ZANCO Journal of Pure and Applied Sciences
The official scientific journal of Salahaddin University-Erbil
https://zancojournals.su.edu.krd/index.php/JPAS

ISSN (print):2218-0230**, ISSN (online):** 2412-3986**, DOI: http://dx.doi.org/10.21271/zjpas**

RESEARCH PAPER

Synthesis and Spectroscopic Characterization of a New Series of Tetrazole Compounds

Bana S. Abdulrahman[1] and Roshna B. Nadr[1]

[1]Department of Chemistry, Faculty of Science and Health, Koya University, Koya KOY45, Kurdistan Region - F.R. Iraq

A B S T R A C T:
The current study involves synthesis and characterization of a new family of tetrazole derivatives. The synthetic pathway includes two steps, as described here: Initial step was synthesis of N-(4-(6-methylbenzothiazol-2-yl) phenyl)-1-(substituted phenyl)methanimine (1-7), via the reaction of 4-(6-methylbenzothiazol-2-yl)aniline with a variety of substituted benzaldehydes in absolute ethanol utilizing glacial acetic acid as catalyst. The next step was synthesis of tetrazole derivatives (8-14) by the reaction of the synthesized imines (1-7) with sodium azide in dry dioxane. Spectroscopic methods (FT-IR, ^{1}H-NMR and ^{13}C-NMR) were used to determine the structures of the produced products. The synthesized compounds were tested for antibacterial activity against two types of bacteria *Staphylococcus aureus* (Gram +ve) and *Escherichia coli* (Gram -ve). The results showed good activities against both types of bacteria.

KEY WORDS: Heterocyclic compounds; Schiff base; Cyclization; Tetrazole.
DOI: http://dx.doi.org/10.21271/ZJPAS.34.6.23
ZJPAS (2022) , 34(6);217-229 .

1.INTRODUCTION :

Tetrazoles are a class of heterocyclic compounds characterized as a five-membered ring that comprises four nitrogen atoms and one carbon atom (Hussein, et al., 2018; Al-Juburi, 2012). The tetrazole ring is a key step in the synthesis of more complex heterocycles through different rearrangements (Roh, et al., 2012). In the medical and pharmaceutical fields, tetrazole and its derivatives have a wide range of biological effects, including antibacterial, antioxidant (Soliman, et al., 2018; Yousif, et al., 2021), antifungal, (Rasheed and Al-Rifaie, 2020; Dhayanithi, et al., 2011; ShukIa, et al., 2008), anti-inflammatory (Pradip and Berad, 2008), anticancer, (Romagnoli, et al., 2012), and antiviral, (Yeung, et al., 2013). In addition, it can be used in other applications such as agriculture, organic chemistry, photography and coordination chemistry, as well as in the synthesis of many substances involving energy materials, polymers, explosives and photosensitive agents (Guggilapu, et al., 2016; Hussein, et al., 2018).

The aim of this research is synthesis of tetrazole derivatives by the reaction of the Schiff bases (1-7) with sodium azide in dry dioxane. And testing synthesized antibacterial activity of tetrazole derivatives against two types of bacteria *Staphylococcus aureus* (Gram +ve) and *Escherichia coli* (Gram -ve).

2. EXPERIMENTAL

2.1 The chemicals and materials

4-Nitrobenzaldehyde: Riedel-de Haen AG (98%); 3-Nitrobenzaldehyde: Riedel-de Haen (97%); 4-Bromobenzaldehyde: Fluka AG (97%); 4-(6-methylbenzothiazol-2-yl)aniline: BATCH NO. 2013120901 (95%); Sodium azide: Riedel-de Haen (99%); 3-Hydroxybenzaldehyde: Riedel-de Haen (98%); Anisaldehyde: SHBC (98%); p-Tolualdehyde: Fluka AG (97%); Ethanol: Scharlau (99.9%); Dioxane: Merck (99%); Glacial acetic acid: GCC (98%) and Benzaldehyde: ROTH (99.5%). All materials were used without further purification.

* **Corresponding Author:**
Bana S. Abdulrahman
E-mail: bana.sardar@koyauniversity.org
Article History:
Received: 16/04/2022
Accepted: 17/10/2022
Published: 20/12 /2022

2.2 Methods of preparing compounds

2.2.1 General procedure for the synthesis of N-(4-(6-methylbenzothiazol-2-yl) phenyl)-1-(substituted phenyl) methanimine (Azeez and Qadir, 2017)

In a round-bottom flask, dissolved 0.01 mol of 4-(6-methylbenzothiazol-2-yl)aniline and suitable aldehyde (0.01 mol) in absolute ethanol 40 mL and a few drops of glacial acetic acid was added. Then the reaction mixture was refluxed for (4-8) hours. The produced was cooled, precipitated, filtered, collected and then absolute ethanol was used to recrystallize the products. Table 1 summarizing the yield and melting points of Schiff bases.

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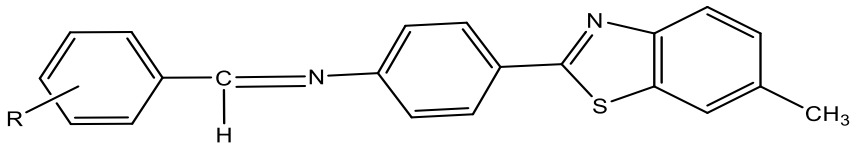


R= H, 4-NO_2, 3-OH, 4-Br, 4-OCH_3, 3-NO_2, 4-CH_3

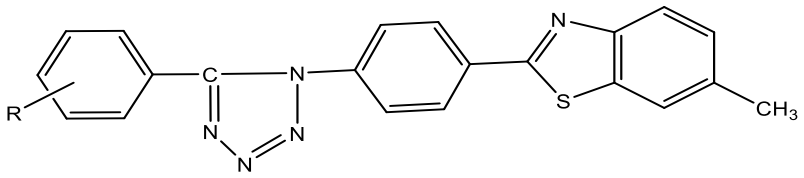
N-(4-(6-methylbenzothiazol-2-yl) phenyl)-1-(substituted phenyl) methanimine

Table 1 Some physical properties for the synthesized N-(4-(6-methylbenzothiazol-2-yl) phenyl)-1-(substituted phenyl) methanimine (1-7) (Aziz and Ali, 2010).

No.	Compounds	Molecular formula	Yield %	Time hrs.	M.P / ^oC
1	N-(4-(6-methylbenzothiazol-2-yl) phenyl)-1-(phenyl) methanimine	$C_{21}H_{16}N_2S$	80	4	188-190
2	N-(4-(6-methylbenzothiazol-2-yl) phenyl)-1-(4-nitro phenyl) methanimine	$C_{21}H_{15}N_3O_2S$	68	8	224-226
3	N-(4-(6-methylbenzothiazol-2-yl) phenyl)-1-(3-hydroxy phenyl) methanimine	$C_{21}H_{16}N_2OS$	75	6	244-246
4	N-(4-(6-methylbenzothiazol-2-yl) phenyl)-1-(4-bromo phenyl) methanimine	$C_{21}H_{15}BrN_2S$	80	5	241-243
5	N-(4-(6-methylbenzothiazol-2-yl) phenyl)-1-(4-methoxy phenyl) methanimin	$C_{22}H_{18}N_2OS$	73	5	185-187
6	N-(4-(6-methylbenzothiazol-2-yl) phenyl)-1-(3-nitro phenyl) methanimine	$C_{21}H_{15}N_3O_2S$	70	8	198-200
7	N-(4-(6-methylbenzothiazol-2-yl) phenyl)-1-(4-methyl phenyl) methanimine	$C_{22}H_{18}N_2S$	72	5	191-193

2.2.2 General procedure for the synthesis of 6-methyl-2-(4-(5-(substituted phenyl)-tetrazol-1-yl)phenyl) benzothiazole (Abood, et al., 2013**)**

Sodium azide (0.026 g, 0. 4 mmole) and synthesized imine (0. 2 mmole) were added to dry dioxane 20 mL and refluxed in a water bath at (75^oC) for (5-7) hours. After, the reaction mixture cools down to ambient temperature, filtered it and recrystallized from ethanol. Summary of Some physical properties for the synthesized 6-methyl-2-(4-(5-(substituted phenyl)-tetrazol-1-yl)phenyl) benzothiazole (8-14) were recorded in (Table 2).



R= H, 4-NO_2, 3-OH, 4-Br, 4-OCH_3, 3-NO_2, 4-CH_3

6-methyl-2-(4-(5-(substitutedphenyl)-tetrazol-1-yl) phenyl) benzothiazole

Table 2 Some physical properties for the synthesized 6-methyl-2-(4-(5-(substitutedphenyl)-tetrazol-1-yl) phenyl) benzothiazole (8-14) (Mohite, et al., 2009).

No.	Compounds	Molecular formula	Yield %	Time hrs.	M.P / ^oC
8	6-methyl-2-(4-(5-(phenyl)-tetrazol-1-yl)phenyl) benzothiazole	$C_{21}H_{15}N_5S$	73	6	205-207
9	6-methyl-2-(4-(5-(4-nitro phenyl)-tetrazol-1-yl)phenyl) benzothiazole	$C_{21}H_{14}N_6O_2S$	62	7	328-330
10	6-methyl-2-(4-(5-(3-hydroxy phenyl)-tetrazol-1-yl)phenyl) benzothiazole	$C_{21}H_{15}N_5OS$	70	5	258-260
11	6-methyl-2-(4-(5-(4-bromo phenyl)-tetrazol-1-yl)phenyl) benzothiazole	$C_{21}H_{14}BrN_5S$	76	6	265-267
12	6-methyl-2-(4-(5-(4-methoxy phenyl)-tetrazol-1-yl)phenyl) benzothiazole	$C_{22}H_{17}N_5OS$	70	7	200-202
13	6-methyl-2-(4-(5-(3-nitro phenyl)-tetrazol-1-yl)phenyl) benzothiazole	$C_{21}H_{14}N_6O_2S$	65	7	311-313
14	6-methyl-2-(4-(5-(4-methyl phenyl)-tetrazol-1-yl)phenyl) benzothiazole	$C_{22}H_{17}N_5S$	60	6:30	211-213

2.3 Antibacterial activity

All tetrazole compounds were tested for their antibacterial activity against *Staphylococcus aureus* (Gram +ve), *Escherichia Coli* (Gram -ve) using sterile discs from 0.3 g of each sample dissolved in 3 mL $CHCl_3$ were absorbed on the small filter paper (5 mm diameter) discs impregnated with stock solutions of each samples in the incubator at 37 °C for 1 hour to dry them.

The bacterial suspension was spread on the surface of Mueller Hinton Agar (MHA) plates by using cotton swab, and then let it dry in room temperature, after that sample pleats or discs were gently pressed on the surface of the agar. All plates were incubated at 37 °C for 18-24 hours. In this research $CHCl_3$ used as a control. The antibacterial action of all tetrazole compounds were estimated by measuring the inhibition zone (mm), and the results of antibacterial activities are listed in (Table 3) (Al-Majidi, et al., 2017).

2.4 Instrumental

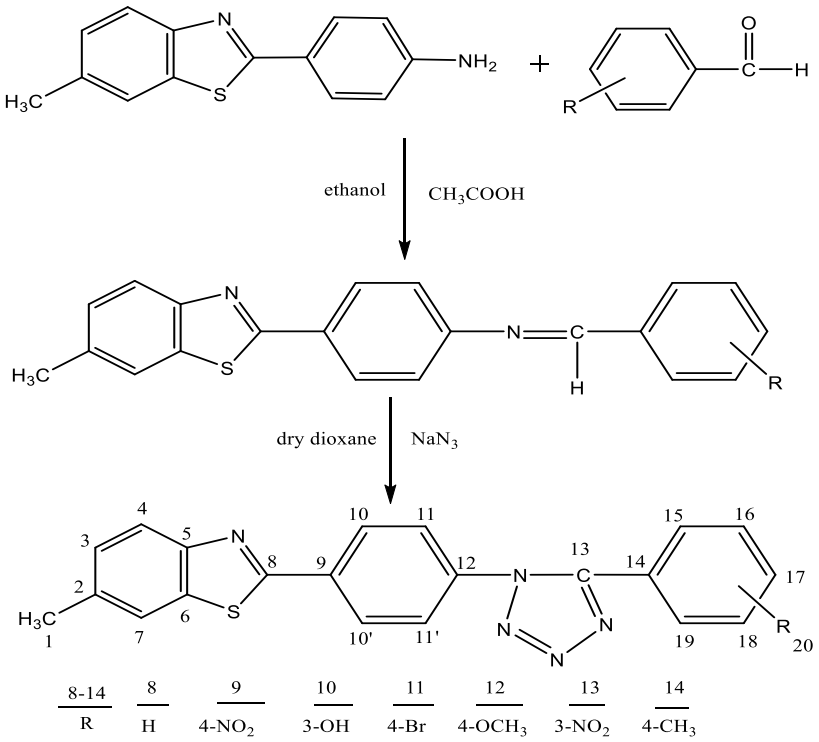
Melting points (M.P.) determined by using the BUCHI B-540 electrothermal melting point instrument. IR-Spectra (Fourier transform

infrared) were recorded using the potassium bromide (KBr) disc method, with spectra recorded in the range 400 - 4000 cm^{-1} using a Bio-Rad Merlin, FT-IR spectroscopy Mod FTS 3000, in Salahaddin University-Erbil.
The ^{1}H-NMR (Proton Nuclear Magnetic Resonance) and ^{13}C-NMR (Carbon Nuclear Magnetic Resonance) spectra were recorded on a Varian-INOVA 500 MHz at Central Lab of Tehran.

3. RESULTS AND DISCUSSION

Characterization of 6-methyl-2-(4-(5-(substituted phenyl)-tetrazol-1-yl)phenyl) benzothiazole:

Through refluxing the synthesized Schiff bases (1-7) with sodium azide in dry dioxane, a novel series of heterocyclic tetrazole derivatives (8-14) were produced, as shown in scheme 1. The reaction time required was (5-7) hours for conventional method. The structure of synthesized tetrazoles (8-14) were demonstrated on basis of FT-IR, ^{1}H-NMR and ^{13}C-NMR.



Scheme 1: The synthesis of Tetrazole compounds.

3.1 FT-IR study

The functional groups of samples were investigated via the FTIR technique, Fig. (1) shows the spectrum of 6-methyl-2-(4-(5-(phenyl)-tetrazol-1-yl)phenyl) benzothiazole (8). It is clear that the disappearance of peak at (1624) cm^{-1} which belongs to (C=N) (imine) and appearance of peaks at (2030, 2150) cm^{-1} related to the azide group's ($-N_3$). (Al-Shimmery and Sammie, 2016; Hussein, et al., 2018). In the FT-IR spectrum of 6-methyl-2-(4-(5-(3-nitrophenyl)-tetrazol-1-yl)phenyl) benzothiazole (13), Fig. (2), it can been seen that the disappearance of peak at (1627) cm^{-1} which belongs to (C=N) (imine) and appearance of peaks at (2036, 2154) cm^{-1} which explained entity of the azide group's ($-N_3$). For the FT-IR spectrum of 6-methyl-2-(4-(5-(4-methylphenyl)-tetrazol-1-yl)phenyl) benzothiazole (14), Fig. (3), the appearance of a peak at (2108) cm^{-1} which belongs to the azide group ($-N_3$) and disappearance of peak at (1633) cm^{-1} relation to the (CH=N) group.

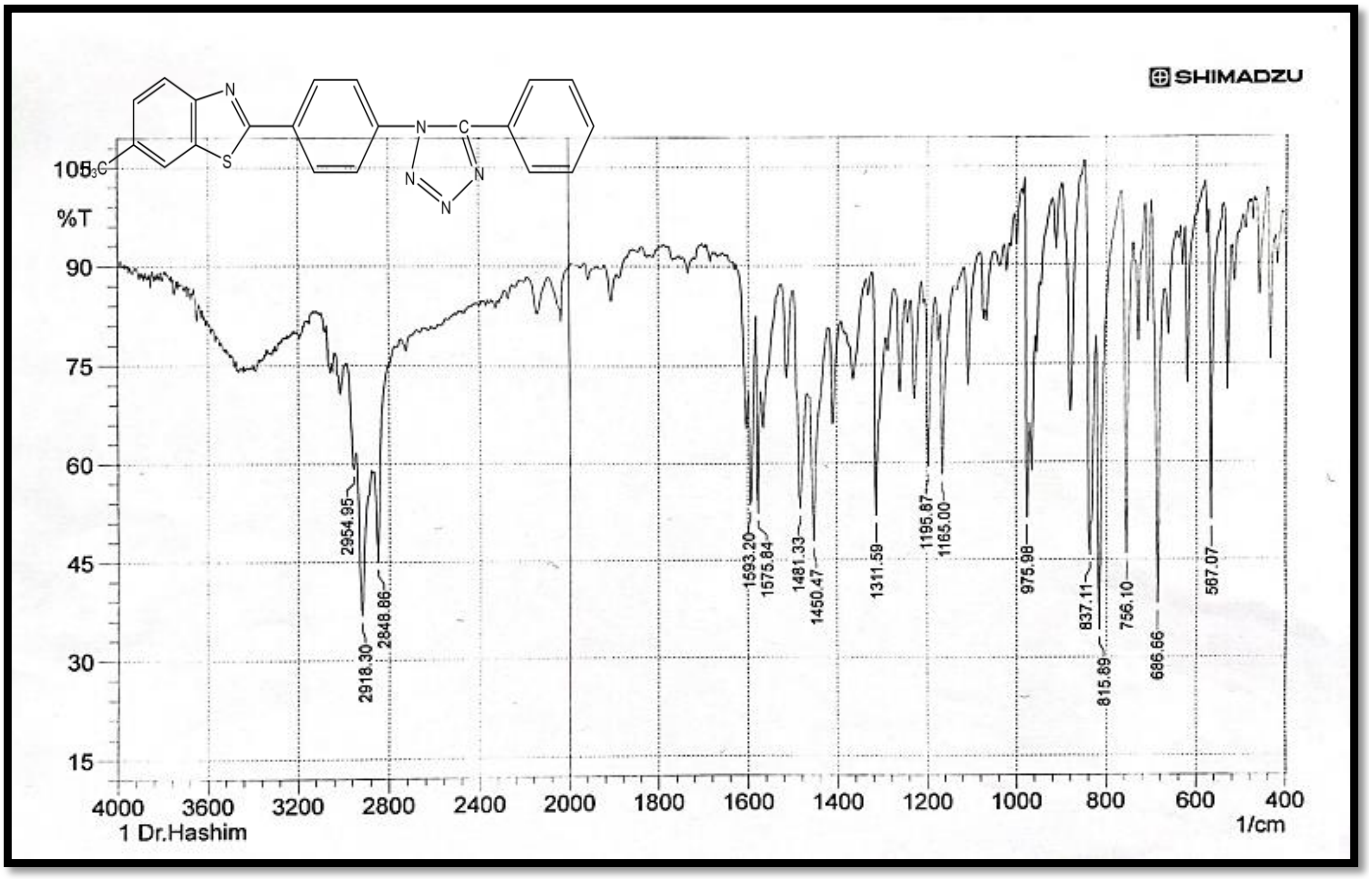


Figure 1: FT-IR spectrum of compound (8)

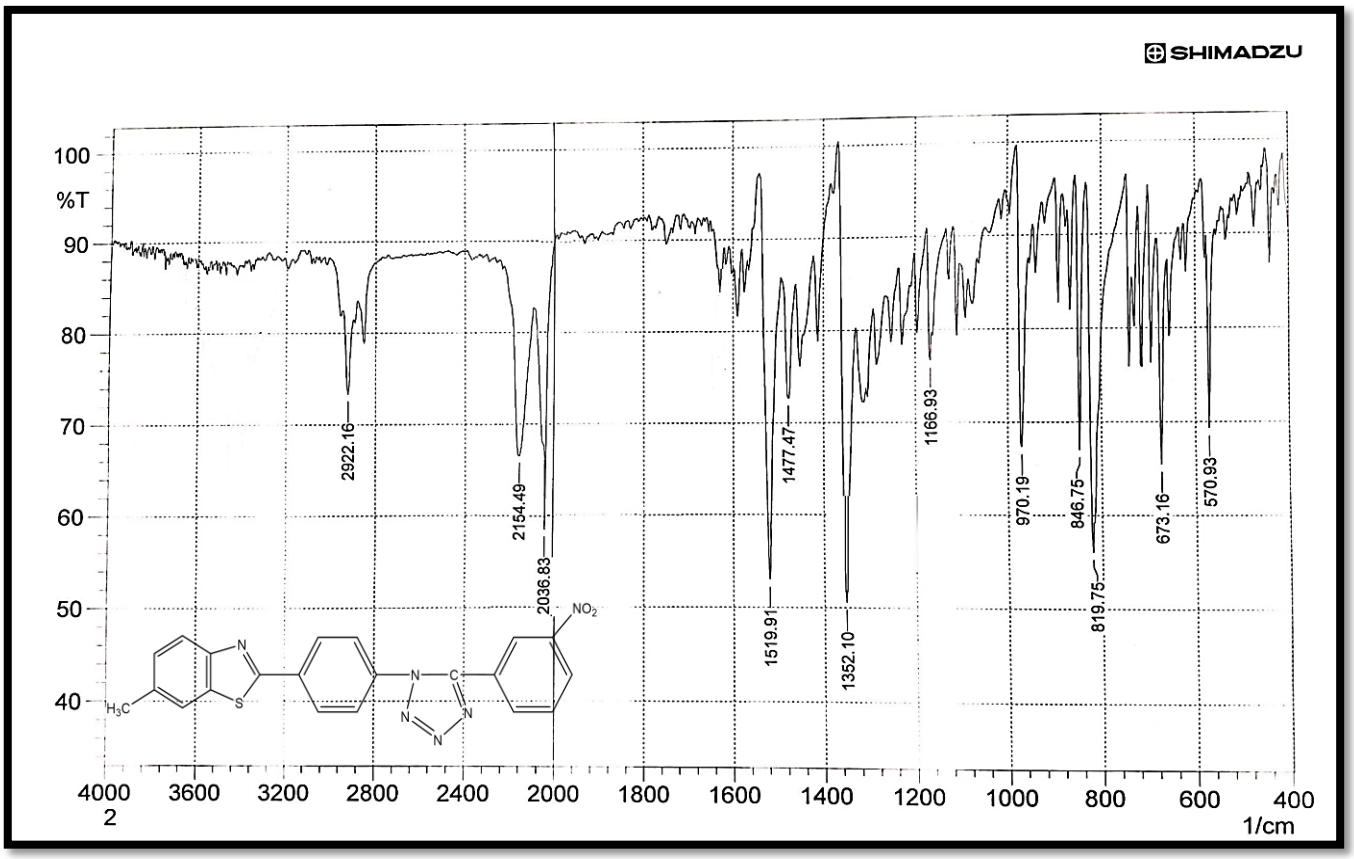


Figure 2: FT-IR spectrum of compound (13)

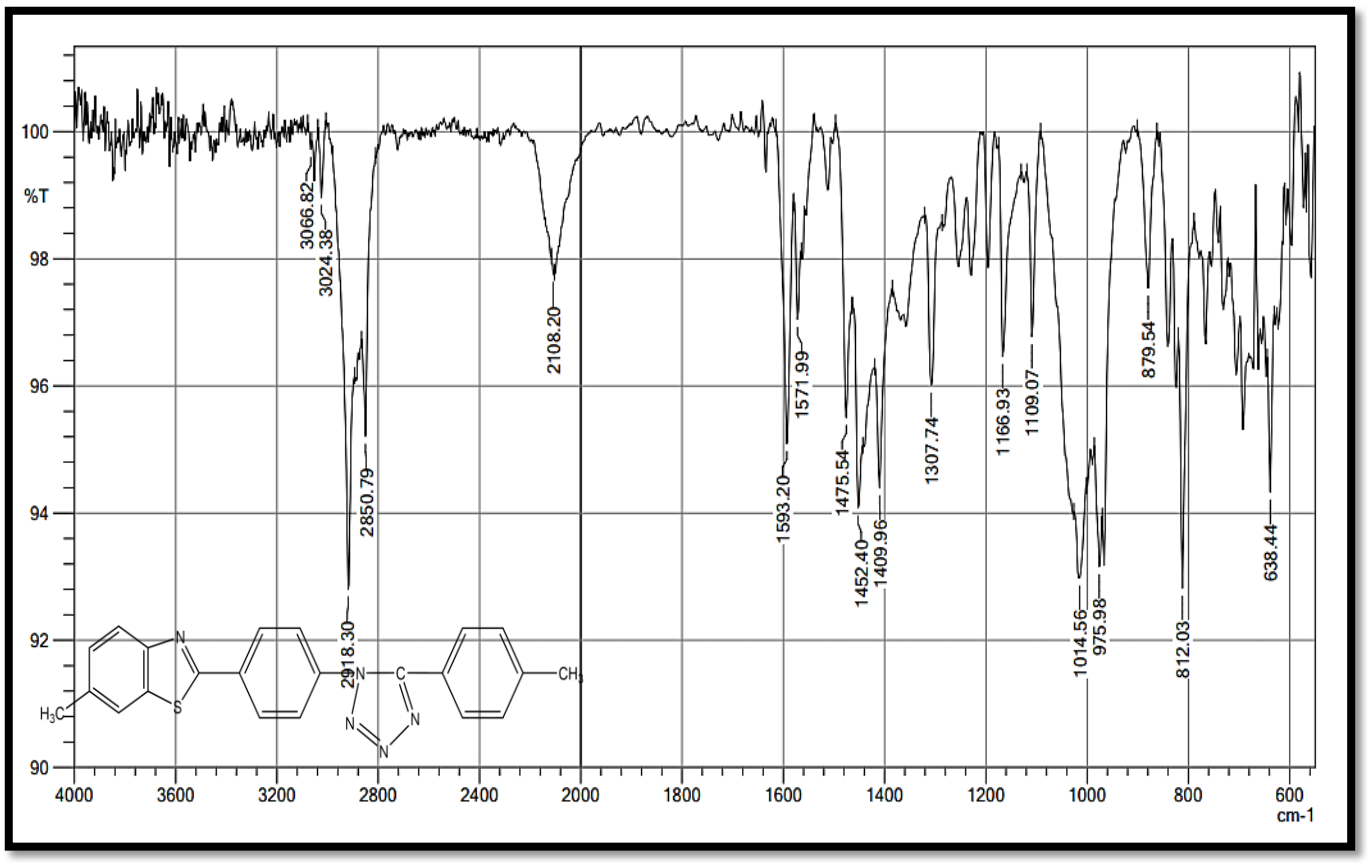


Figure 3: FT-IR spectrum of compound (14)

3.2 ^{1}H-NMR study

The functional groups of samples were further investigated via the ^{1}H-NMR technique, Fig. (4) showed the spectrum of 6-methyl-2-(4-(5-(substituted phenyl)-tetrazol-1-yl)phenyl) benzothiazole (8). The results found that the disappearance of (CH=N-) signal at (8.53) ppm, a singlet signal at (2.27) ppm which belongs to the three protons of CH_3 group, and the multiplet peaks at (7-7.87) ppm are belong to protons of aromatic ring. In case of ^{1}H-NMR spectrum of compound (13) presented in Fig. (5), the peaks showed disappearance of signal for (CH=N-) at (8.7) ppm, in addition to a singlet signal at (2.29) ppm is due to the three protons of CH_3 group, and the multiplet signals at (7-8.3) ppm for aromatic protons. (Al-Majidi, et al., 2017; Mohite, et al., 2009). Fig. (6) exhibits the 1H-NMR spectrum of compound (14), it can be seen from the data in Fig. (6) that the disappearance of (CH=N-) signal at (8.47) ppm, two singlet signals at (2.48 and 2.52) ppm related to protons of two CH_3 groups, and the multiplet bands at (7.2-8.3) ppm for protons of aromatic rings.

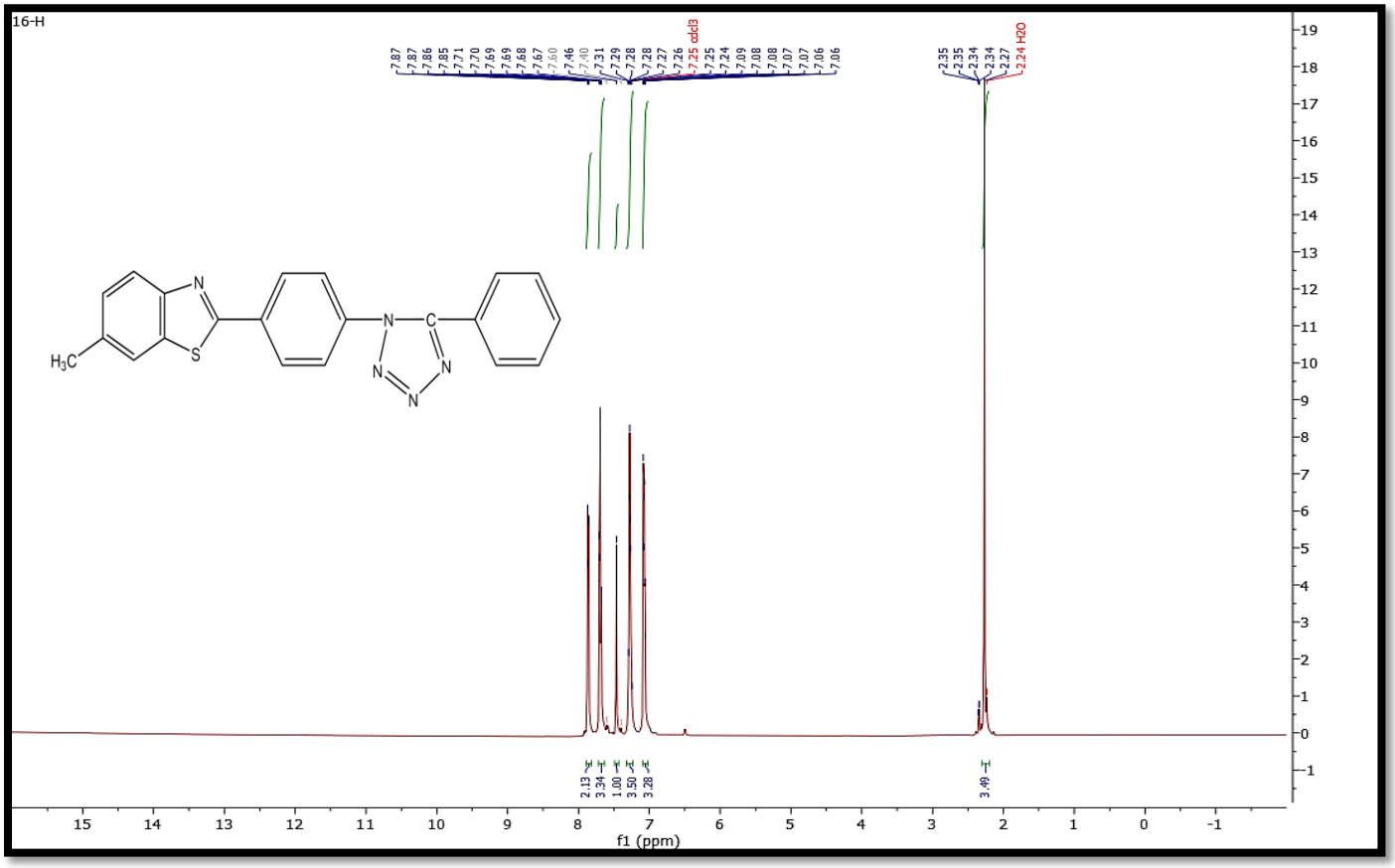


Figure 4: ^{1}H-NMR spectrum of compound (8)

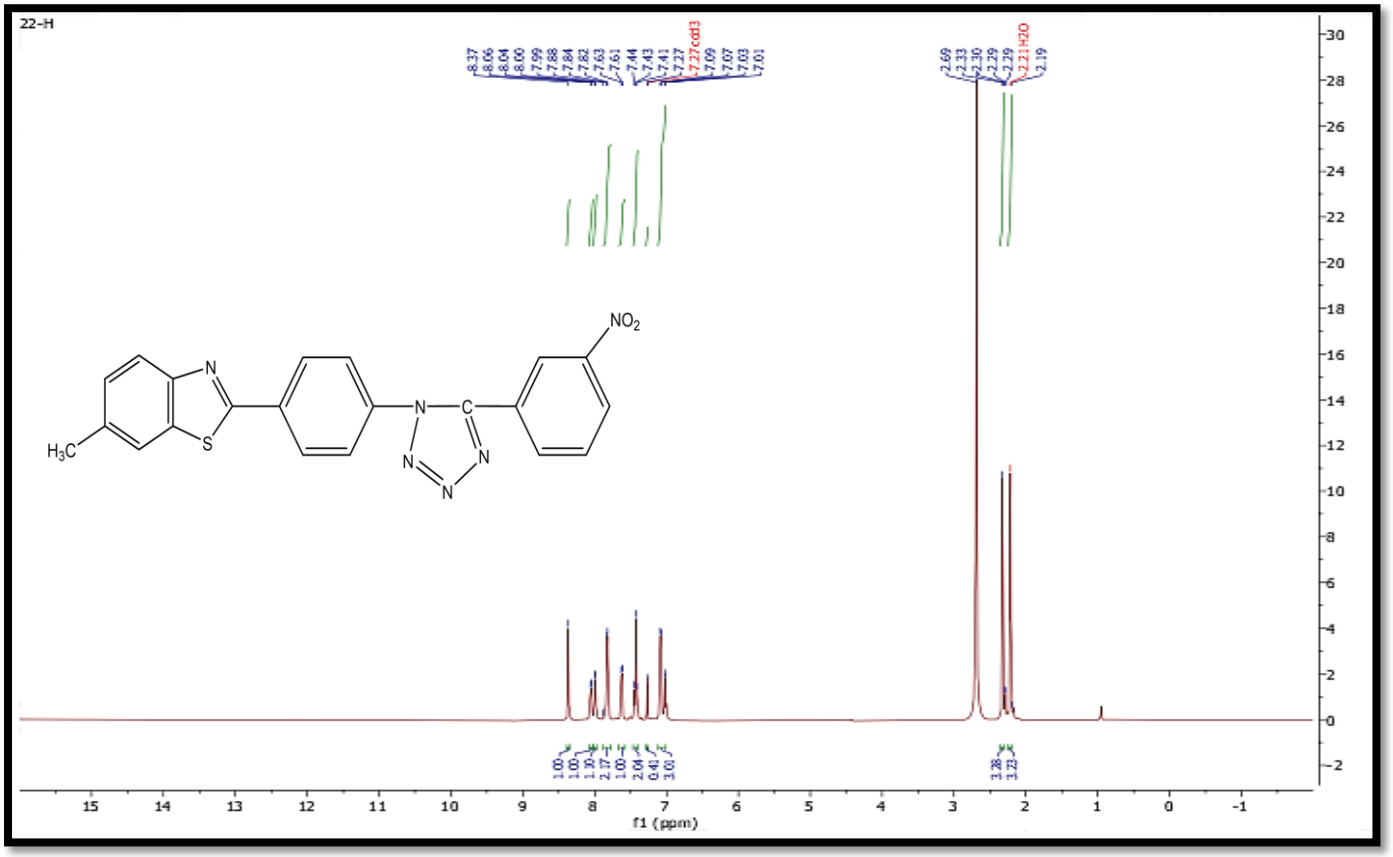


Figure 5: ^{1}H-NMR spectrum of compound (13)

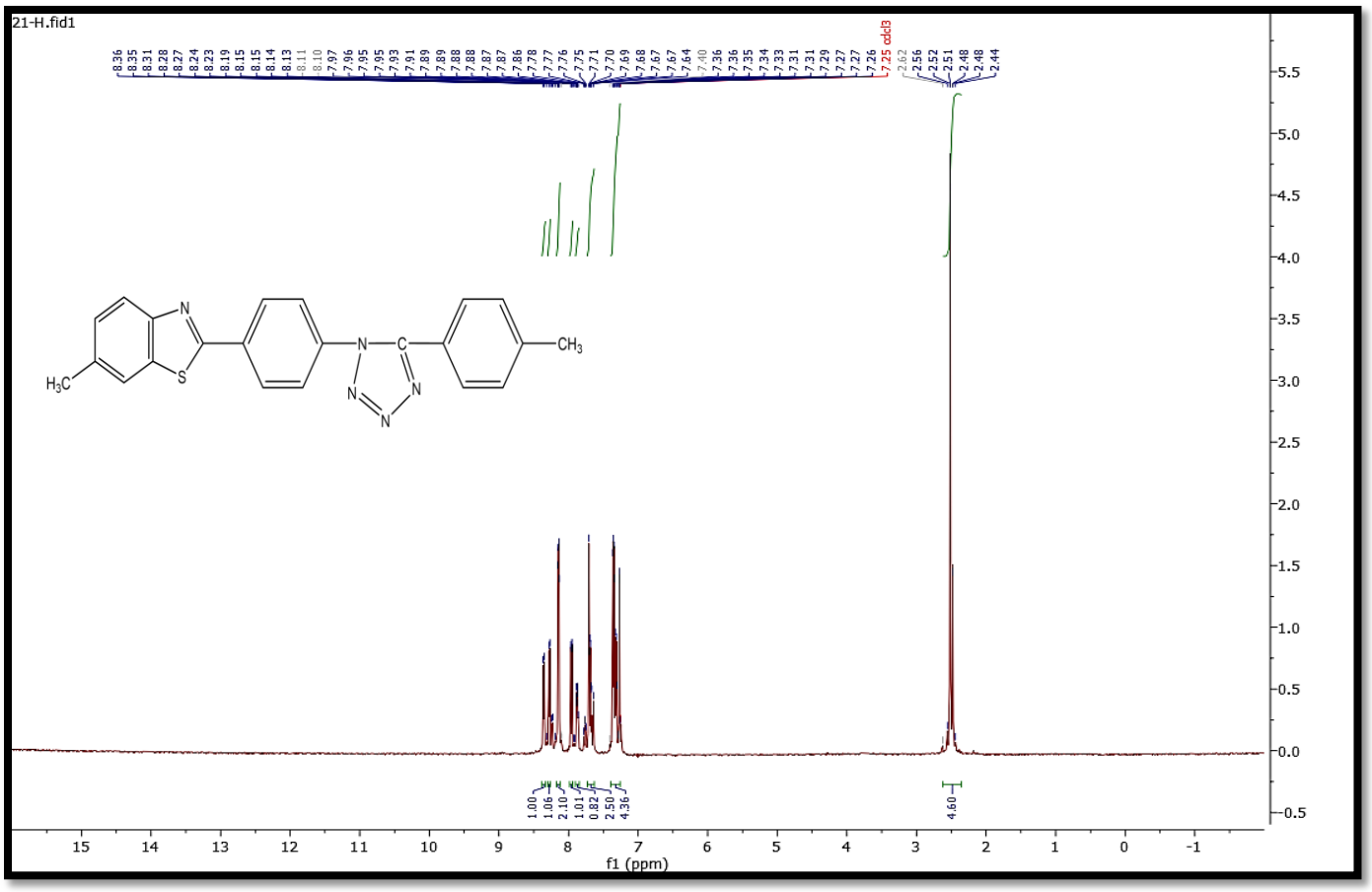


Figure 6: ^{1}H-NMR spectrum of compound (14)

3.3 ^{13}C-NMR study

In this work, ^{13}C-NMR spectroscopy was also used to further investigation the functional groups of synthesised samples (i.e., compounds 8, 13 and 14). Fig. (7) showed the spectrum of 6-methyl-2-(4-(5-(substituted phenyl)-tetrazol-1-yl)phenyl) benzothiazole (8). The results found that the peak at (21.56) ppm attributed to the carbon atom of methyl (-CH_3) group and signals for aromatic carbon of three phenyl ring appears at (135.28, 127.93, 122.59, 154.20, 135.96, 121.36, 166.55, 152.35, 121.50, 129.02, 131.39, 161.05, 131.76, 128.43, 128.85 and 135.20) ppm were fitted to the (C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, $C_{10,10'}$, $C_{11,11'}$, C_{12}, C_{13}, C_{14}, C_{15},$_{19}$, $C_{16,\ 18}$ and C_{17}) respectively. (Dofe, et al., 2017). In the ^{13}C-NMR spectrum of compound (13), Fig. (8), the signal at (21.32) ppm belongs to the carbon atom of methyl (-CH_3) group and signals of aromatic carbon for three phenyl ring appears at (134.89, 123.08, 121.49, 152.66, 135.25, 121.49, 165.82, 137.36, 125.59, 128.18, 127.83, 158.13, 131.77, 121.23, 151.98, 122.23, 129.84 and 134.45) ppm were fitted to the (C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, $C_{10,10'}$, $C_{11,11'}$, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18} and C_{19}) respectively.

In the ^{13}C-NMR spectrum of compound (14), Fig. (9), the signal for two methyl groups carbons appeared at δ (21.57 and 29.70) ppm and signals for aromatic carbons of three phenyl rings appears at (135.23, 125.88, 121.58, 152.33, 135.47, 121.58, 157.89, 137.61, 129.88, 134.22, 128.03, 152.84, 127.59, 123.66, 128.52, 132.26, 128.52 and 122.69) ppm were fitted to the (C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, $C_{10,10'}$, $C_{11,11'}$, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18} and C_{19}) respectively.

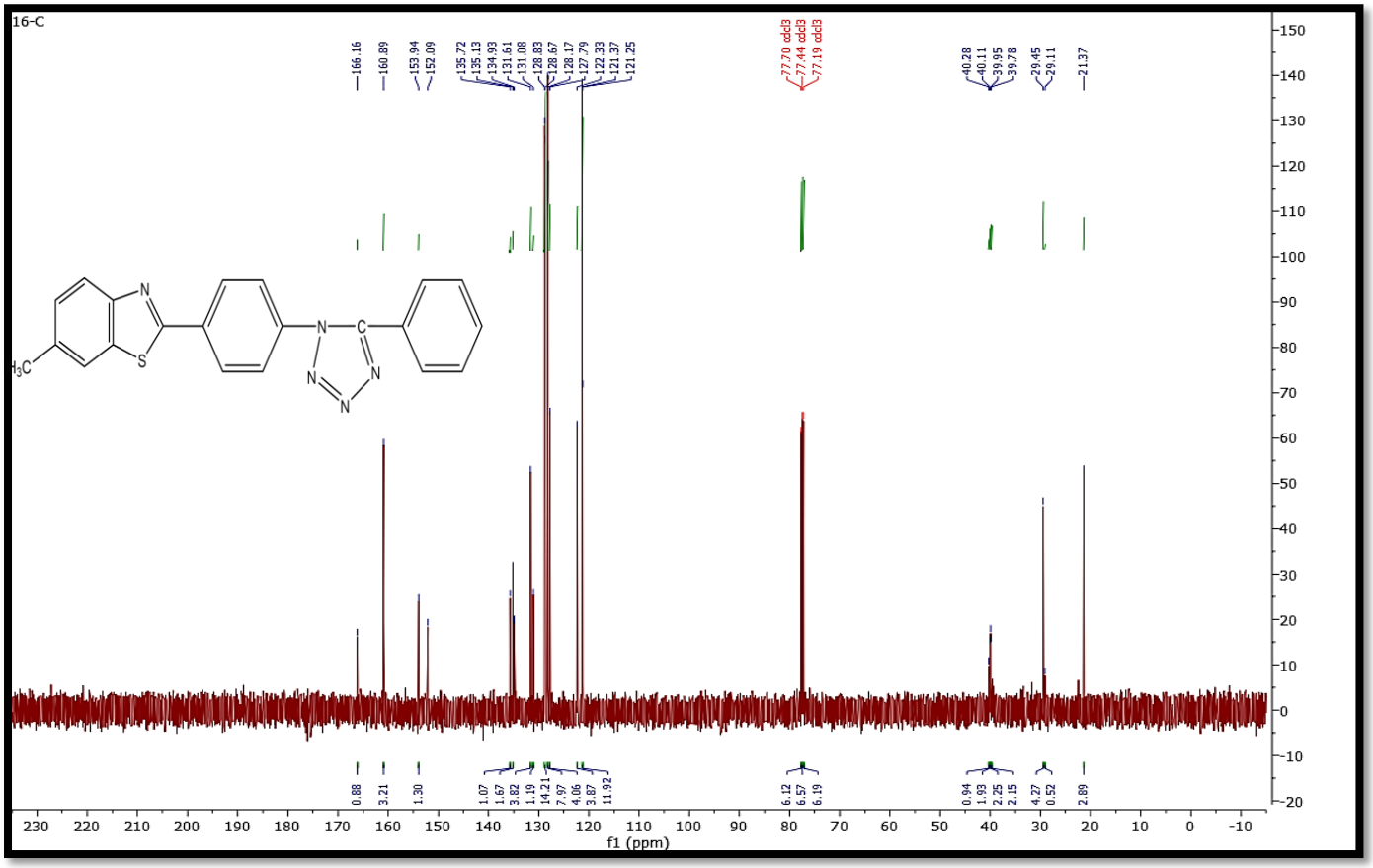


Figure 7: ^{13}C-NMR spectrum of compound (8)

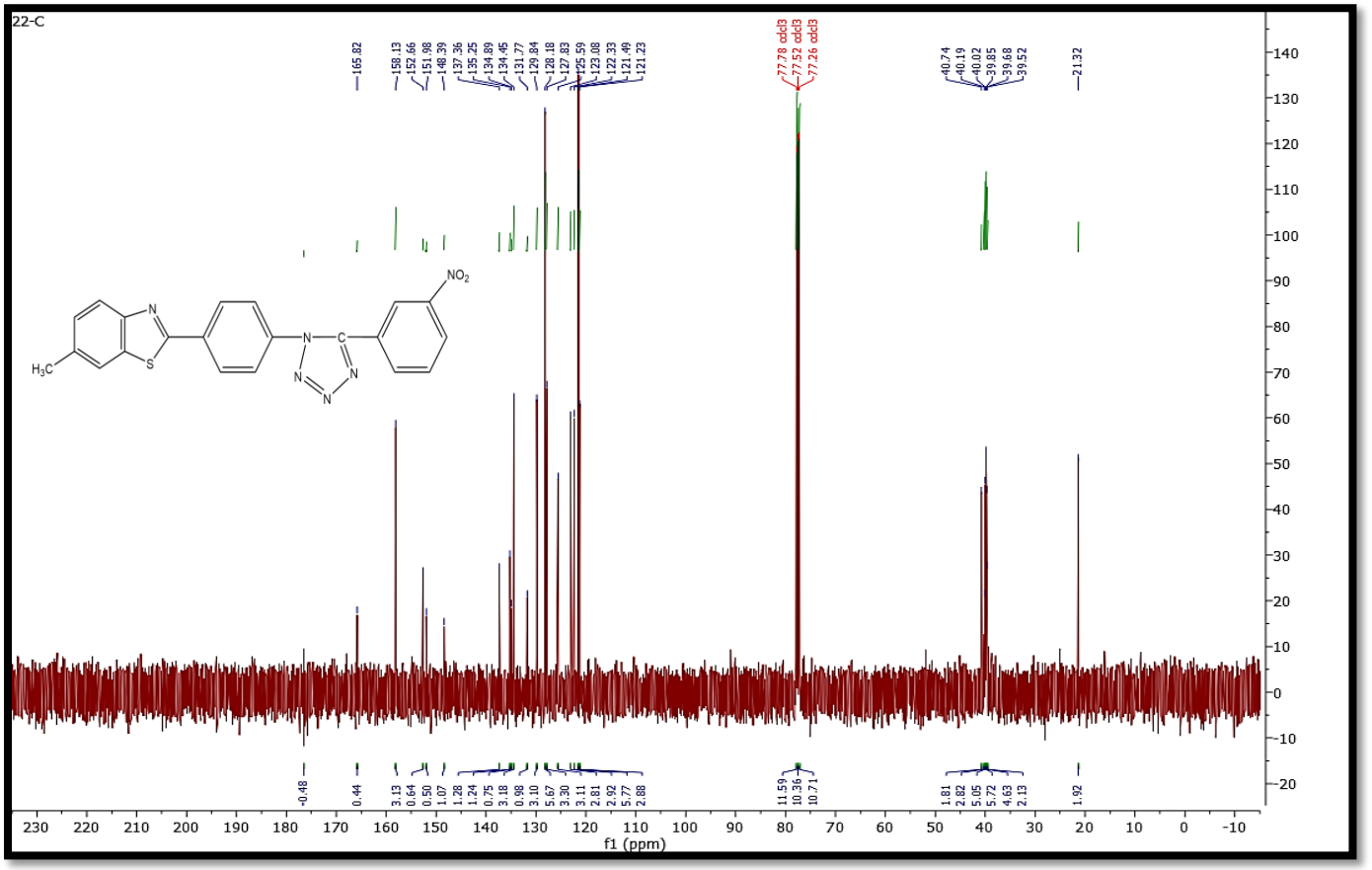


Figure 8: ^{13}C-NMR spectrum of compound (13)

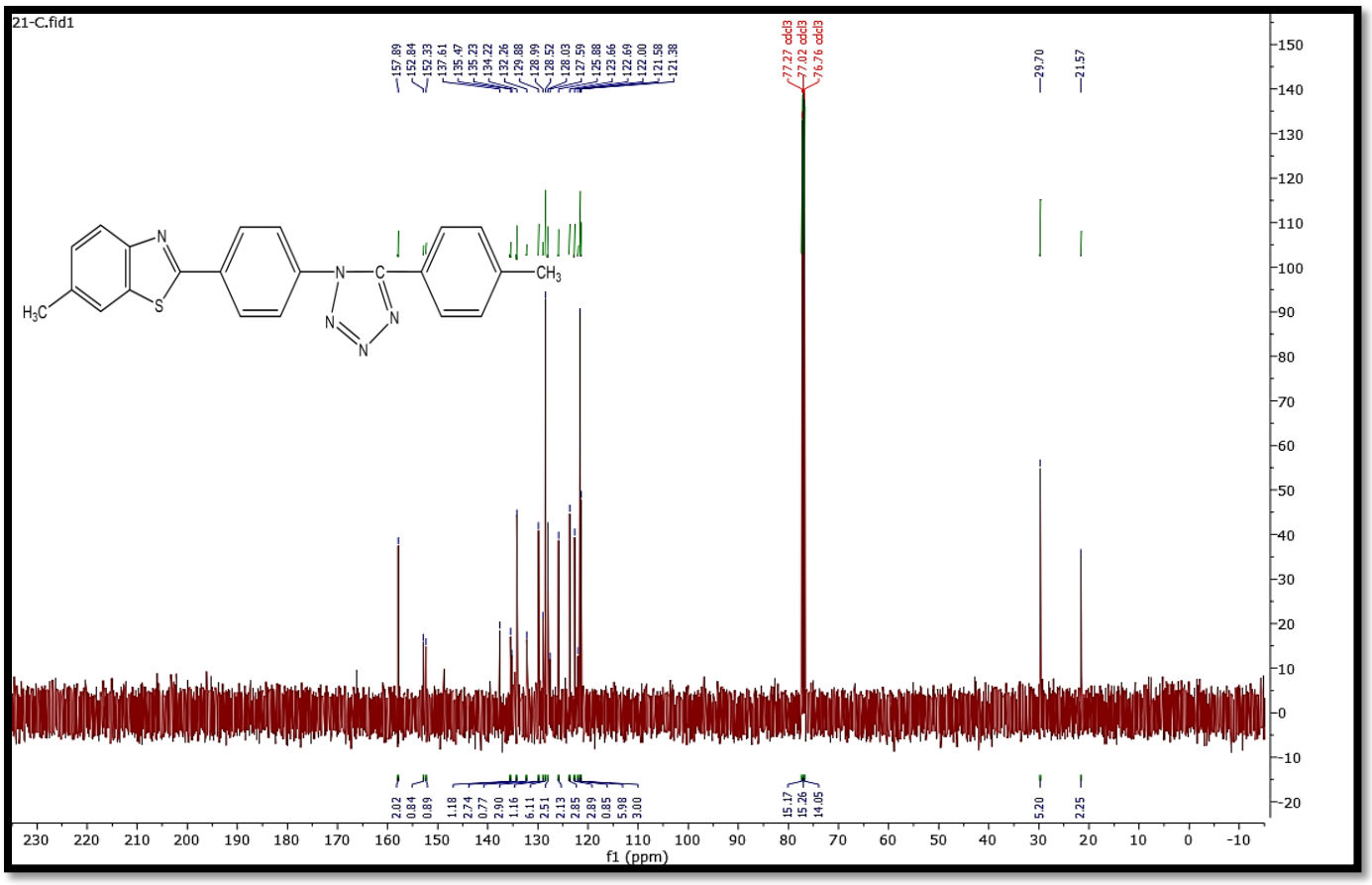


Figure 9: ^{13}C-NMR spectrum of compound (14)

3.4 BIOLOGICAL ACTIVITY

The antibacterial activities for synthesized tetrazole derivatives were determined by the agar diffusion method, which the zone of inhibition was measured in mm. The synthesized tetrazole compounds were tested against the ***Staphylococcus aureus*** **(Gram +ve)** bacteria and ***Escherichia coli*** **(Gram -ve)** bacteria. The synthesized compounds (8-14) were effective against the ***Staphylococcus aureus*** and ***Escherichia coli*** bacteria, among them 6-methyl-2-(4-(5-(phenyl)-tetrazol-1-yl)phenyl) benzothiazole (8) and 6-methyl-2-(4-(5-(4-bromo phenyl)-tetrazol-1-yl)phenyl) benzothiazole (11) have a very good inhibition action on the cultured bacteria's media ***Staphylococcus aureus***. The antibacterial activity of these compounds (8-14) is shown in **Table (3)** and figures 10 and 11.

Table (3): The antibacterial activity of the synthesized tetrazole derivatives, the inhibition zone diameters in (mm) scale against two strains of bacteria.

Compounds	Zone of inhibition in mm	
	Gram + ve Staphylococcus aureus	Gram – ve Escherichia coli
8	+ + +	+
9	+	+
10	+	+
11	+ + +	+ +
12	+	+

13	+ +	+
14	+	+

According to the reported procedure (Soliman, et al., 2018) highly active + + + (inhibition zone > 20 mm; moderately active + + (inhibition zone 16-19 mm); slightly active + (10-15 mm).

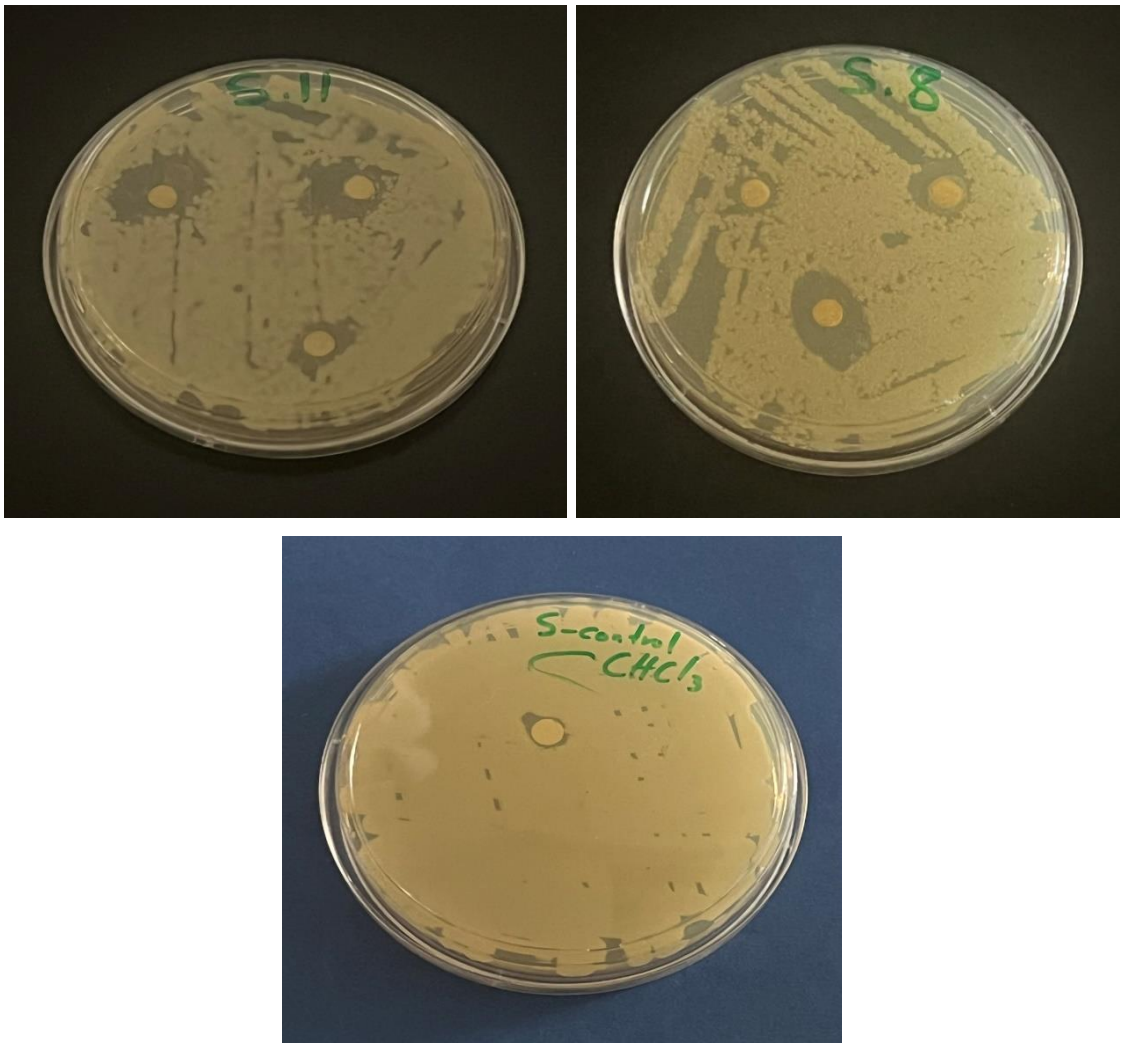


Figure 10: Anti-bacterial activities of the synthesized tetrazoles against *Staphylococcus aureus* as Gram positive

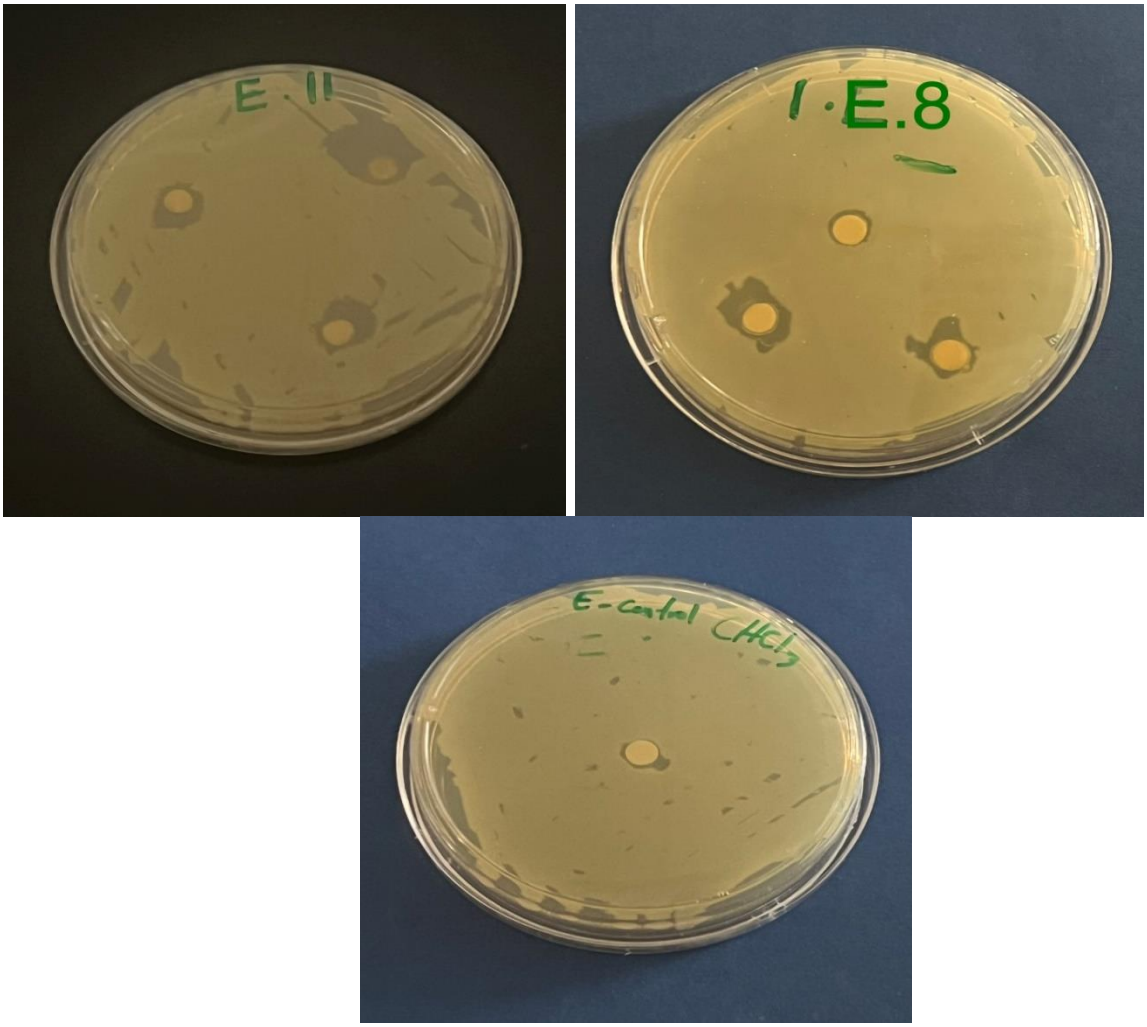


Figure 11: Anti-bacterial activities of the synthesized tetrazoles against *Escherichia-coli* as Gram-negative

4. CONCLUSION

In this work, the synthetic route was designed to prepare 6-methyl-2-(4-(5-(substituted phenyl)-tetrazol-1-yl)phenyl) benzothiazole by using practical method and simple way to obtain desire product. The synthesized tetrazole compounds characterized by different chemical techniques such as FTIR, ^{13}C-NMR and ^{1}H-NMR melting points and physical properties. The biological activity for all heterocyclic of synthesized tetrazole derivatives were studied against two different types of bacteria, ***Staphylococcus aureus*** and ***Escherichia coli***.

ACKNOWLEDGMENT

The authors sincerely thank the department of chemistry/ Faculty of Science and Health/ Koya University for providing research requirements in this work. Authors are also thankful for Mr. Awara Khdir in the Biology Department helping in the biological study.

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