

Synthesis and Evaluation of Antibacterial Activity for Some New 1,5-Disubstituted Tetrazoles Containing Benzothiazole and Thiadiazole moieties

تحضير و تقييم الفعالية ضد البكتريا لبعض مشتقات التترازول ثنائية التعويض في المواقع 1،5 الحاوية على وحدتي البنزوثيازول و ثياديازول

Zeid Hassan Abood* and Nooralhuda Mohammed Abdul Hussain
Chemistry Department, College of Science, University of Kerbala,
Kerbala, Iraq.

*Corresponding author: E-mail: zeid.ab2013@yahoo.com

البحث مستل

Abstract

In this work new 1,5-disubstituted tetrazoles containing 1,3,4-thiadiazole, benzothiazole moieties and azo group have been synthesized. At first, 2-aminobenzothiazole was converted to the corresponding azoaldehyde derivatives **1** via coupling reaction of its diazonium salt with 2-hydroxybenzaldehyde, which dissolved in sodium hydroxide solution, as coupling reagent. Next, the resulting azoaldehyde derivative **1** was introduced in acid-catalyzed condensation reactions with both 2-amino-5-mercapto-1,3,4-thiadiazole and 2-aminobenzothiazole to give two azoimine derivatives **2** and **3** containing 1,3,4-thiadiazole and benzothiazole moieties, respectively. Later, the resulting azoimines **2** and **3** were introduced in [3+2] cycloaddition reactions with sodium azide in tetrahydrofuran to obtain two new 1,5-disubstituted tetrazoles **4** and **5**, respectively. The structures of new synthesized tetrazoles have been confirmed using the spectroscopic means including FT-IR, ¹H NMR and Mass. The new synthesized tetrazoles have been tested for their antibacterial activity against two types of bacteria, *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative), The results indicated that both synthesized tetrazoles showed medium activity against Gram-positive bacteria. On the other hand, both tetrazoles showed no effect against Gram-negative bacteria.

Keywords: 2-aminobenzothiazole, Azoimines, [3+2] cycloaddition, 1,5-disubstituted tetrazoles

الخلاصة:

في هذا العمل تم تحضير مشتقي تترازول جديدين ثنائيي التعويض في المواقع 1،5 الحاويين على وحدتي 1،3،4-ثياديازول و البنزوثيازول و مجموعة الازو. في البداية تم تحويل المركب 2-امينوبنزوثيازول الى مشتق الازو الديهايد المقابل **1** عن طريق تفاعل الازدواج ما بين ملح الدايازونيوم لهذا الامين ومركب 2-هيدروكسي بنزالديهايد المذاب في محلول هيدروكسيد الصوديوم ككاشف ازدواج. تم بعد ذلك ادخال مشتق الازو الديهايد الناتج **1** في تفاعلات تكثيفية محفزة بحامض مع كل من 2-امينو-5-مركبتو-1،3،4-ثياديازول و 2-امينوبنزوثيازول على التوالي في الايثانول المطلق فتم الحصول على مشتقي الازوايمين **2** و **3** الحاويين على وحدتي 1،3،4-ثياديازول و البنزوثيازول. تم ادخال مشتقي الازوايمين الناتجين **2** و **3** لاحقا و على التوالي في تفاعلات الاضافة الحلقية [3+2] مع ازيد الصوديوم في التتراهيدروفوران فتم الحصول على مشتقي التترازول **4** و **5** الثنائية التعويض في المواقع 1،5. شخص تركيب كل من مشتقي التترازول الجديدين المحضرين بواسطة الطرائق الطيفية المتضمنة مطيافية الأشعة تحت الحمراء والرنين النووي المغناطيسي للبروتون بالاضافة الى مطيافية الكتلة. تم فحص الفعالية البايولوجية لمشتقي التترازول المحضرين ضد نوعين من البكتريا هما (*Staphylococcus aureus*) الموجبة لصبغة كرام و (*Escherichia coli*) السالبة لصبغة كرام، وقد بينت نتائج الاختبار الاولى بأن كلا المشتقين أظهرتا فعالية تثبيطية متوسطة تجاه البكتريا الموجبة لصبغة كرام. من جهة اخرى , وجد أن كلا المشتقين لم يظهر اي تأثير تجاه البكتريا السالبة لصبغة كرام.

Introduction

Tetrazoles are a representative class of poly-aza-heterocyclic compounds, which consisting of a 5-membered ring of four nitrogen and one carbon atoms¹. The first tetrazole was prepared by the Swedish chemist Bladin² in 1885. Katritsky et al. synthesized 1,5-disubstituted tetrazoles in high yields from imidoylbenzotriazoles includes short reaction times and mild reaction conditions³. Tetrazoles are unknown in the nature the ring systems of tetrazoles are very resistant to reduction⁴. Tetrazoles are a class of heterocycles with a wide range of applications including nanomaterials⁵ and specialty explosives⁶. The tetrazoles are representative of active pharmacophores for several therapeutic active molecules such as antiallergic⁷, anti-inflammatory⁸, antibiotic⁹, antihypertensive¹⁰ and antitubercular agents¹¹. For example, the β -lactam antibiotics **A** of the cephalosporin¹² class is an example of drugs containing a 1,5-disubstituted tetrazole moiety. Losartan **B** is sartan derivatives that was the first nonpeptide angiotensin receptor antagonist to appear on the market followed by Valsartan **C** which include the regulation of blood pressure and volume homeostasis^{13,14}. Kaplancıklı¹⁵ et al. synthesized a new class of tetrazole-hydrazone derivatives including chloro-substituted phenyl moiety **D** to perform anticancer activity screening.

Azo compounds have been studied more than any other class of dyes due to their popular application, as biological activities¹⁶, pharmaceutical¹⁷, cosmetic¹⁸ and food¹⁹.

Benzothiazoles have been studied and found to have various chemical reactivity, biological and pharmacological activities such as anti-bacterial²⁰ and anti-fungal²¹. Benzothiazole nucleus containing molecules are also reported as anti-diabetic²², anti-tumor²³ and anti-inflammatory²⁴.

1,3,4-thiadiazoles have very interesting biological properties²⁵ and important applications in many pharmacological interest²⁶ and biological activities, such as anticancer²⁷, antimicrobial²⁸ and antifungal²⁹ activity.

The present work aims to synthesize two new 1,5-disubstituted tetrazoles containing the biologically active benzothiazole, thiadiazole moieties and azo group, then the antibacterial activity of them against *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative) will be tested.

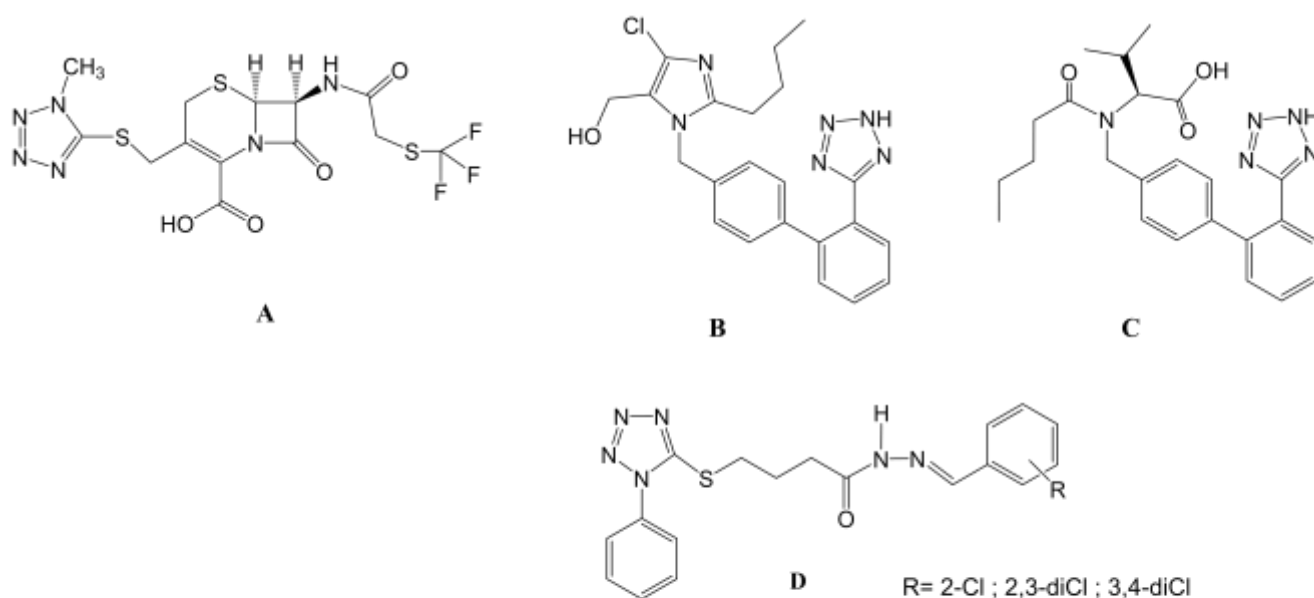


Fig-1: Some bioactive tetrazole derivatives

Experimental

General

All chemicals, reagents and solvents were purchased from Fluka, sigma aldrich, GCC, Merck and S.D.Fine, BDH, Scharlau and were used without further purification. Silica TLC plates were used with an aluminum backing (0.2 mm, 60 F₂₅₄). The reactions were monitored by TLC and visualized by development of the TLC plates with iodine vapor. Melting points were determined on an Electro thermal Stuart SMP 30 capillary melting point apparatus. Infrared spectra were recorded on SHIMADZU FTIR-8400S Infrared Spectrophotometer as potassium bromide discs. ¹H NMR spectra was collected on NMR spectrometer 400 MHz, Avance III 400 Bruker, Germany at 400 MHz in DMSO-*d*₆ as solvent and TMS as an internal standard at Esfahan University, Iran. Mass spectra were obtained on MS ACQUISITION PARAMETERS Agilent 5975c with Triple-axis direct insert probe SIS at Tehran University, Iran.

Synthesis of azoaldehyde derivative: (E)-5-(benzo[d]thiazol-2-yl diazenyl)-2-hydroxy benzaldehyde (1)

A solution of 2-aminobenzothiazole (8.1 g, 0.054 mol) in H₂SO₄ (12mL) was cooled to 0°C. To this solution a cold solution of sodium nitrite (3.726 g, 0.054 mol) dissolved in distilled water (20 mL) was added drop wise with constant stirring. When the addition was completed, the resultant reaction mixture was left in ice-chest for 1h. The ice cold solution of diazonium bisulfate was then added drop wise to the cold solution of 2-hydroxy benzaldehyde (6.588 g, 0.054 mol) dissolved in (44 mL) of (10% w/v) sodium hydroxide with constant shaking. A dark dye resulted which darkened on adding more alkaline solution of phenol derivative. When the addition was completed, the resultant reaction mixture was vigorously stirred and filtered off. A saturated solution of the last compound in water was neutralized with concentrated hydrochloric acid. A solid separated out which was allowed to stand at room temperature for 30 min., then filtered off, washed well with distilled water and recrystallized from ethanol³⁰. Table-1 shows some physical properties and other characteristics for the synthesized azoaldehyde derivative 1.

Synthesis of azoimine derivative: 4-((E)-benzo[d]thiazol-2-yl diazenyl)-2-((E)-((5-mercapto-1,3,4-thiadiazol-2-yl)imino)methyl)phenol (2)

Azoaldehyde derivative 1 (1.132 g, 0.004 mol) was dissolved in absolute ethanol (30 mL) containing two drops of glacial acetic acid, then equimolar amount (0.532 g, 0.004 mol) of 2-amino-5-mercapto-1,3,4-thiadiazole was added. The reaction mixture was refluxed with stirring on a water bath at 70 °C for 22 h and monitored by TLC. The mixture was then allowed to cool down to room temperature and the colored precipitate was filtered, then recrystallized from ethanol. Table-1 shows some physical properties and other characteristics for the synthesized azoimine derivative 2.

Synthesis of azoimine derivative: 4-((E)-benzo[d]thiazol-2-yl diazenyl)-2-((E)-(benzo[d]thiazol-2-ylimino) methyl)phenol (3)

Azoaldehyde derivative 1 (1.132 g, 0.004 mol) was dissolved in absolute ethanol (30 mL) containing two drops of glacial acetic acid, then equimolar amount (0.6 g, 0.004 mol) of 2-aminobenzothiazole was added. The reaction mixture was refluxed with stirring on a water bath at 70 °C for 32 h and monitored by TLC. The mixture was then allowed to cool down to room temperature and the colored precipitate was filtered, then recrystallized from ethanol. Table-1 shows some physical properties and other characteristics for the synthesized azoimine derivative 3.

Synthesis of 1,5-disubstituted tetrazole derivative: (E)-4-(benzo[d]thiazol-2-yl diazenyl)-2-(1-(5-mercapto-1,3,4-thiadiazol-2-yl)-1H-tetrazol-5-yl)phenol (4)

A mixture of imine derivative 2 (0.398 g, 0.001 mol) and sodium azide (0.065 g, 0.001 mol) in tetrahydrofuran (20 mL) was refluxed with stirring on a water bath at 70 °C for 24h and monitored by TLC. The reaction mixture was then allowed to cool down to room temperature. The solvent was removed by evaporation under reduced pressure and the colored precipitate was recrystallized from ethanol. Table-1 shows some physical properties and other characteristics for the synthesized 1,5-disubstituted tetrazole derivative 4.

Synthesis of 1,5-disubstituted tetrazole derivative: (E)-2-(1-(benzo[d]thiazol-2-yl)-1H-tetrazol-5-yl)-4-(benzo[d]thiazol-2-yl)diazenylphenol (5)

A mixture of imine derivatives **3** (0.4565 g, 0.001 mol) and sodium azide (0.065 g, 0.001 mol) in tetrahydrofuran (20 mL) was refluxed with stirring on a water bath at 70 °C for 35h and monitored by TLC. The reaction mixture was then allowed to cool down to room temperature. The solvent was removed by evaporation under reduced pressure and the colored precipitate was recrystallized from ethanol. Table-1 shows some physical properties and other characteristics for the synthesized 1,5-disubstituted tetrazole derivative **5**.

Table- 1 Some physical properties and other characteristics for the synthesized compounds **1-5**

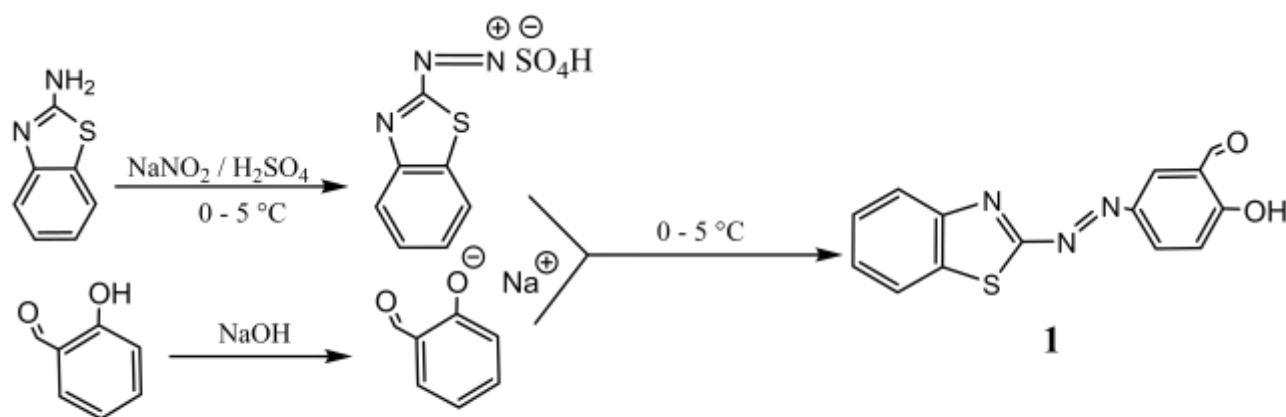
Product	Physical state	R _f (eluent)	Mp (°C)	Time (h)	Weight (g) / Yield (%)
1	Dark brown solid	0.68(<i>n</i> -hexane/EtOAc,1:3)	141-143	-	7.79/51
2	Brown solid	0.71(<i>n</i> -hexane/EtOAc,1:2)	198-200	22	1.3532/85
3	Brown solid	0.73(<i>n</i> -hexane/EtOAc,1:3)	204-206	32	0.83/50
4	Purple solid	0.58(<i>n</i> -hexane/EtOAc,1:2)	116-118	24	0.3863/88
5	Brown solid	0.60(<i>n</i> -hexane/EtOAc,1:2)	152-154	35	0.3762/75

Antibacterial test method

The antibacterial test has been carried out according to the disc diffusion method³¹. The synthesized 1,5-disubstituted tetrazoles **4** and **5** have been examined for their antibacterial activity in vitro against one type of Gram-positive bacteria (*Staphylococcus aureus*) and one type of Gram-negative bacteria (*Escherichia coli*). Prepared agar and petri dishes have been sterilized by autoclaving for 15 min. at 121°C. The agar plates have been surface- inoculated uniformly from both culture of the tested bacteria. In the solidified medium suitably spaced apart holes were made all 6mm in diameter. These holes were filled with 40 µL of the prepared compounds (5mg of the compound dissolved in 1mL of DMSO solvent). These plates have been incubated at 37 °C for 24 h for both bacteria. The zones of bacterial growth inhibition around the discs have been measured in (mm).

Results and Discussion

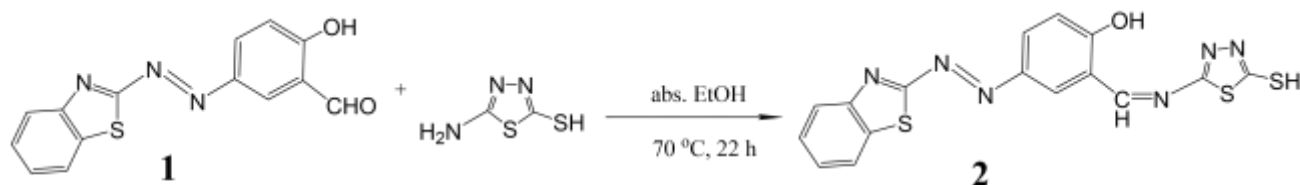
A coupling reaction between the diazonium salt of 2-aminobenzothiazole and 2-hydroxybenzaldehyde dissolved in sodium hydroxide solution at (0-5) °C afforded azoaldehyde derivative **1**. Scheme-1.



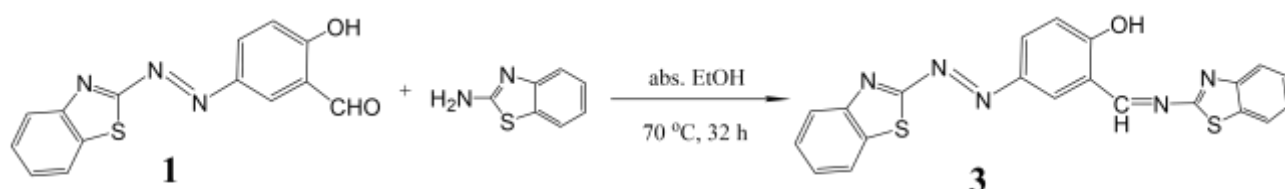
Scheme-1

FT-IR spectrum of azoaldehyde derivative **1**, figure-3 showed disappearance the sharp bands at 3398 cm^{-1} and 3273 cm^{-1} attributed to asymmetric and symmetric stretching vibrations of ($-\text{NH}_2$) group in 2-aminobenzothiazole, figure-2, also disappearing the sharp strong band at 1641 cm^{-1} for bending vibration of ($-\text{NH}_2$) group in the same compound and appearing strong band at 1651 cm^{-1} attributed to the stretching vibration of ($\text{C}=\text{O}$) group which gives good evidence that the reaction proceeded successfully and yielded the desired azoaldehyde **1**. The intramolecular hydrogen bonding between carbonyl group oxygen atom and *o*-hydroxy group causes a shifting in the stretching vibration of carbonyl group towards lower frequency. The band of azo group ($\text{N}=\text{N}$) stretching did not appear due to decrease the dipole moment value of this group in azoaldehyde derivative **1**. Other bands were listed in table-2.

A condensation reactions between azoaldehyde derivative **1** and the primary aromatic amines (2-amino-5-mercapto-1,3,4-thiadiazole and 2-aminobenzothiazole) respectively in the presence of glacial acetic acid as catalyst in absolute ethanol resulted formation of azoimines **2** and **3** as shown in schemes-2 and 3.



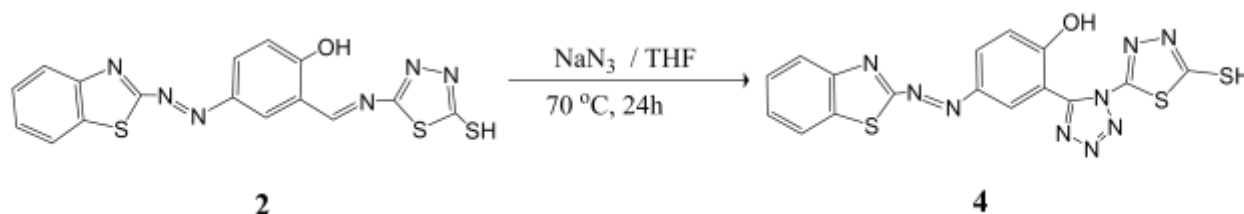
Scheme -2



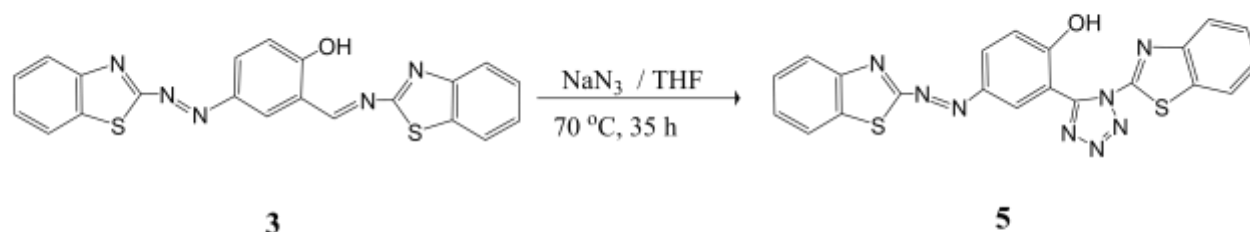
Scheme -3

FT-IR spectra, figures-4 and 5 of the synthesized azoimines **2** and **3** illustrate good evidence that the reactions happened successfully by disappearing the strong band at 1651cm^{-1} belong to the stretching vibration of (C=O) group and appearing medium band at lower frequency at 1622 cm^{-1} and 1602 cm^{-1} respectively attributed to the stretching vibration of imine group (C=N). Also, the spectra were devoid of the sharp bands for asymmetric and symmetric stretching vibrations of (-NH₂) group at the general range ($3400\text{-}3250\text{ cm}^{-1}$). Other characteristic bands with their interpretation were summarized in table-2.

The reaction of azoimine derivatives **2** and **3** with sodium azide in tetrahydrofuran produced a 1,5-disubstituted tetrazoles **4** and **5** respectively, as shown in schemes-4 and 5.

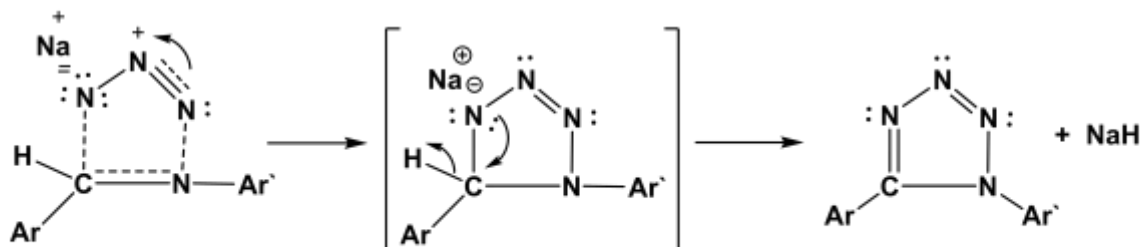


Scheme -4



Scheme -5

This reaction was classified as [3+2] cycloaddition. The common features of this type of reactions are best accommodated by the transition state geometry in which the dipolarophile molecule and its ligands lie in one plane, and the azide as a 1,3- dipolar group lies in a parallel plane above or below, so that the orbitals perpendicular to the planes interact to form bonds, as shown in Scheme-6³².



Scheme-6 The proposed mechanism for the formation of tetrazole ring

FT-IR spectra of the synthesized 1,5-disubstituted tetrazoles **4** and **5**, figures-6 and 7 showed disappearance of the medium band at 1622 cm^{-1} and 1602 cm^{-1} which is attributed to the stretching vibration of (C=N) group in azoimine derivatives **2** and **3**, respectively and appearance of broad strong band at lower frequency at 1564 cm^{-1} and 1566 cm^{-1} assigned to the stretching vibration of (C=N) inside tetrazole ring which is interacted with stretching vibrations of (C=C) and (C=N) in

benzene and benzothiazole rings respectively. Beside this, the FT-IR spectra of these derivatives were devoid of a strong band at 2133 cm^{-1} attributed to the stretching vibration of azide group in sodium azide. It is clear that FT-IR data refer to the successful proceeding of cycloaddition reactions and forming tetrazole ring. Other characteristic bands with their interpretation were summarized in table-2.

Table-2 FT-IR data of the synthesized compounds **1-5** in cm^{-1}

Com. no.	FT-IR bands
1	3269 _{br} ($\nu_{\text{O-H}}$), 3064 ($\nu_{\text{C-H}}$, benzene rings), 2868 and 2756 ($\nu_{\text{C-H}}$, aldehyde), 1651 ($\nu_{\text{C=O}}$), 1593 and 1464 ($\nu_{\text{C=C}}$, benzene rings and $\nu_{\text{C=N}}$, benzothiazole, vib. coupling), 750 ($\delta_{\text{o.o.p C-H}}$, benzene rings).
2	3273 ($\nu_{\text{O-H}}$), 3082 ($\nu_{\text{C-H}}$, benzene rings), 1622 ($\nu_{\text{C=N}}$), 1498 ($\nu_{\text{C=C}}$, benzene, $\nu_{\text{C=N}}$, thiadiazole and $\nu_{\text{C=N}}$, benzothiazole, vib. coupling), 1132 ($\nu_{\text{C=S}}$, thioketone form), 746 ($\delta_{\text{o.o.p C-H}}$, benzene rings).
3	3317 _{br} and 3182 _{br} ($\nu_{\text{O-H}}$), 3061 ($\nu_{\text{C-H}}$, benzene rings), 1602 ($\nu_{\text{C=N}}$), 1523 and 1454 ($\nu_{\text{C=C}}$, benzene and $\nu_{\text{C=N}}$, benzothiazole, vib. coupling), 748 ($\delta_{\text{o.o.p C-H}}$, benzene rings).
4	3406 _{br} ($\nu_{\text{O-H}}$ and $\nu_{\text{C-H}}$, benzene rings, vib. coupling), 1564 ($\nu_{\text{C=N}}$, tetrazole, $\nu_{\text{C=C}}$, benzene rings, $\nu_{\text{C=N}}$, benzothiazole and $\nu_{\text{C=N}}$, thiadiazole, vib. coupling), 1408 ($\nu_{\text{N=N}}$), 756 ($\delta_{\text{o.o.p C-H}}$, benzene rings).
5	3417 _{br} ($\nu_{\text{O-H}}$ and $\nu_{\text{C-H}}$, benzene rings, vib. coupling), 1566 ($\nu_{\text{C=N}}$, tetrazole), 1440 ($\nu_{\text{C=C}}$, benzene rings and $\nu_{\text{C=N}}$, benzothiazole, vib. coupling), 1406 ($\nu_{\text{N=N}}$), 756 ($\delta_{\text{o.o.p C-H}}$, benzene rings).

^1H NMR spectra of the synthesized 1,5-disubstituted tetrazoles 4 and 5

^1H NMR spectrum of compound **4**, figure-8 appeared ten signals, overall integration = 9H, belong to seven nonequivalent types of aromatic protons in addition of phenolic (O-H) proton and S-H, N-H proton in each thiol and thione tautomeric forms, respectively as follow: δ (ppm) = 3.75 (s, 1H, S-H)³³, 7.24 (s, 1H, H_a), 7.39 (s, 1H, H_b), 7.53 (d, $J = 7.0\text{ Hz}$, 1H, H_c), 7.61 (s, 1H, H_d), 7.78 (s, 1H, H_e), 8.18 (s, 1H, H_f), 8.51 (s, 1H, H_g), 8.74 (s, N-H, thione form), 9.37 (s, 1H, O-H). The singlet signals of DMSO and absorbed H₂O in DMSO appeared at 2.52 ppm and 3.39 ppm, respectively.

^1H NMR spectrum of compound **5**, figure-9 showed ten signals, overall integration = 12H, attributed to nine nonequivalent types of aromatic protons in addition of phenolic (O-H) proton as follow: δ (ppm) = 7.06 (s, 1H, H_a), 7.26 (s, 1H, H_b), 7.43 (d, $J = 8.3\text{ Hz}$, 2H, 2H_c), 7.63 (s, 1H, H_d), 7.73 (s, 1H, H_e), 7.75 (d, $J = 7.4\text{ Hz}$, 2H, 2H_f), 7.94 (s, 1H, H_g), 8.14 (s, 1H, H_h), 8.5 (s, 1H, H_i), 9.47 (s, 1H, O-H). DMSO and absorbed H₂O in DMSO appeared singlet signals at 2.51 ppm and 3.41 ppm, respectively.

Mass spectra of the synthesized 1,5-disubstituted tetrazoles 4 and 5

The mass spectra of the synthesized 1,5-disubstituted tetrazoles **4** and **5**, figures-10 and 11, respectively, appeared the molecular ion peak at (m/z) value is equal to the corresponding calculated mass as indicated below:

Compound 4	Estimated molecular weight (g/mol) 439.49	Molecular ion mass (m/z) 439.45
Compound 5	Estimated molecular weight (g/mol) 456.50	Molecular ion mass (m/z) 456.40

Antibacterial activity

In this work, the antibacterial activity of the synthesized 1,5-disubstituted tetrazoles **4** and **5** has been tested. The results of antibacterial action have been described in table-3 and photographs of growth inhibition zones have been illustrated in figures-12 and 13.

Table-3 The antibacterial activity for synthesized 1,5-disubstituted tetrazoles **4** and **5**

Com. No.	<i>Staphylococcus aureus</i> (Gram-positive)	<i>Escherichia coli</i> (Gram-negative)
	Diameter of inhibition zone in (mm)	
Gentamycin as control drug (10 Mg/mL)	18	15
4 (5 Mg/mL)	13	0
5 (5 Mg/mL)	15	0

Highly active (inhibition zone > 15 mm)
Moderately active (inhibition zone 11-15 mm)

Conclusions

The cycloaddition reaction of imines with sodium azide has been considered a new general method for the synthesis of 1,5-disubstituted tetrazoles. The synthesized 1,5-disubstituted tetrazoles **4** and **5** have relatively high solubility in water. The synthesized 1,5-disubstituted tetrazoles have biological activity against Gram-positive bacteria only.

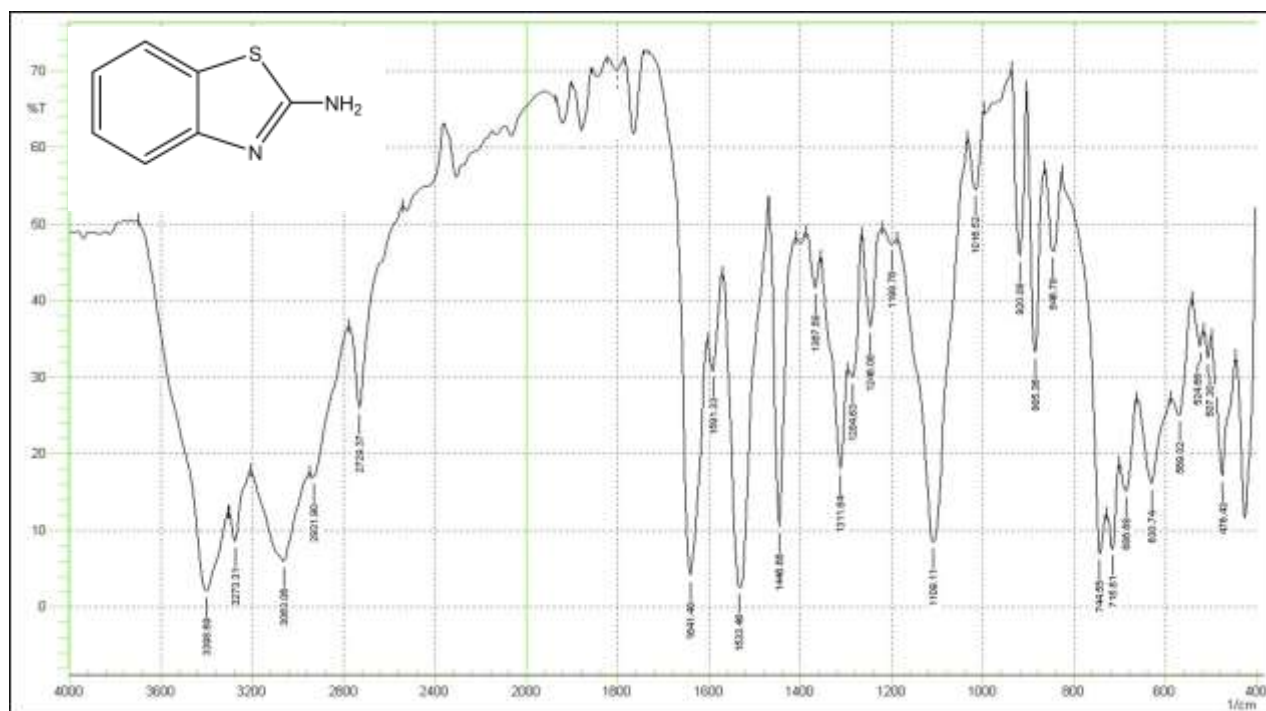


Fig-2: FT-IR spectrum of 2-Aminobenzothiazole

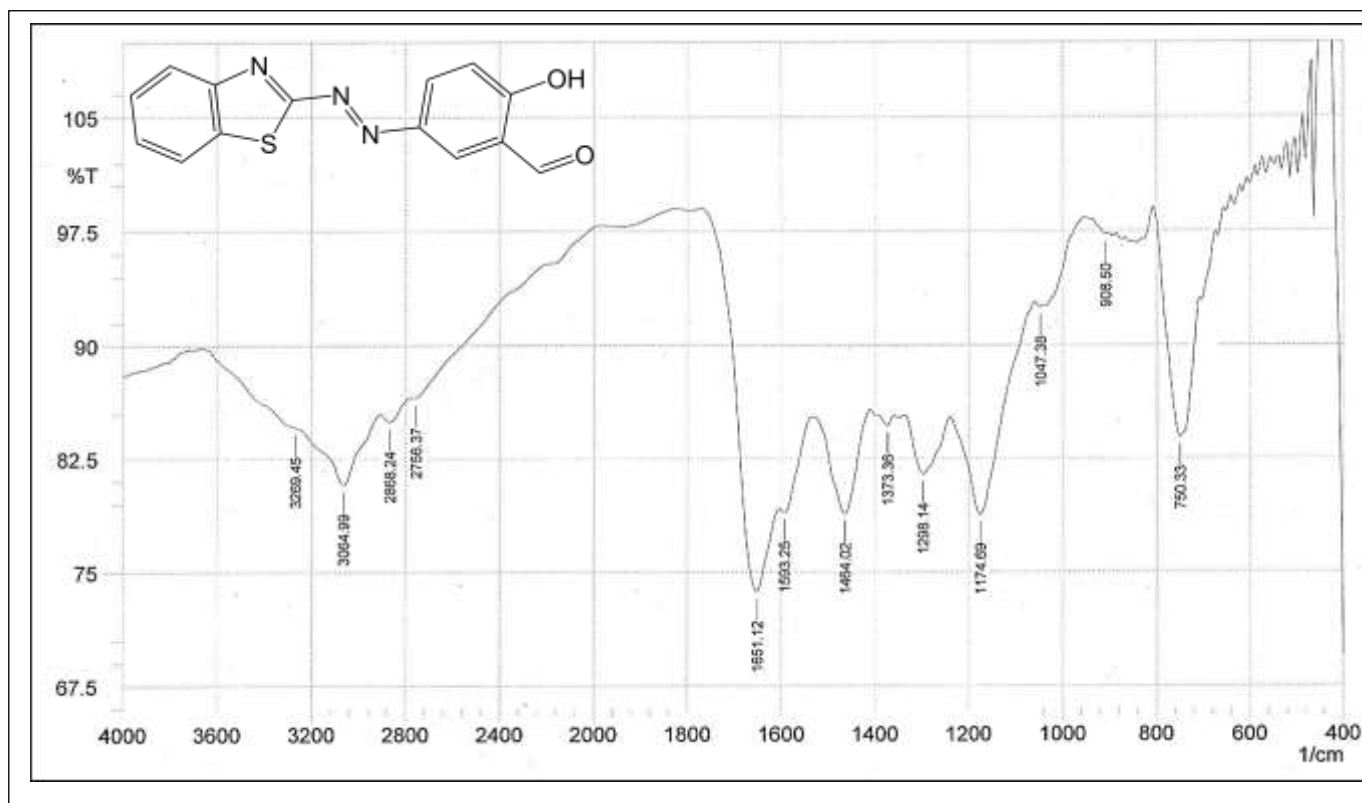


Fig-3: FT-IR spectrum of compound 1

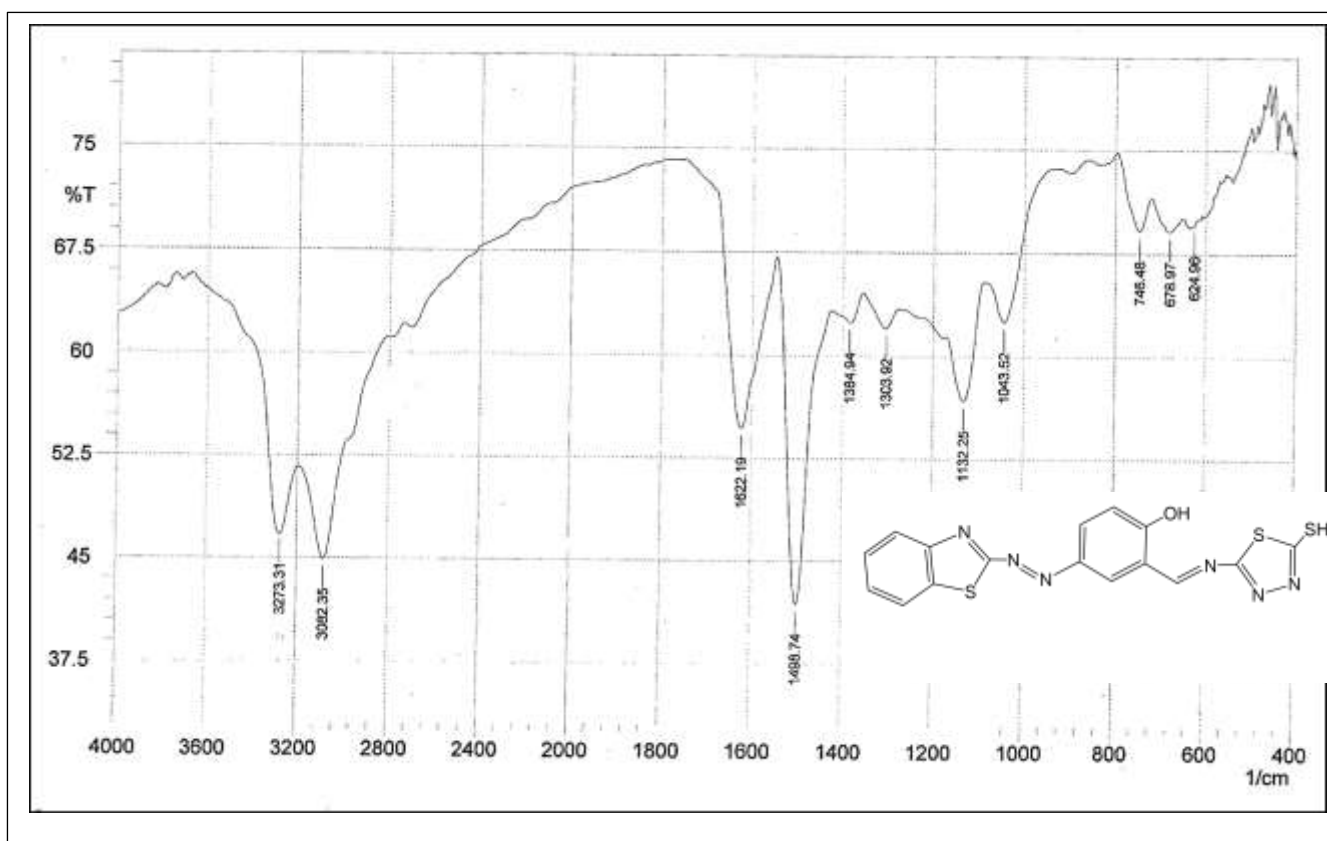


Fig-4: FT-IR spectrum of compound 2

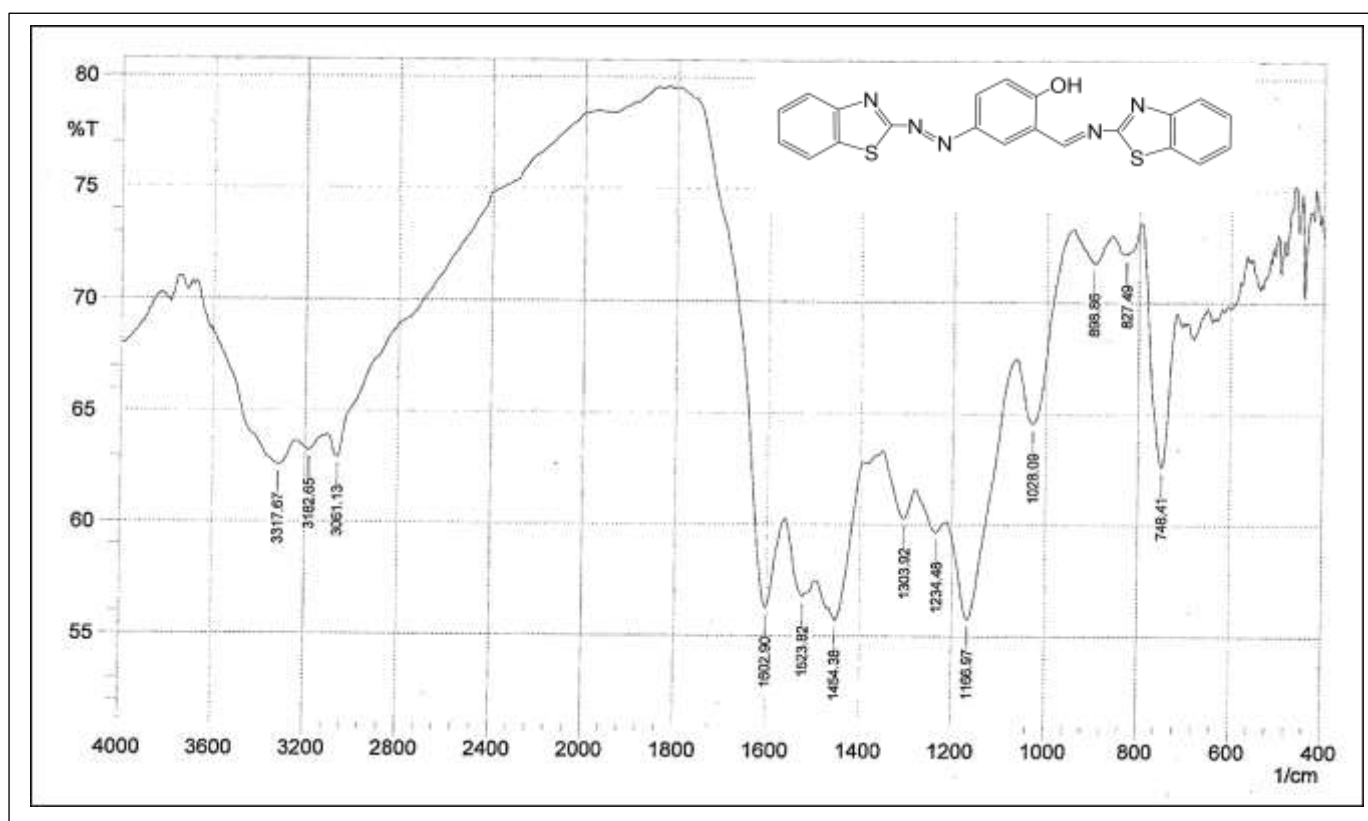


Fig-5: FT-IR spectrum of compound 3

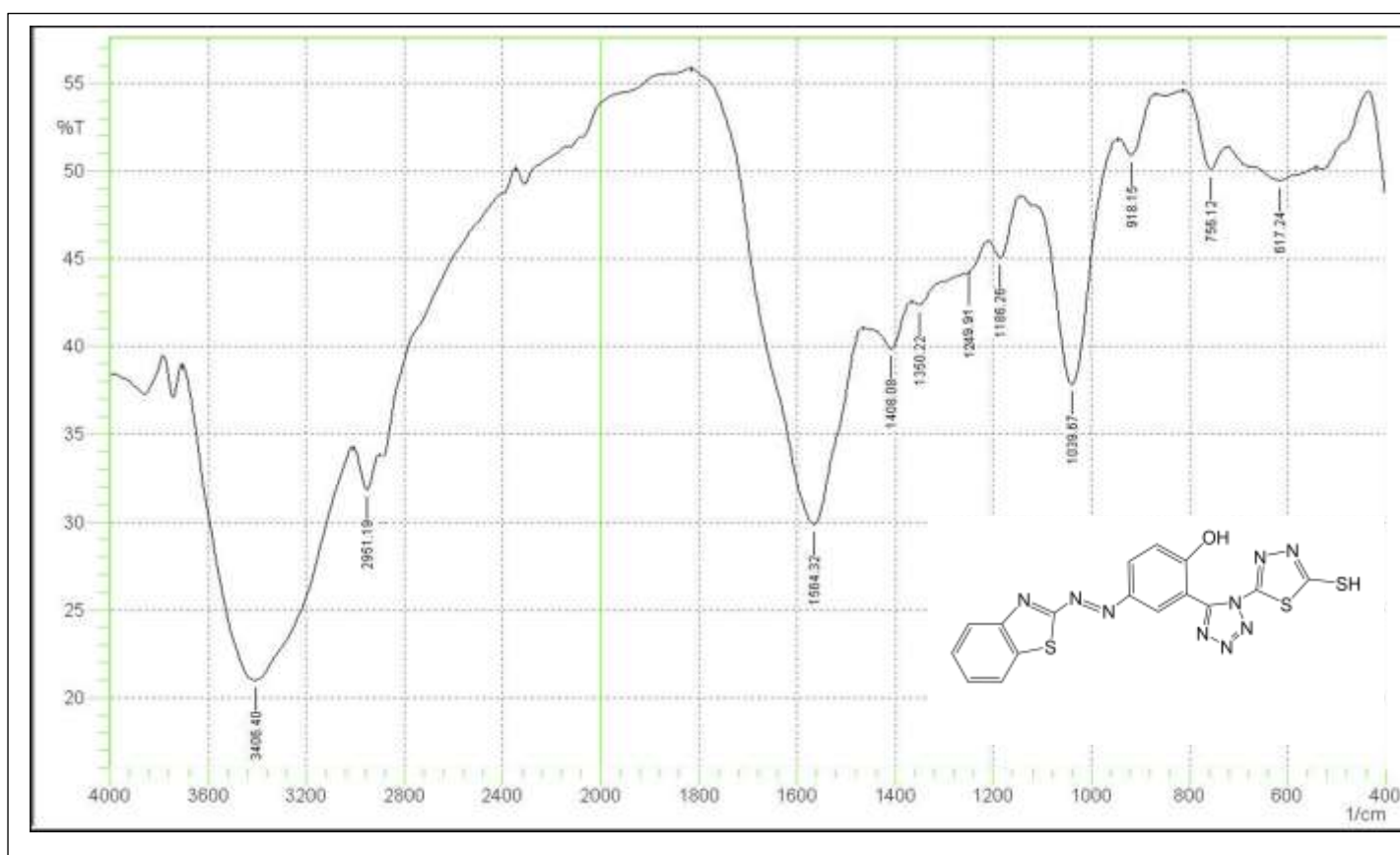


Fig-6: FT-IR spectrum of compound 4

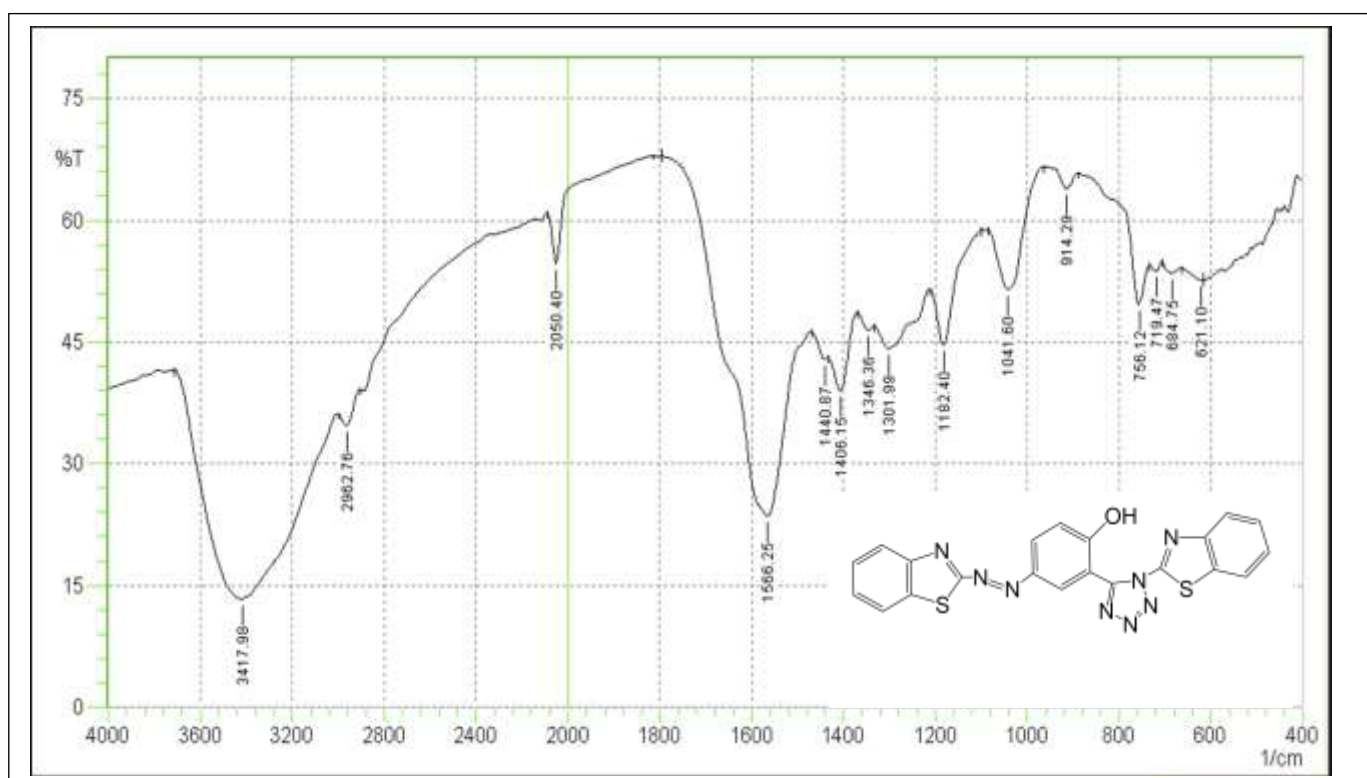


Fig-7: FT-IR spectrum of compound 5

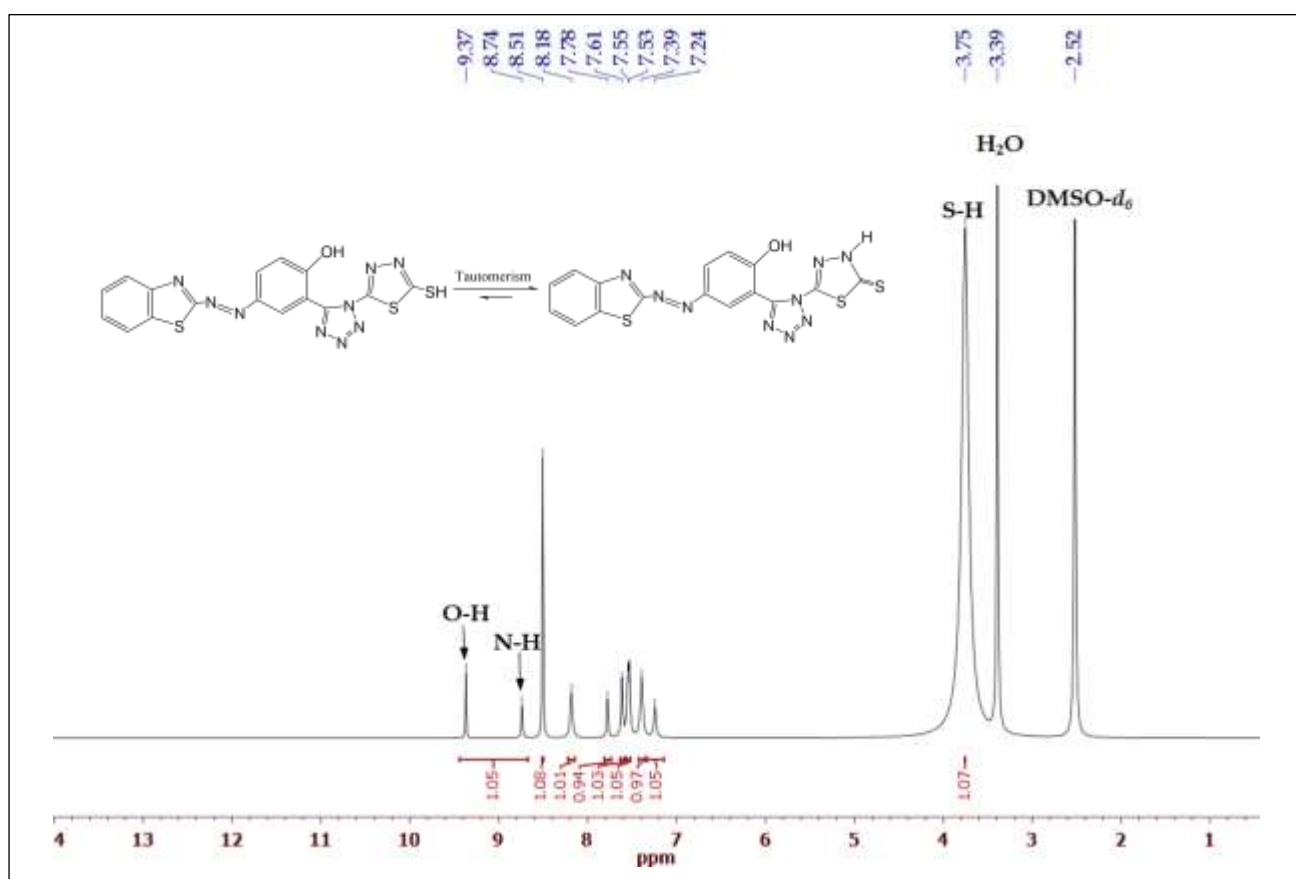


Fig-8: ^1H NMR spectrum of compound 4

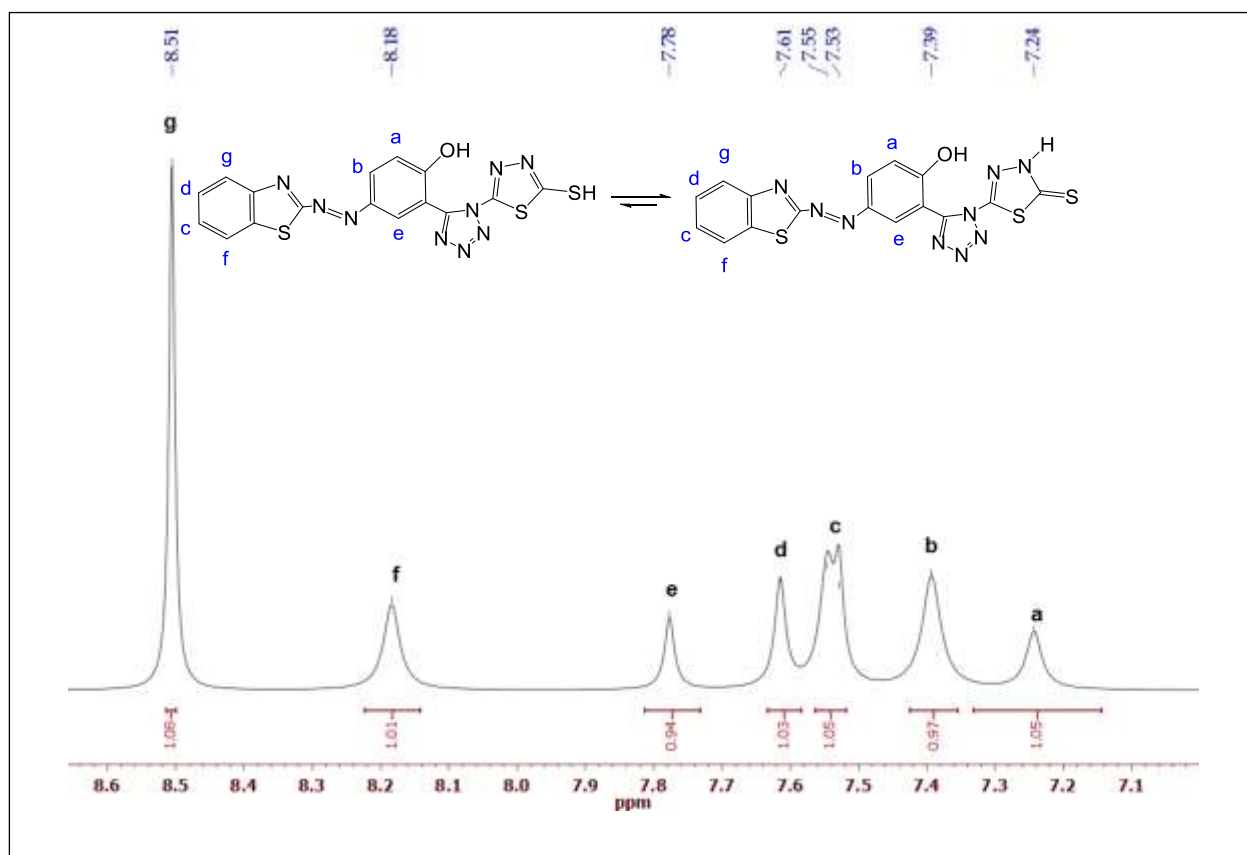


Fig-8a: Expanded ^1H NMR spectrum of compound 4 in ppm

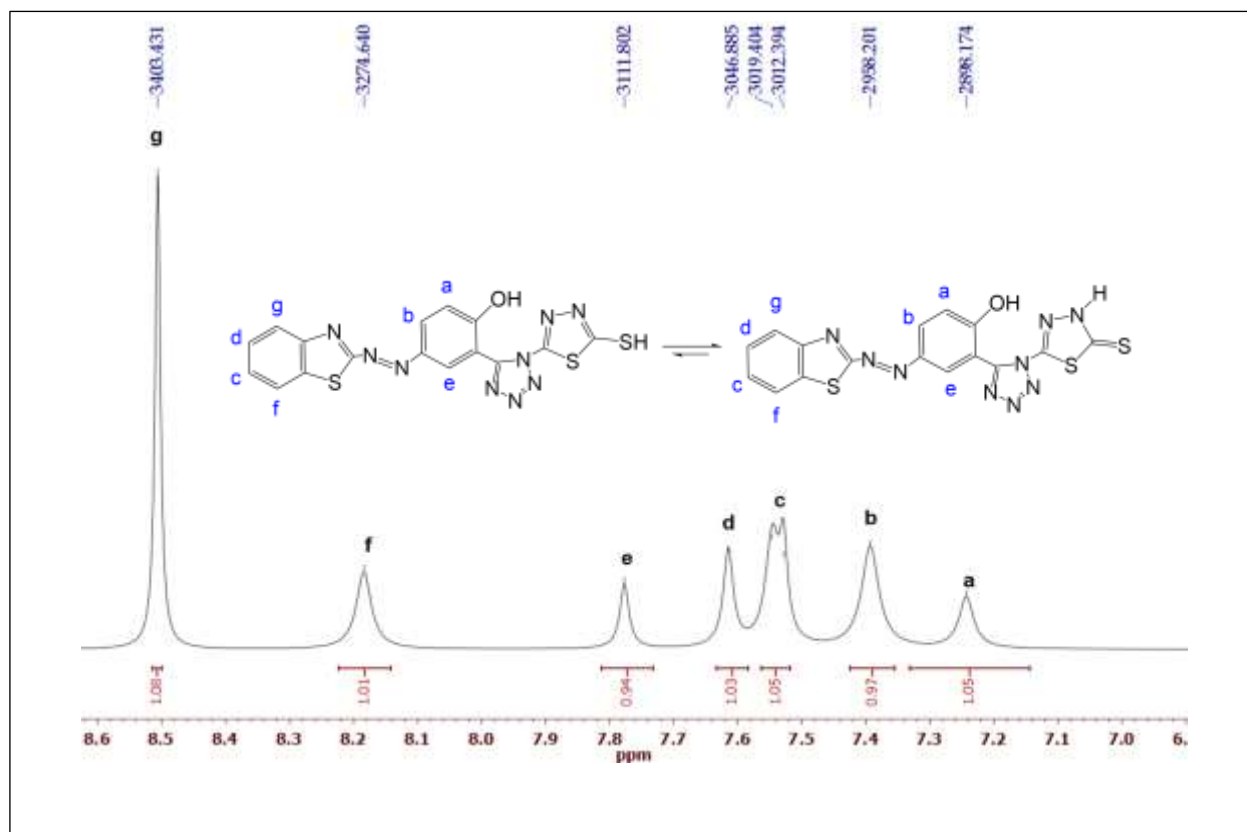


Fig- 8b: Expanded ^1H NMR spectrum of compound 4 in Hz

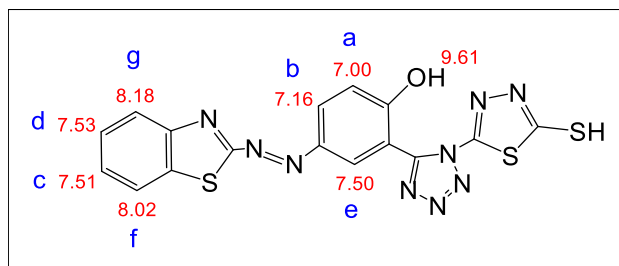


Fig- 8c: Theoretical δ (ppm) values of compound 4

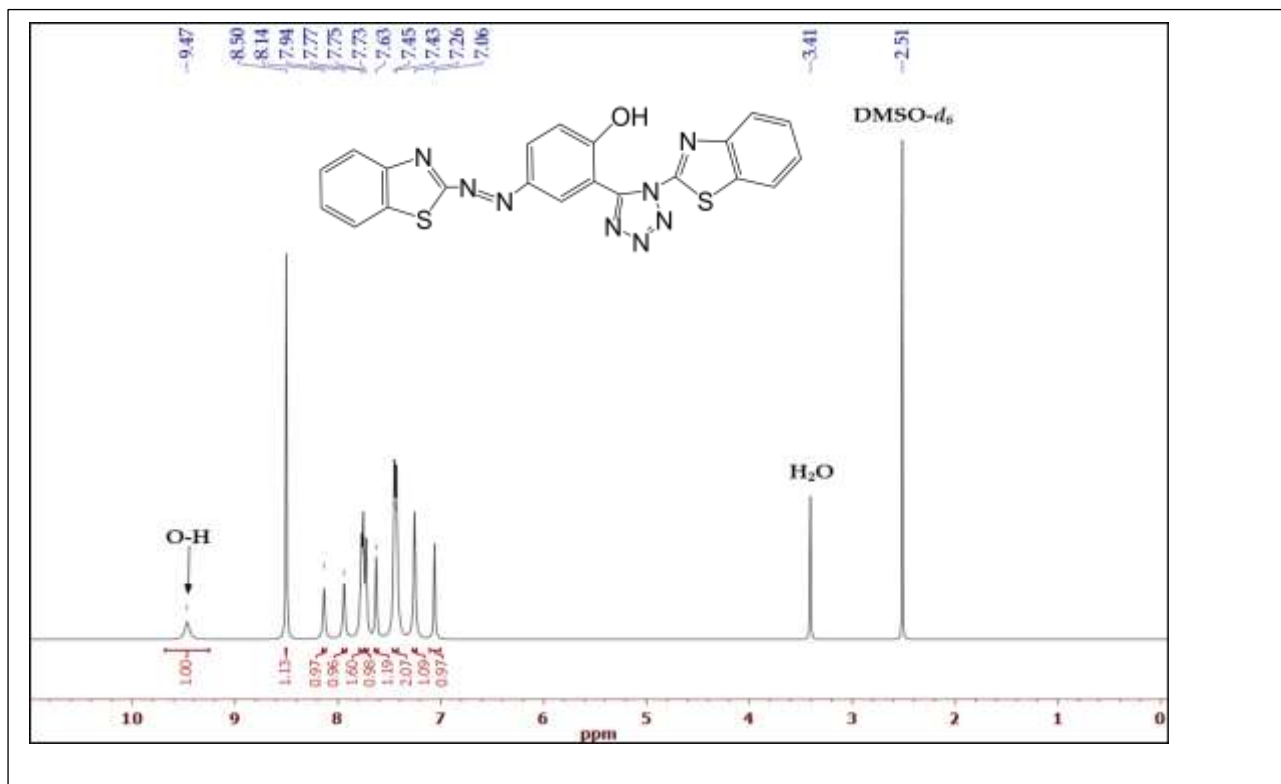


Fig-9: ^1H NMR spectrum of compound 5

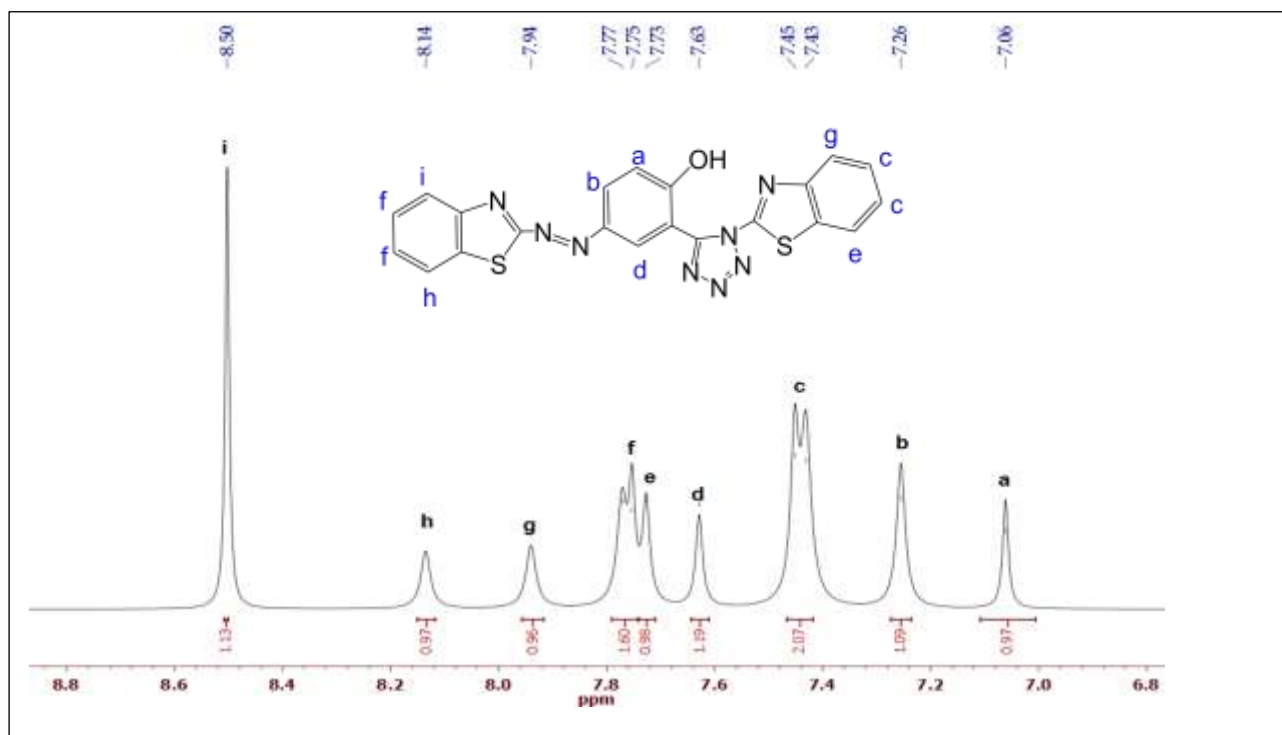


Fig-9a: Expanded ^1H NMR spectrum of compound 5 in ppm

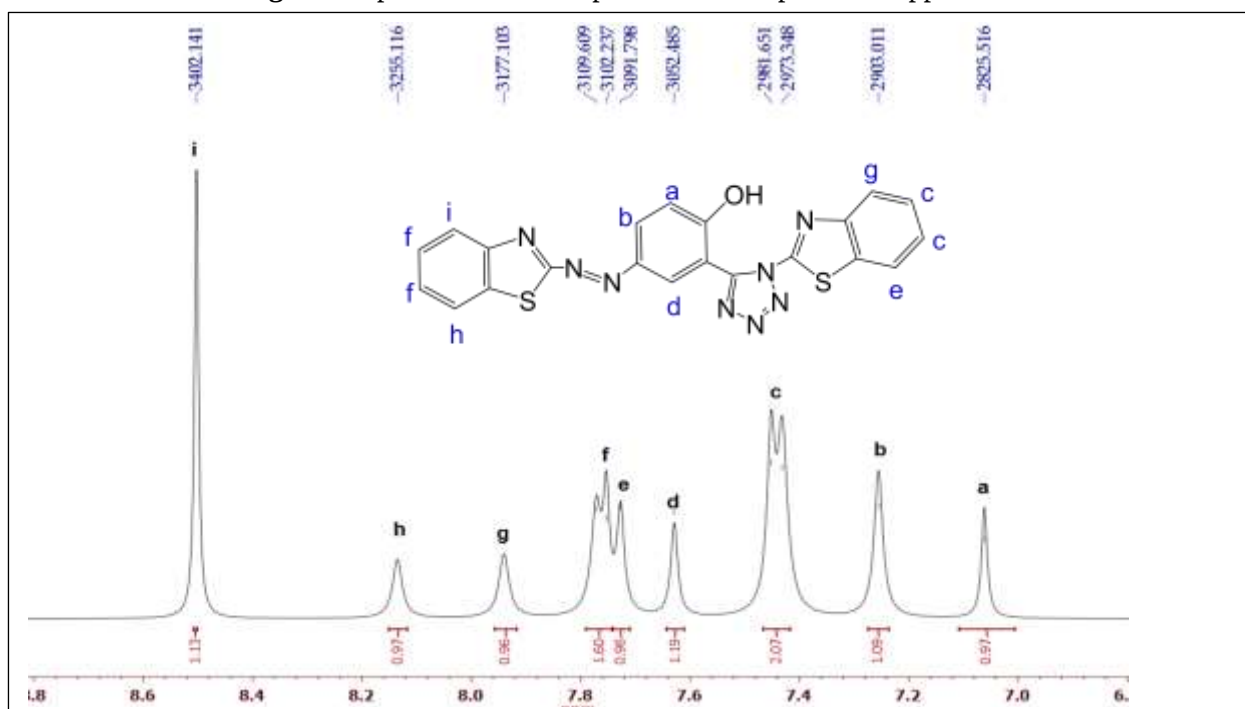


Fig-9b: Expanded ^1H NMR spectrum of compound 5 in Hz

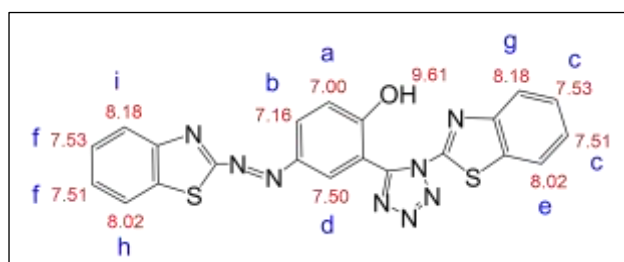


Fig-9c: Theoretical δ (ppm) values of compound 5

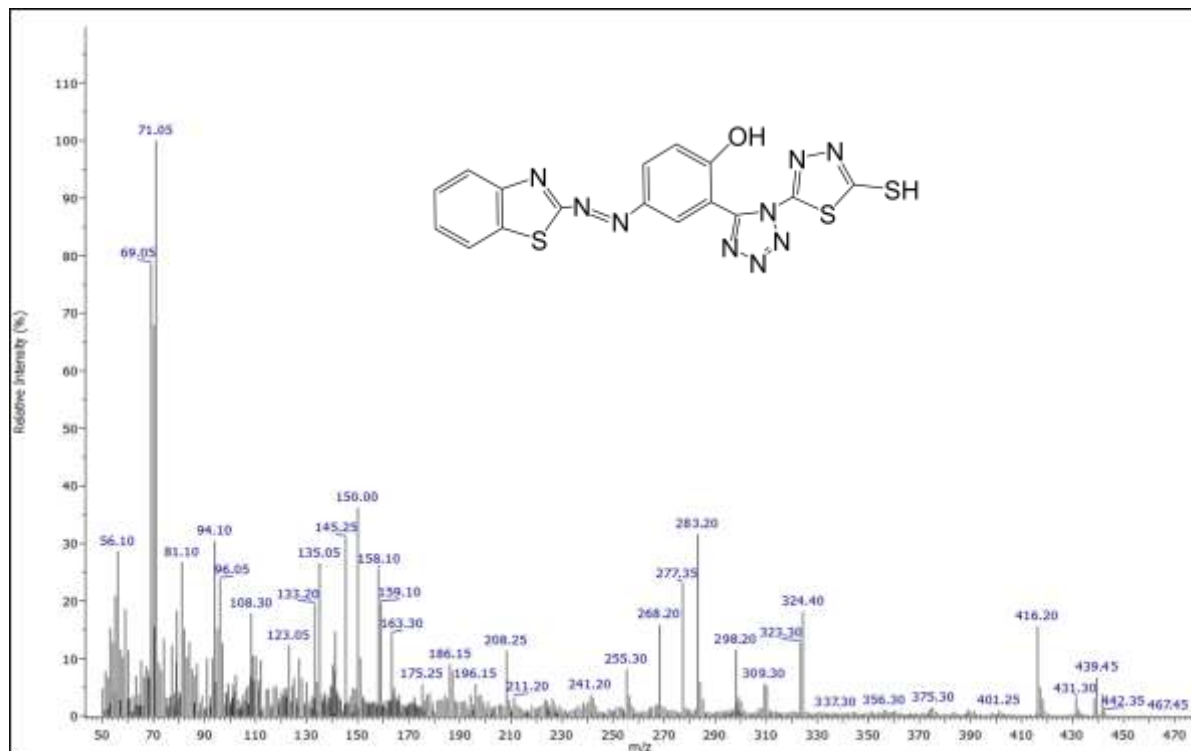


Fig-10: Mass spectrum of compound 4

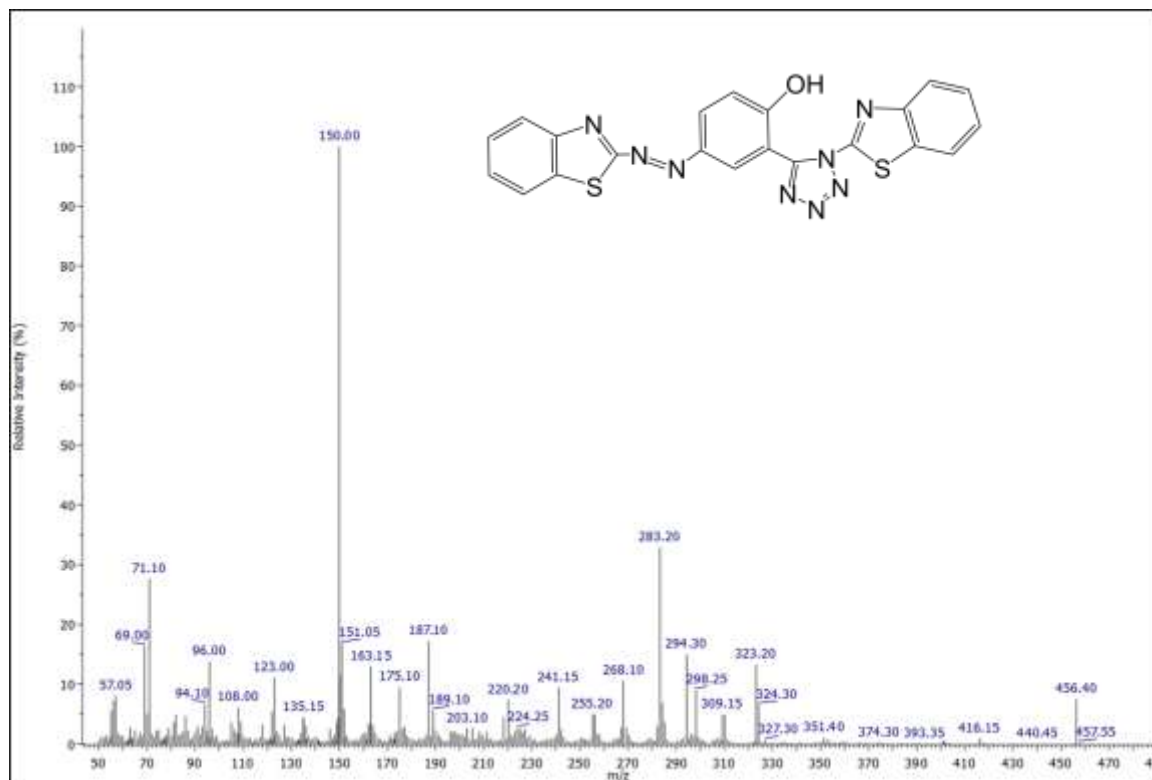


Fig-11: Mass spectrum of compound 5

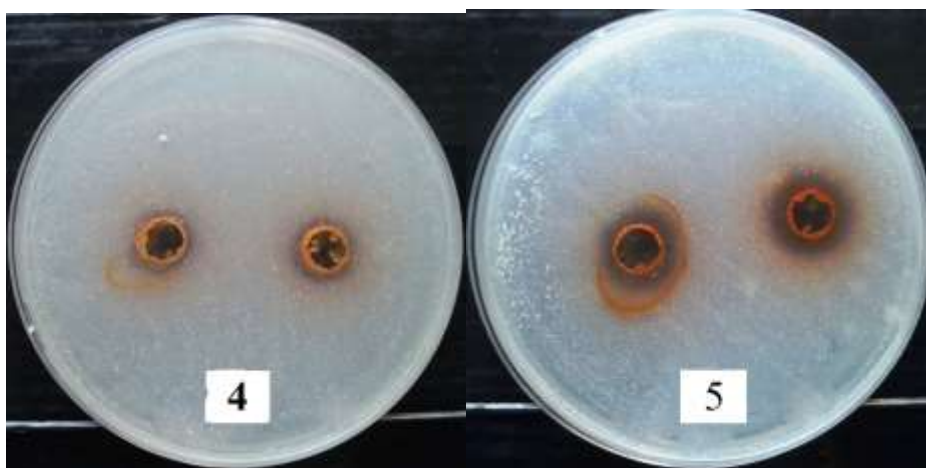


Fig-12: Antibacterial photographs of 1,5-disubstituted tetrazoles **4** and **5** against *staphylococcus aureus*

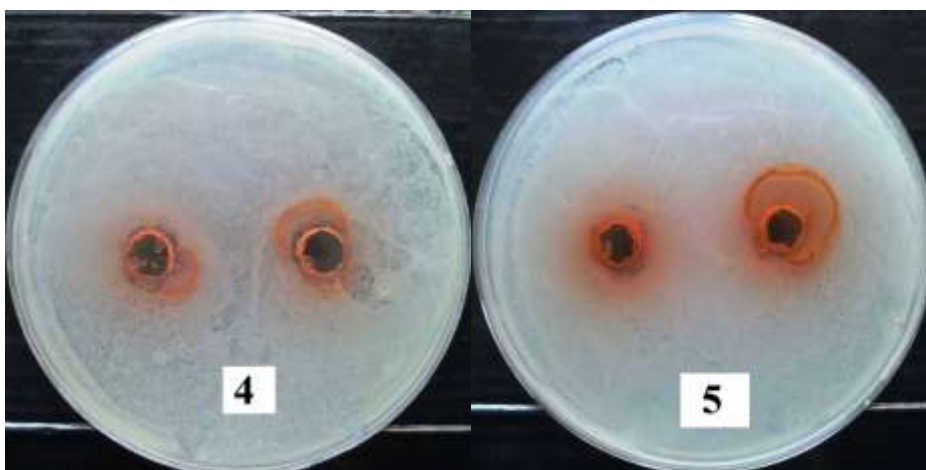


Fig-13: Antibacterial photographs of 1,5-disubstituted tetrazoles **4** and **5** against *Escherichia coli*

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