia were used to test the biological activity of various produced compounds (A1, H3, and H6). The results were compared with the standard antibacterial (Fluconazole), and showed that these compounds have the ability to Inhibition is good to medium

by using different concentrations of compounds (0.1 mg/ml), (1 mg/ml), (10 mg/ml) compared to the inhibition with the standard antibacterial (Fluconazole) with a concentration of 5 mg/ml. Shown in Table (7).

Table 7: Anti-bacterial activity data for compounds (A1, H3, H7) and measured mm

Com No.	***Conc.%***	***E. coli***	***Staphylococcus aureus***	***Streptococcus pyogenes***	***Klebsiella pneumonia***	**Control**
A1	0.1 1 10	1mm 2mm 2mm	5mm 10mm 25mm	-- -- 10mm	5mm 7mm 15mm	-- -- --
H3	0.1 1 10	3mm 3mm 3mm	36mm 47mm 55mm	3mm 5mm 15mm	5mm 10mm 15mm	-- -- --
H6	0.1 1 10	1mm 2mm 2mm	3mm 10mm 25mm	-- -- --	-- -- --	-- -- --

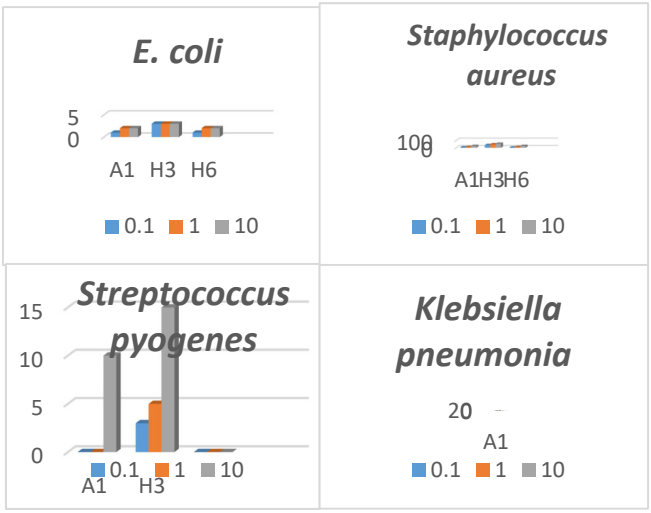


Diagram (1): Inhibitory activity of synthesized compounds (A1, H3, H6) against E. coli , S. aureus, S. pyogenes and K. Pneumonia

4. CONCLUSION

Thiazines-4-on compounds were synthesized and characterized. The study indicates the possibility of preparing 2-Amino benzothiazol with good product ratios, and used to preparing the azomethene group as a intermediate group. The findings indicated that the tested compounds exhibited varying degrees of effectiveness against the bacteria at different concentrations (0.1, 1, and 10 mg/ml), with some demonstrating good to modera activity.

REFERENCES

[1] Sanaa A. Alsahib, Characterization and Biological Activity of Some New Derivatives Derived from Sulfamethoxazole Compound, Baghdad Science Journal, 2020.

[2] Jordan, Alfonzo D., et al. Potential anxiolytic agents. Part 4: novel orally-active N5-substituted pyrido [1, 2-a] benzimidazoles with high GABA-A receptor affinity. Bioorganic & medicinal chemistry letters, 12 (17)2381-2386(2002).

[3] J. K Malik , F. V. Manvi , B. K. Nanjwade1 , S. Singh1 , P. Purohit ,.Review of the 2-Amino Substituted Benzothiazoles: Different Methods of the Synthesis. Der Pharmacia Letter, 2 (1) 347- 359(2010).

[4] Alessia C., Ivana D., Marilena M., Antonio C., Françoise Van B., Antonio R., Filomena C., Carlo F. 2-Aminobenzothiazole derivatives: Search for new antifungal agents. European Journal of Medicinal Chemistry, 64, 357-364(2013).

[5] SP Rathod; AP Charjan; PR Rajput. *Rasayan. J. Chem*., 2010, 3(2), 363-367.

[6] SK Doifode; MP Wadekar; S Rewatkar. *Orient. J. Chem*., 2011, 27(3), 1265-1267.

[7] LDS Yadav; A Singh. *Tetrahedron Lett*., 2003, 44, 5637-5640.

[8] VV Dabholkar; SD Parab. *Heterolett.org*., 2011, 1, 176-188.

[9] Paul, S.; Gupta, R.; Loupy, A.; Rani, B.; Dandia, A. Dry media synthesis of 4H-1, 4- Benzothiazines under microwave irradiation using basic alumina as solid support. *Synth. Commun.,* 2001, *31*(5), 711-717.

[10] Fu, L. Xu, J.; Yao, H.; Wu, X. A synthesis of 4H-1, 4-benzothiazines. *J. Chem. Res.,* 2008, *10*, 566-567.

[11]Dostert, C.; Czajkowski, D.; Müller, T.J.J. 2,6-Difunctionalization of N-Substituted Dithienothiazines via Dilithiation. Synlett 2014, 25, 371–374.

[12] Nau, J.; Schneeweis, A.P.W.; Müller, T.J.J. Dithienothiazine dimers, trimers and polymers – novel electron-rich donors with red-shifted luminescence. Mater. Chem. Front. 2020, 4, 621–630.

[13] Donald L. Pavia, Gary M. Lampman, George S. Kriz, James R. Vyvyan, Introduction to Spectroscopy, fif th edd i tion, Cengage Learning, (2015).

[14] Nuclear T, Resonance M. Experimental Approaches of NMR Spectroscopy. Experimental Approaches of NMR Spectroscopy. 2018.

[15] Malath Khalaf Rasheed, Deena Saady Mohammed Subhi and Amenh Mohammed Abdulrahman. Synthesis, characterization of amic acids and cyclic imides derived from acriflavine and evaluation of their antibacterial and antioxidant activity.*Materials Today: Proceedings*,2020, 43, 2051-2058.