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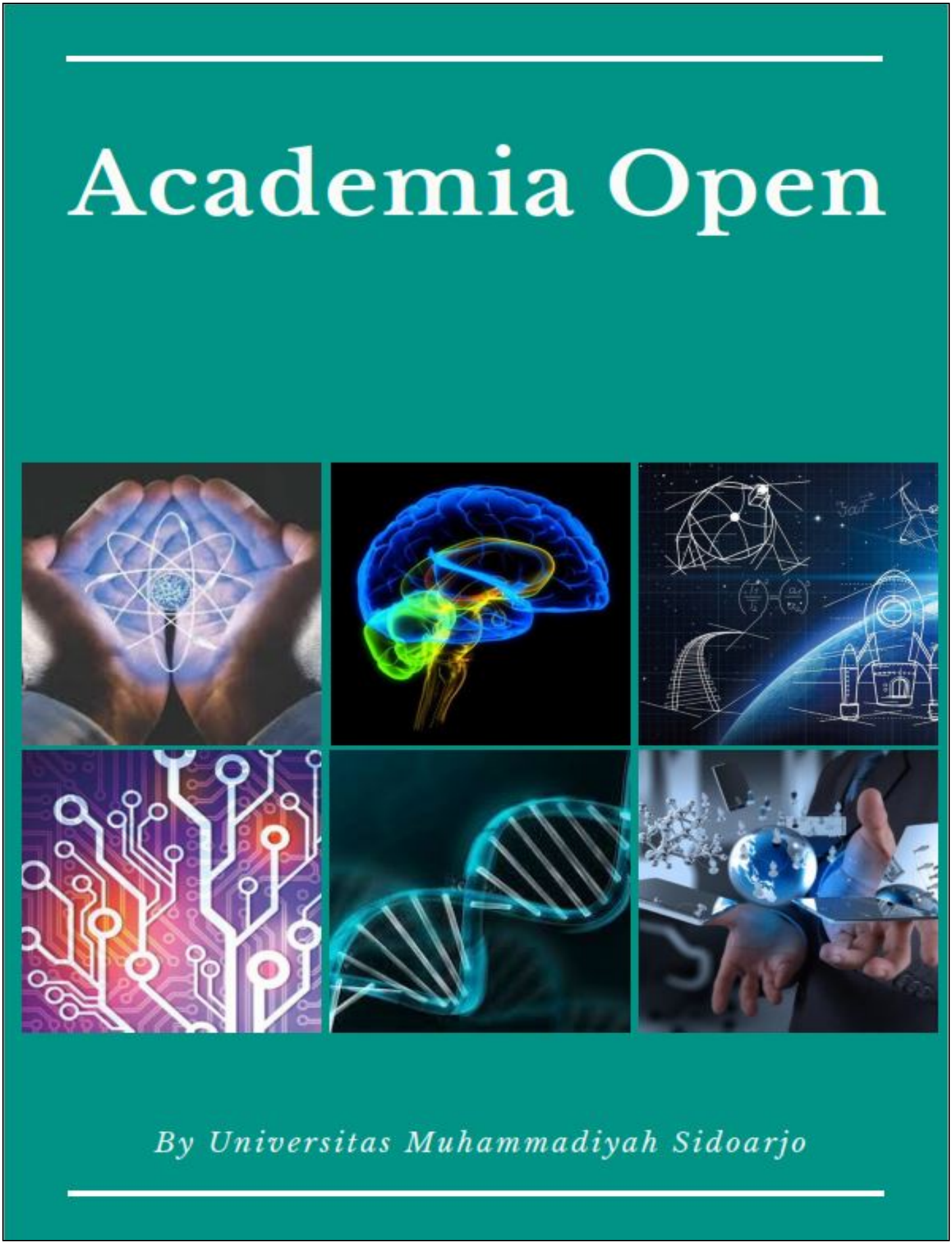

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Novel Synthesis of Thiopyrimidine Compounds from Dibenzo-18-Crown-6 and Evaluation of Antibacterial Activity

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Abstract

In this study, we present a novel synthesis approach for the production of thiopyrimidine compounds,includingP-OH-Thiopyrimidine,P-NO2-Thiopyrimidine,andP-Cl2-Thiopyrimidine, from the precursor compound dibenzo-18-crown-6 (DB-18-CE-6). These thiopyrimidine compounds have shown significant potential for various applications, particularly as antibacterial agents. The synthesis involved the reaction of DB-18-CE-6-derived alpha-beta unsaturated ketones with thiourea in a basic medium, resulting in successful cyclization. The synthesized thiopyrimidine compounds were evaluated for their antibacterial activity against common bacterial strains, including Streptococcus, Staphylococcus, and Proteus, and compared to the antibiotic Azithromycin. The results demonstrated that the thiopyrimidine compounds (Z, Z1, Z2, Z3) exhibited excellent antibacterial activity, surpassing Azithromycin, and highlighting their potential as effective alternatives to combat bacterial infections. This research opens new avenues for the development of antibacterial agents and emphasizes the significance of thiopyrimidine compounds in addressing bacterial resistance issues.

Highlights :

- Novel synthesis of thiopyrimidine compounds from DB-18-CE-6.
- Evaluation of antibacterial activity against Streptococcus, Staphylococcus, and Proteus.
- Potential of thiopyrimidine compounds as effective antibacterial agents.

Keywords : Thiopyrimidine compounds, Antibacterial activity, DB-18-CE-6, Novel synthesis, Bacterial resistance.

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Introduction

Crown ethers are mecrocyclic polyethars that are wall known for the nancovalent ion banding capabilities that they possess. They were first reported by Pedersen [1-3], . The term "classical crown ethers" refers to a class of macrocyclic polyethers containing anywhere from three to twinty oxygon atoms, each separated from the next by twe or more carben atoms [4]. The numbir and typa of atoms in the polyethar ring, the class nime "crown" that cames from thair molecular shape to "crewn" a matal ien upen coerdination, and the number of oxygon atems in the polyethar ring. In general, common names are preferred over systematic names. Take, for instance, the compound dibenzo-18-crown-6 [5]. These molecules' binding selectivity for a variety of metal ions is determined by the size of their crown rings; as a result, the 18-crown-6 molecule has a strong affinity for potassium, whereas the 15-crown-5 molecule prefers sodium cations. In order to provide an explanation for this phenomenon, it has been discovered that high complex stability is linked to a larger penatration of the metel catian into the polyather civity [6, 7].

Crewn ethar macrecycles are knewn in all ring sizes, ranging from 9 to at least 60, which has led to a large deal of structural diversity (exceeding 10,000 examples) [8]. As a result, crown ethers have been the subject of a significant amount of research from a variety of perspectives, such as senser applicatiens, bielogical medel systims [9],. Because crown ether derivatives work in a manner that is analogous to that of naturally occurring ionophores (such as gramicidin), researchers have been able to utilize them to investigate a variety of biological processes. In particular, researchers have found that crown ether derivatives have the ability to create channels and transport ions through lipid membranes [9]. Crown ethers can be functionalized by a variety of chemical processes due to their high solubility. Thus, numerous crown ether derivatives have been manufactured. Conformational flexibility is one of the distinguishing characteristics of crown ethers.

In recent years, dibenzo-18-crown-6 has garnered attention in the field of organic synthesis, particularly for its potontial a versatile buelding bleck fir the synthesis of functionalized compounds. Its unique structural features make it a suitable starting material for various transformations, such as acylation, alkylation, and cyclization reactions [10].

In the present work the cyclization of thiopyrimidine of dibenzo-18-crown-6, was accomplished by the reaction of alfa beta unsaturated ketone of DB-18-CE-6 who synthesis by dissolve (0.444g, 0. 1 mmole) of acytal-DB-18-CE-6 in 5ml of absolute ethanol then added (3-5 drops) of (60%KOH in ethanol) slowly with constant stirring follow added (0.106g, 0.2mmole) benzyldehyde which dissolved in absolute ethanol. The reaction mixture was kept in refrigerator overnight. The product was filtered and washed with cold water

until the filtered were neutral to litmus, the product was dried and recrystilized to get pale yellow color product [1]. As in the reaction who attended previously in first paper of synthesis, characterization, and preliminary of new antimicrobial activity of alfa beta unsaturated ketone of dibenzo-18-crown-6. Follow reaction with thiourea ,the mixture of alfa-beta unsaturated ketone (0.31g 0.001mmole) and thiourea (0.152g 0.002mmole) dissolve in absolute ethanol 5ml, with 5 drops of (40% KOH in ethanol) wes edded slewly with constent strring. The reection mexture allewed to reflex in a watar beth .. The ppt. obtained was filtered, washed with water, and dried. The product was recrystallized using dichloromethane, dried overnigh [2]. The goal is to synthesis cyclization thiopyrimidine of DB-18- CE-6 compounds to explore the potential antibacterial of these compounds.

In this experiment we made compared between the thiopyrimidine compounds of DB-18-CE-6 and control azithromycin antibiotic which is macrolide antibiotic.

Macrolide antibiotics are known for their wide range of efficacy. They are effective against Gram-positive and Gram-negative bacteria in equal measure. Although the action spectrum of macrolides may vary very slightly from one another azithromycin was one of the drugs that was used the most at the onset of the SARS-CoV2 epidemic. Because it encourages the development of drug-resistant bacterial strains. Regarding azithromycin, the main mechanism for increasing bacterial resistance to this antibiotic is changing the target of the active ingredient on the ribosome [11, 12].

Material and methods

Alfa beta unsaturated ketone of DB-18-CE-6compounds, thiourea, KOH. The progress of reaction was monitored by TLC (Silica gel 60 F254). IR spectra were recorded on Perkin-Elmer spectrometer. The ^{1}HNMR ,^{13}CNMR with Chloroform/d/DMSO-d6 as solventand TMS as internal standard. Melting points were determined in an open capillary tube.

Synthesis of thiopyrimidine of DB-18-CE-6 (Z)

The mixture of alfa-beta unsaturated ketone of DB-18-CE-6 (0.31g 0.1mmole) and thiourea (0.152g 0.2mmole) dissolve in absolute ethanol 5ml, with 5 drops of (40% KOH) in watar bith In between TLG wes monitored chock the complation of the reection., let to dried overnight. fully charecterized by elemantal anilysis (FTt-IR,^{1}Hh-NMR,

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and ^{13}Cc-NMR).

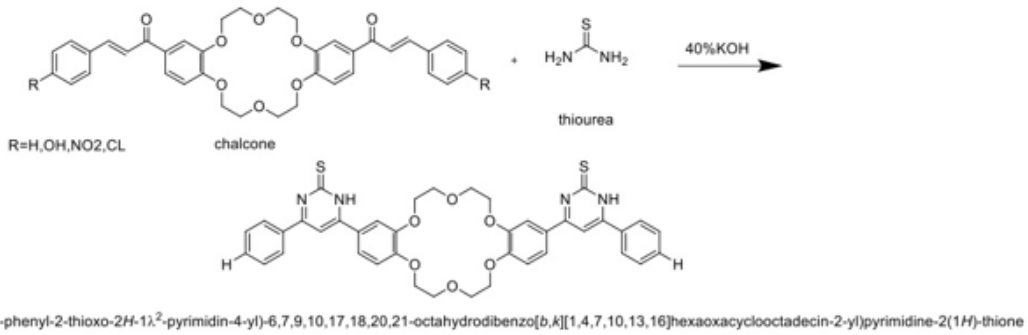

Figure 1. ***Scheme 1 Thiopyrimidine dibenzo-18-crown-6 synthesis***

Synthesis of P-OH-thiopyrimidine of dibenzo-18-crown- 6(Z 1)

The mixture of alfa-beta unsaturated ketone of DB-18-CE-6 (0.32g 0.1mmole) and thiourea (0.152g 0.2mmole) dissolve in absolute ethanol 5ml, with 5 drops of (40% KOH in ethanol) wes addid slewly weth constint stiring. The rection mixtur allowed to reflex in a water bath In between TLG was menitored to chieck the complition of the rection. aftr compltion of the rection, let to dried overnight. fully characterized by elemental analysis (FTt-IRr,^{1}Hh-NMRr, and ^{13}Cc-NMR).

Synthesis of p-NO2-thiopyrimidine of dibenzo-18-crown- 6(Z 2)

The mixture of alfa-beta unsaturated ketone of DB-18-CE-6 (0.355g 0.1mmole) and thiourea (0.152g 0.2mmole) dissolve in absolute ethanol 5ml, with 5 drops of (40% KOH in ethanol) let to dried overnight. fully characterized by elemental analysis (FTt-IRr,^{1}Hh-NMRr, and ^{13}Cc-NMR).

Synthesis of p-cl2-thiopyrimidine of dibenzo-18-crown- 6(Z 3)

The mixture of alfa-beta unsaturated ketone of DB-18-CE-6 (0.344g, 0.1 mmole) and thiourea (0.152g, 0.2 mmole) dissolve in absolute ethanol 5ml, with 5 drops of (40% KOH in ethanol) lit to dried overnight. fully characterized by elemental analysis (FT-IR,^{1}H-NMR, and ^{13}C-NMR).

Antibacterial activity

The antibacterial potential of the prepared Samples (Thiopyrimidine compunds of dibenzo-18- crown-6Z, Z1, Z2, Z3, Azithromycin) was investigated against Gram's negative and Gram's positive bacterial strains using agar well diffusion assay [13]. Into the bored wells, different concentrations (50, 150, 200, 250, 400 ppm) of the Samples (Z, Z1, Z2, Z3, Azithromycin) were used. The cultured plates containing the Samples (Z, Z1, Z2, Z3, Azithromycin, and the test organisms were incubated overnight at 37°C before measuring and recording the average the zones of inhibition diameter [14].

Result and Discussion

Crown ethers can be functionalized by a variety of chemical processes due to their high solubility. Thus, numerous crown ether derivatives have been manufactured. Conformational flexibility is one of the distinguishing characteristics of crown ethers [8].The focus on the cyclization of alfa beta unsaturated ketones of dibenzo-18-crown-6 by reaction with thiourea into thiopyrimidine of dibenzo-18-crown-6, The goal is to explore the potential antibacterial of these compounds. By utilizing dibenzo-18-crown-6 as a precursor, it is expected to obtain thiopyrimidine of dibenzo-18-crown-6 compounds with enhanced biological activity and potentially novel mechanisms of action [5, 8, 16].

In this experiment cyclization of thiopyrimidine of dibenzo-18-crown-6, was accomplished by the reaction of alfa beta unsaturated ketone of dibenzo-18-crown-6 who synthesis by dissolve (0.222mg ,0.5mmole) of acytaldibenzo-18-crown-6-ether in 5ml of absolute ethanol then added (3-5 drops) of (60%KOH in ethanol) slowly with good stirring follow by added (0.106g, 1mmole) of benzyldehyde dissolved it in ethanol absolute was added to the mixture slowly with for 2hr. Then added ice crush from deionized water then filter and let dry at R.T follow reaction with thiourea.in basic medium.

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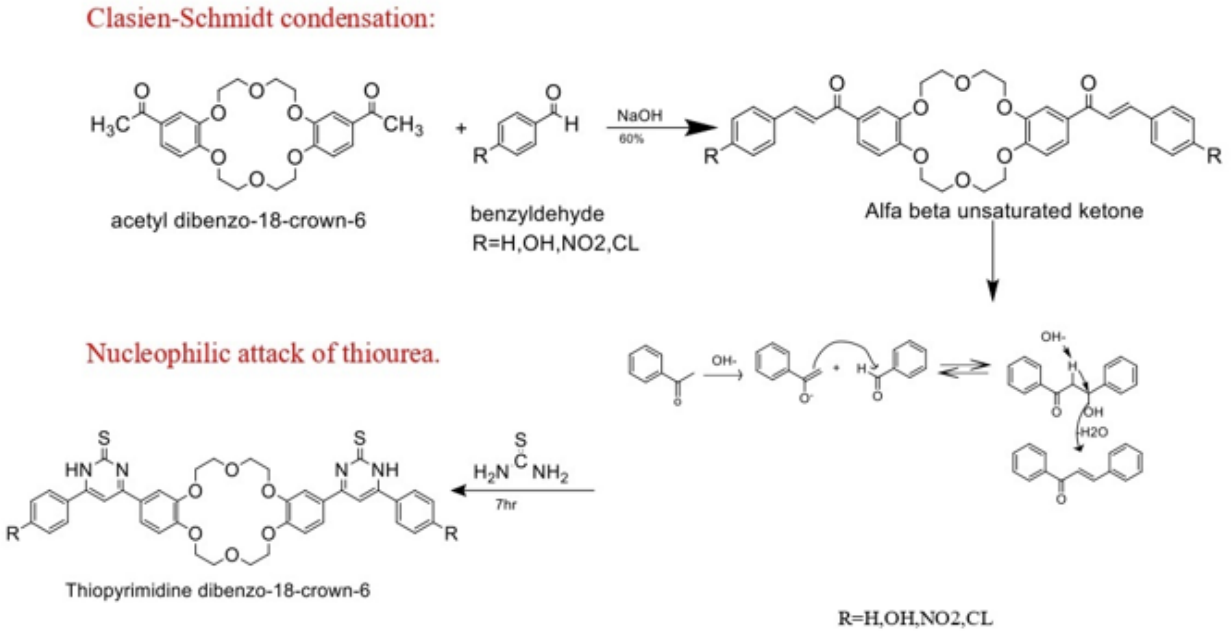

Figure 2. ***Scheme 2 General mechanism of thiopyrimidine dibenzo-18-crown-6 synthesis***

All the newly produced derivative compounds Z, Z1, Z2, Z3, have FT-IR spectra that share similarities in certain fingerprint-like bands and other bands. The essential functional group vibration bands are presented in Table (1 and 2) and the corresponding compound IR spectra are displayed in Figures (1) to (4).

All the predicted bands for normal Compound, as well as the bonded of add groups are present in all FT-IR spectra of derivatives.

The carboxylic groups bond of O-H present in Z3, performing a robust and broad extending band vibration in the range of 3367-3450 cm^{-1}. Furthermore, the N-H bond can be assigned a medium band in the range of 3275-3488 cm^{-1}. The compounds Z-Z3 of IR spectra show a band at a range of 3064-3172 cm^{-1} because of aromatic straining C-H, as well as 3 powerful bands to moderate ones at the range of 997.2-736.81 cm^{-1} because of the bending of C-H bond aromatic. A weak band was observed at the range of 2949-2835 cm^{-1} due to asymmetrical straining of aliphatic C-H bands, whereas a moderate band emerged at the range of 1398-1325 cm^{-1} for the bending of aliphatic C-H bond. Aromatic (C=C) asymmetrical and symmetrical stretching could be associated with two prominent bands that popped up in the 1544-1455 cm-1 and 1597-1415 cm-1 ranges, and between. Further to that, the compounds and Z-Z3 of FT-IR spectra illustrate a strong band that is attributed to (C=N) at the range of 1724-1610 cm^{-1} and assigned to (C-O) at the range of 1085- 1051 Cm^{-1} of all compound.

	O-HStretching	N-HStretching	C-HStretching(Aromatic)	C-HStretching(aliphatic)	C=N	C=CStretching	C-HBending(Aliphatic)	C-O-CStretching	C-OStretching	C-HBending(Out plane)	C-O-Hbending
Z	-	3381.21 3275.13	3172.90	2927.94 2877.79	1610.56	1415.75-1504.48	1325.10	1126.43 1215.15 1251.8	1060.85 1085.92	943.197 36.81	626.874 89.92
Z1	-	3439.08 3419.79	3062.96	2949.16 2927.94 2877.79	1724.36 1616.35	1597.061506.41 1454.33	1398.39 1340.53 1328.95	1253.73 1217.08 1128.36	1058.92	997.295 6.69943 .19779. 24774.5 2	599.86
Z2	-	3421.72	3064.89	2949.16 2926.01 2883.58	0	1595.131510.26 1454.33	1330.88	1290.38 1255.66 1232.51 1132.21	1060.85 1051.20	997.293 5.48779 .24740. 67	597.934 97.63
Z3	3367-3 448	3448-3 367	3064.89	2949.16 2926.01 2883.58	0	1597.061510.26 1454.33	1330.88	1290.38 1255.66 1230.58 1132.21	1058.92	997.293 5.48779 .24742. 59	597.934 97.63

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Table 1. ***The data and vibrational mode description of FTIR spectra of Z- Z3***

The antibacterial potential of the prepared samples (Z, Z1, Z2, Z3) and Azithromycin were investigated against Gram's negative and Gram's positive bacterial strains using agar well diffusion assay. 6 mm-diameter wells were bored on the agar plates using of a sterile tip. Into the bored wells, different concentrations of the Samples (Z, Z1, Z2, Z3, Azithromycin) were used. The cultured plates containing the samples (Z, Z1, Z2, Z3, Azithromycin) were incubated overnight at 37°C before measuring and recording the average the zones of inhibition diameter [14], will show in the tables below.

The rise in antibiotic resistance that can be attributed to a number of different sources has led researchers to explore for novel chemicals that are effective against infections that are resistant to several drugs. In this experiment. Thiopyrimidine compounds displayed a diversity of pharmacological properties, and its derivatives possess a high degree of structural variance. As a result, there is a critical demand for the development of novel antibacterial medication candidates [17]. Antibiotic resistance is a rising problem, reducing the effectiveness of macrolides, the first-line treatment for many diseases. *Staphylococci* frequently exhibit multiple molecular determinants of resistance to macrolides. Research into new macrolide antibiotics could help in the fight against drug-resistant bacteria, hence it's crucial to understand the processes of macrolide resistance. The comparative analysis with azithromycin indicated the potential of thiopyrimidine compoundsas an effective alternative in resist bacterial infection [11, 18] As in the scheme below show the bacterial inhibition for the thiopyrimidine compounds with different concentration against *Streptococcus*, *Staphylococcus and Proteus* as we see in concentration 50pmm,100ppm,150ppm,200ppm,400ppm [10]. The bacterial inhibition for thiopyrimidine compound (Z) in (400ppm) against *Streptococcus*has inhibition zone (22mm) larger than Azithromycin in (400ppm) have inhibition zone(14mm) that is mean the effect of thiopyrimidine compound have a good antibacterial activity against streptococcus, While inhibition zone of compound (Z) in (400ppm) against *Stapholococcus* is (12mm) for Azithromycin the inhibition zone is (14mm) And the inhibition zone for compound (Z) against

*Proteus*is (11mm), for Azithromycin is (16mm).

Conclusions

Evaluation of activity Conduct comprehensive antibacterial activity assays using a range of bacterial strains. Determine the minimum inhibitory concentrations (MICs) of thiopyrimidine compounds against various pathogens to assess their potency and efficacy. Comparative studies with known antibiotics like Azithromycin can provide valuable insights into their relative effectiveness.

Table (3) Explain the antibacterial activity of thiopyrimidine compounds of dibenzo-18-crown-6 Z=Thiopyrimidine of DB-18-CE-6, Z1=P-OH-thiopyrimidine of DB-18-CE-6, Z2=P-NO2- thiopyrimidine, Z3=P-CL-thiopyrimidine

sample		A	B	C	D	E	F
Streptococcus	Z	6	15	17	18	20	22
	Z1	6	16	17.5	18.5	19.5	20.5
	Z2	6	15	16	17	18	19
	Z3	6	16	18	20	22	24
Azithromycin		6	8	9	10	13	14
Staphylococcus	Z	6	6	7	8	10	12
	Z1	6	6	6.5	7	9	10
	Z2	6	7	8	9	12	13
	Z3	6	6.5	8	9	12	13
Azithromycin		6	7	9	10	12	14
Proteus	Z	6	6	7	9	10	11
	Z1	6	6	7	10	11	12
	Z2	6	9	10	11	12	13
	Z3	6	6	7	9	12	13
Azithromycin		6	12	13	14	15	16

Table 2. ***Antibacterial analysis (Zone of inhibition)***

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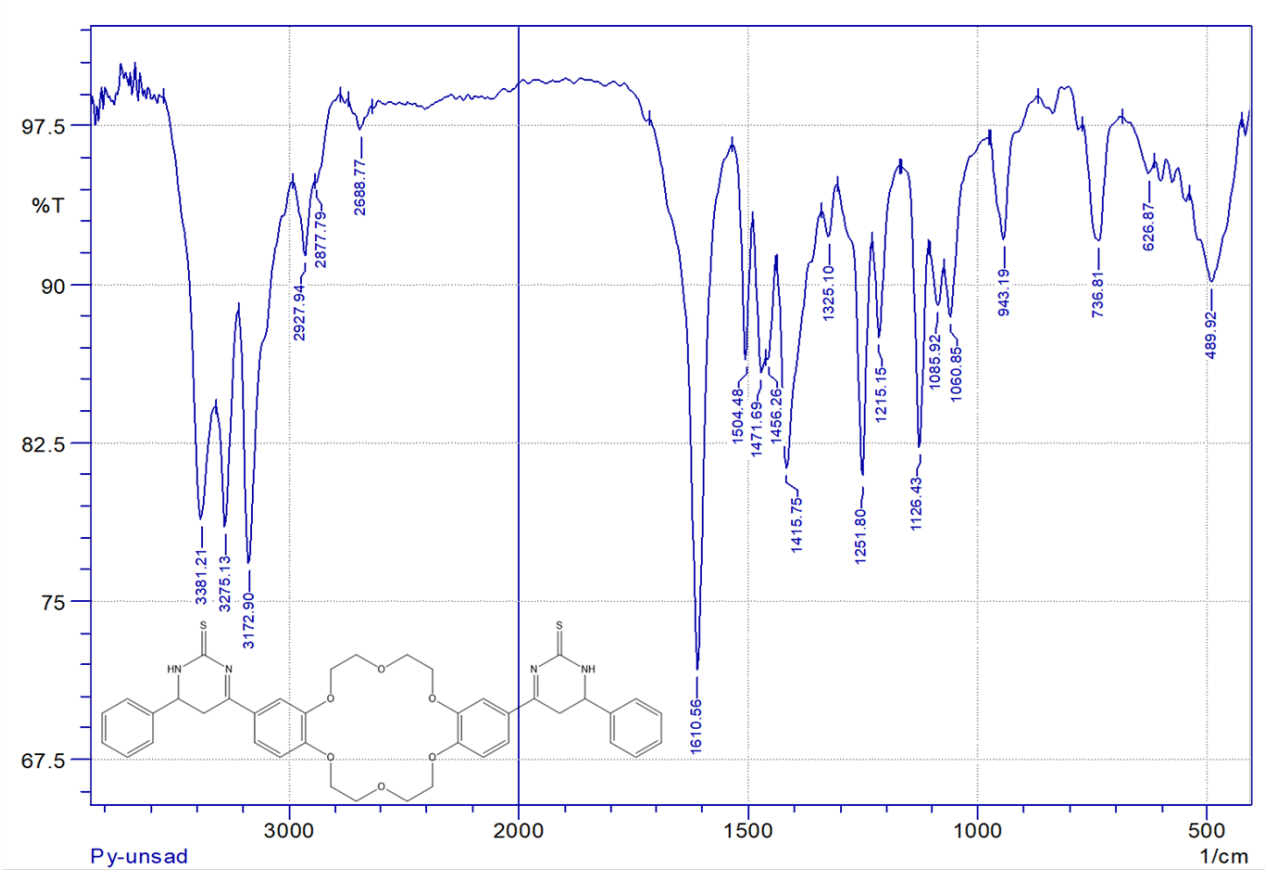

Figure 3. ***The FTIR Spectra of compound Z***

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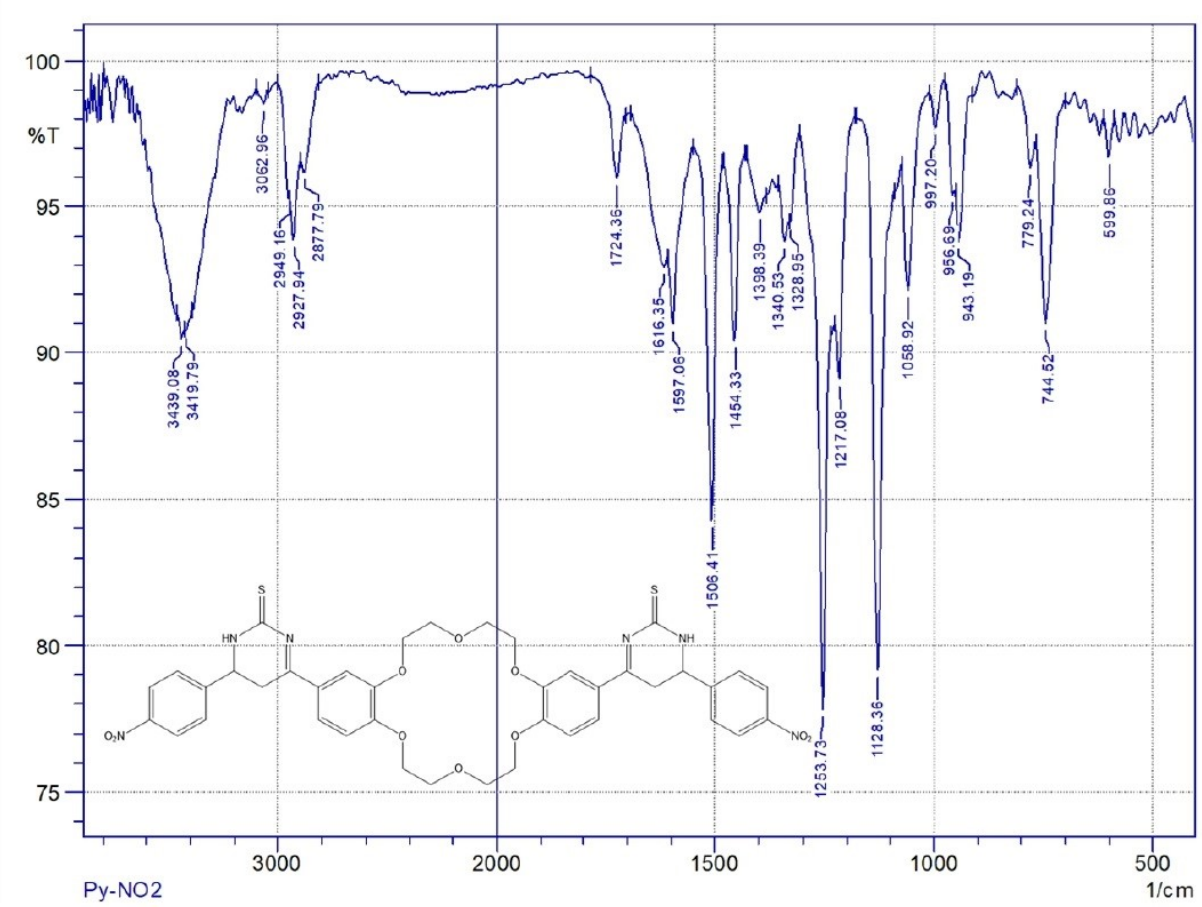

Figure 4. ***The FTIR Spectra of compound Z1***

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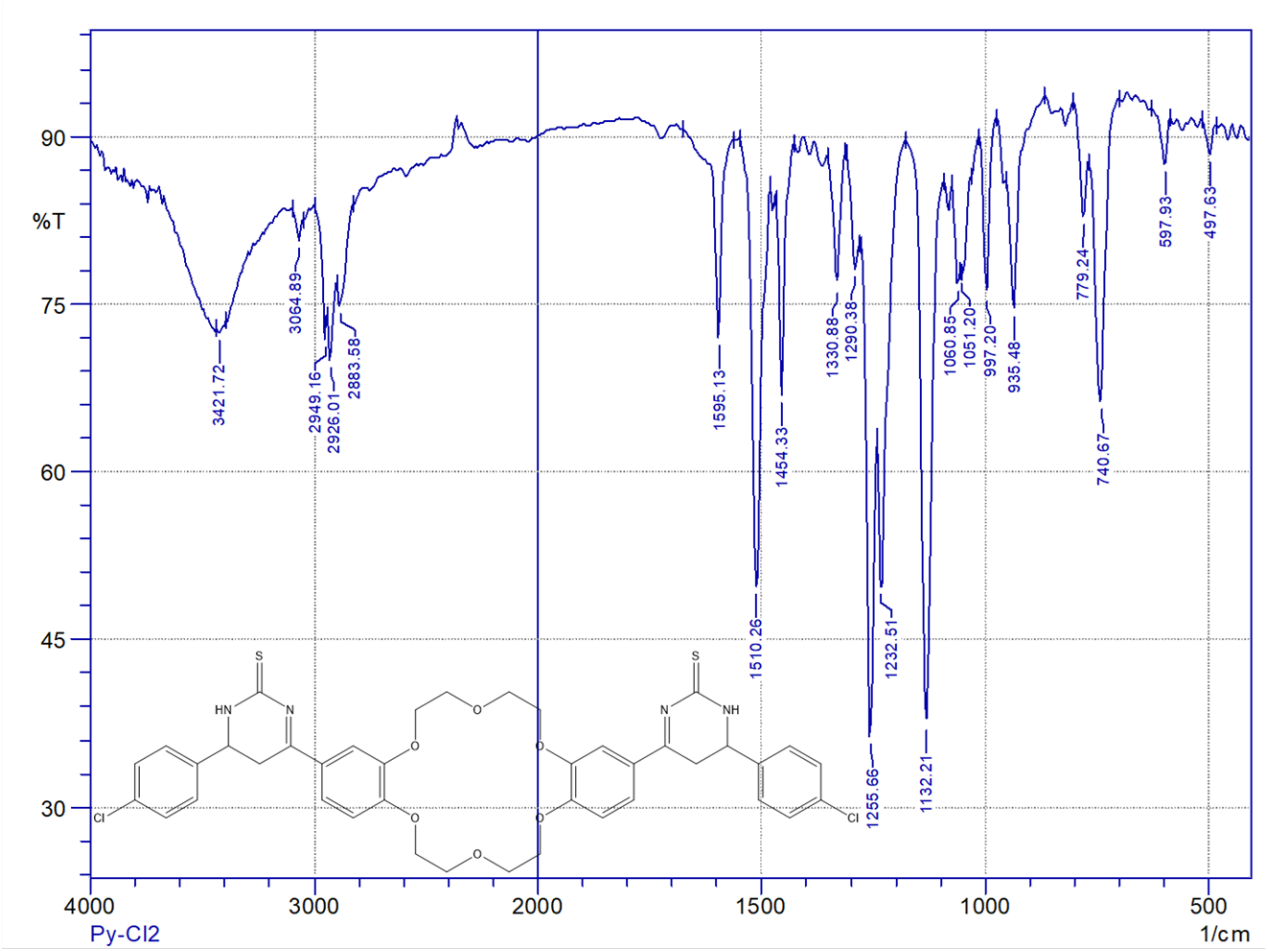

Figure 5. ***The FTIR Spectra of compound Z2***

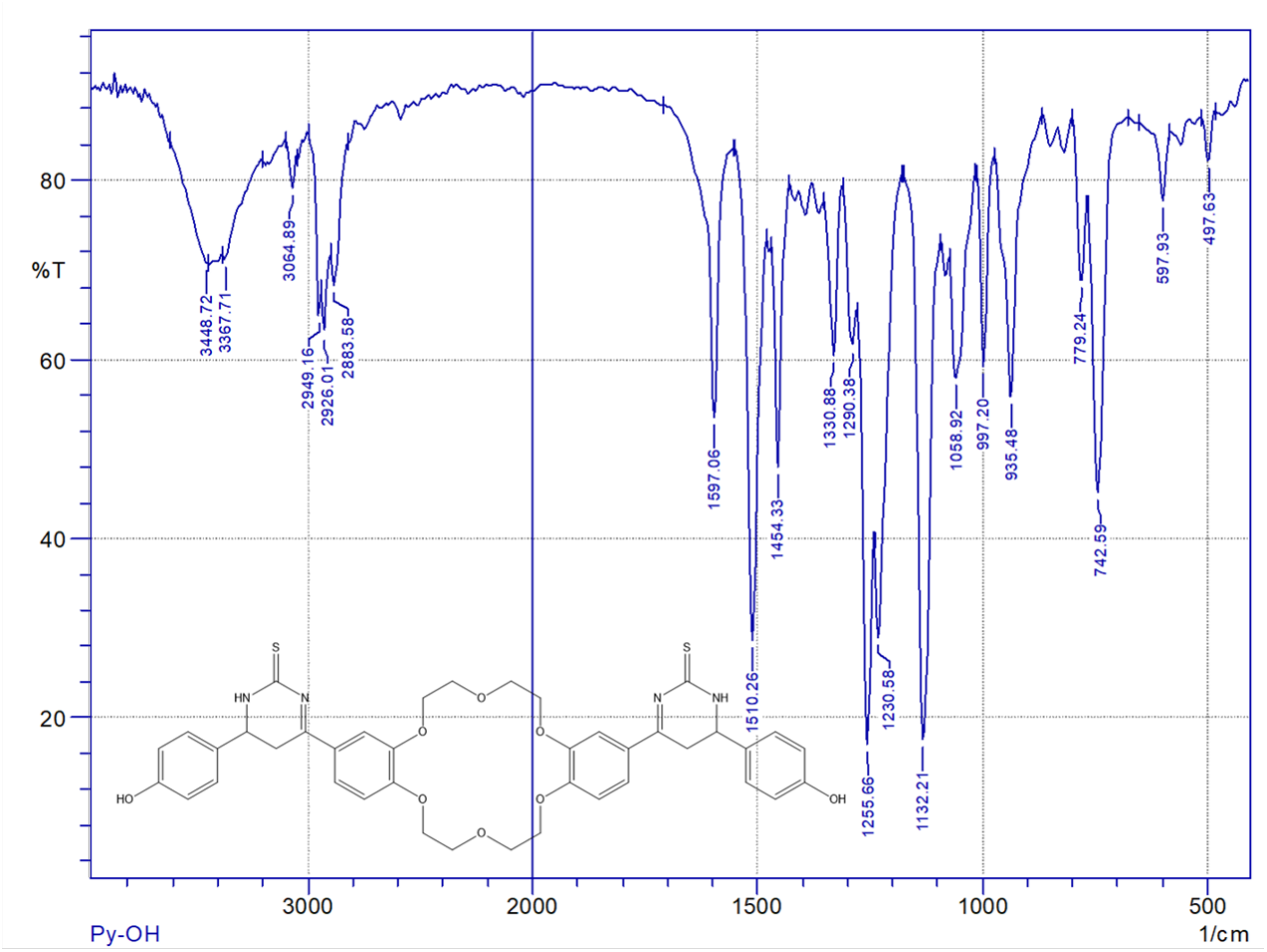

Figure 6. ***The FTIR spectra of compound Z3***

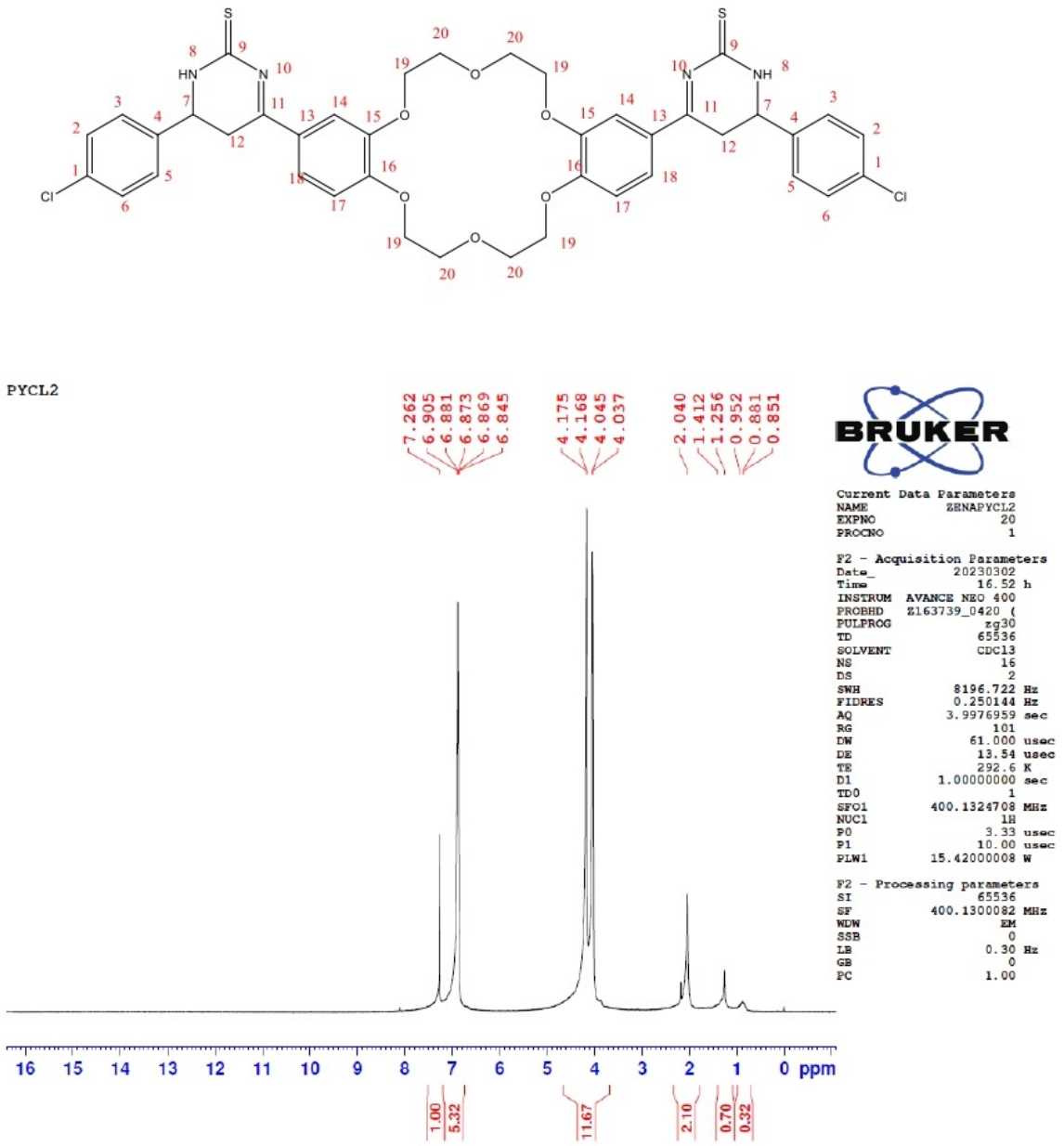

Figure 7. ***The 1H NMR spectrum of c ompound Z2***

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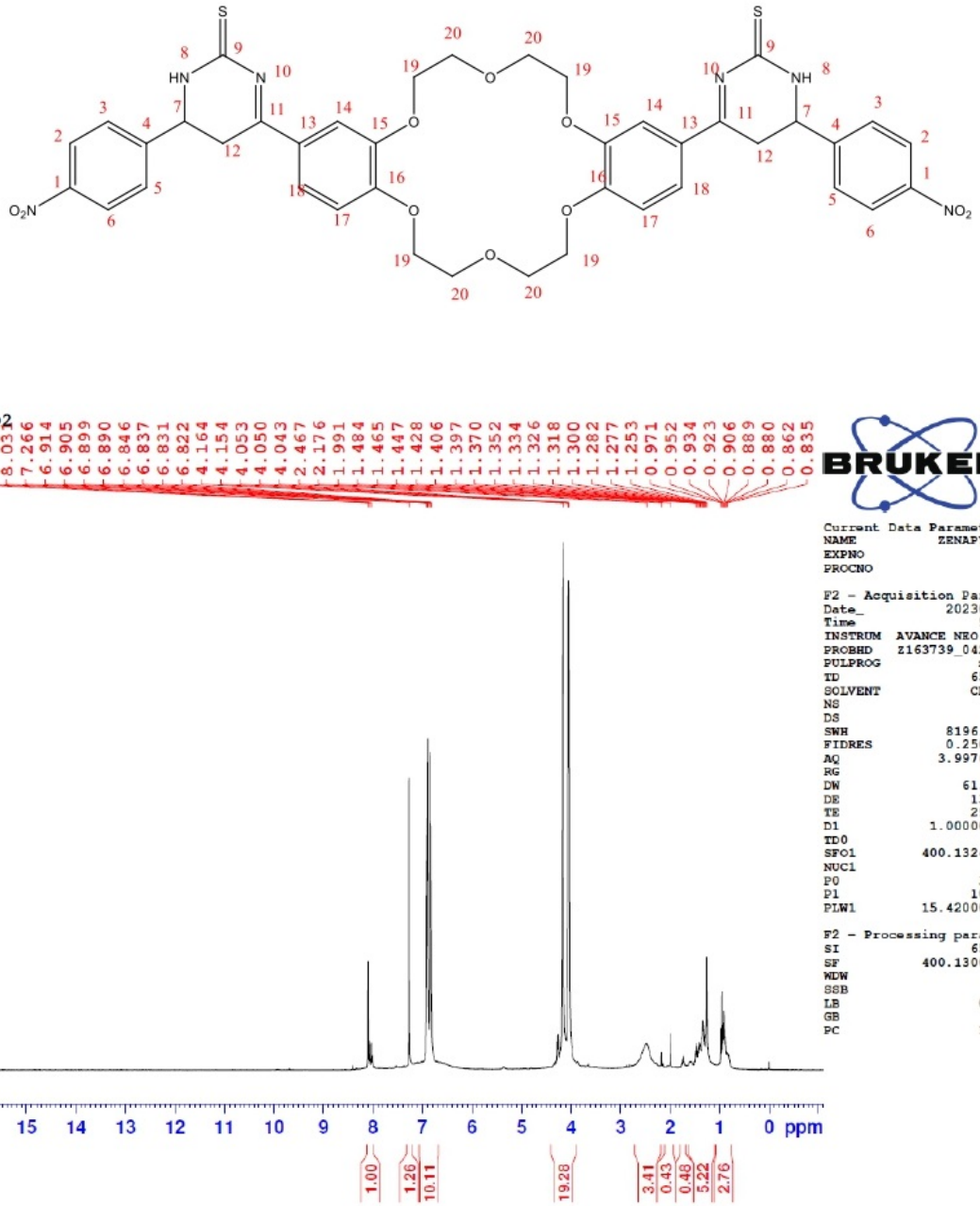

Figure 8. ***The 1H NMR spectrum of c ompound Z1***

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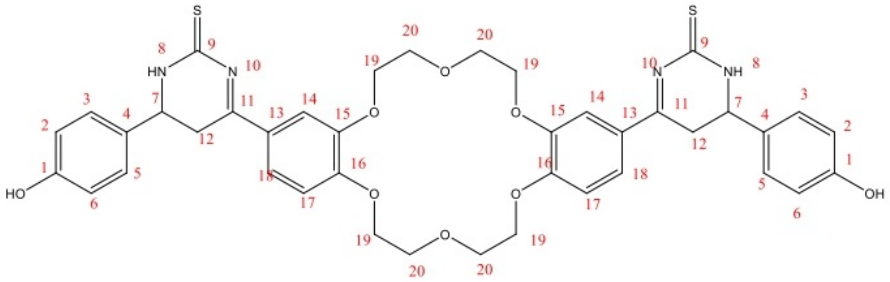

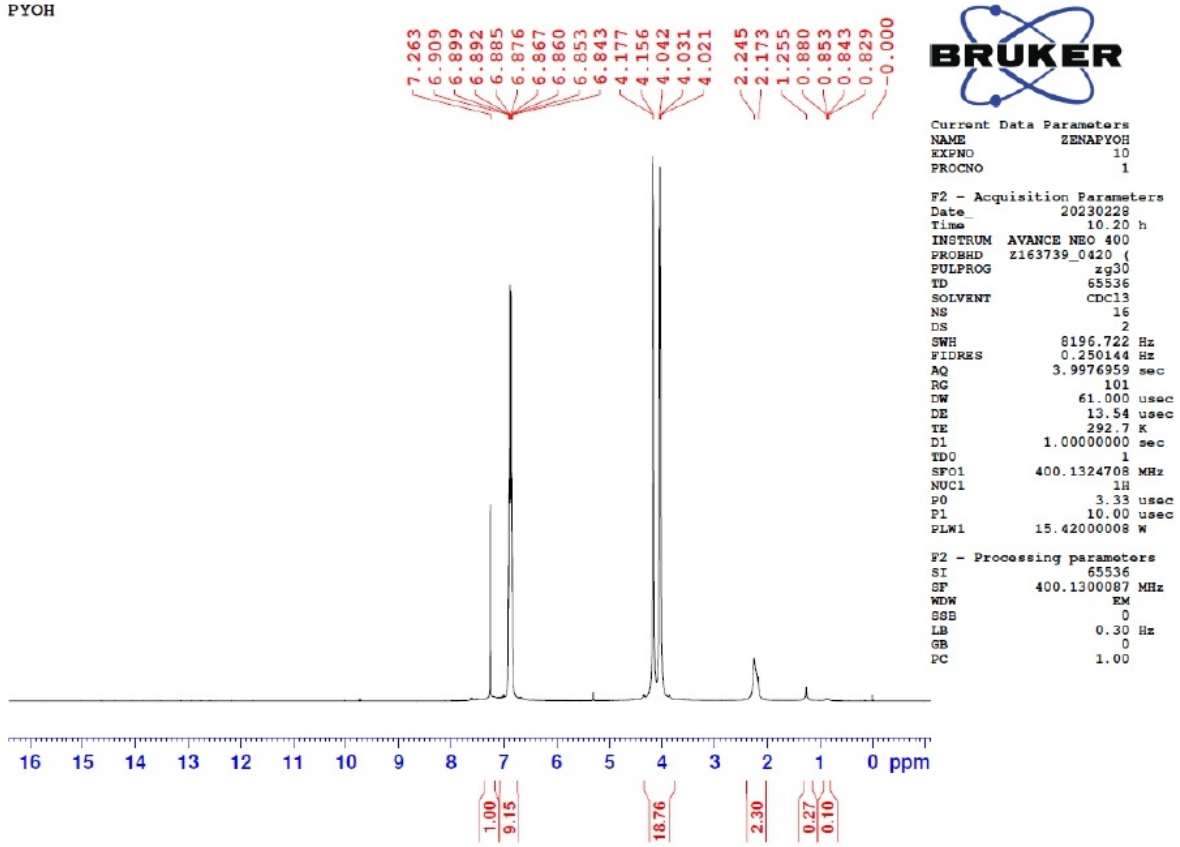

Figure 9. ***The 1H NMR spectrum of c ompound Z3***

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