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Synthesis, Characterization of thiophene derivatives and its biological applications

Shashidhara GS, Sahana KP, Shazia, Tejaswini and Madavi Sunitha *

Department of Studies and Research in Chemistry, UCS, Tumkur University, Tumakuru, Karnataka-572103, India.

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Abstract

In this research work, titled "Synthesis, Characterization of thiophene derivatives and its biological activity" is related to studies towards the synthesis of Sulphur containing ligands that is thiophene derivatives. The newly synthesized compounds are characterized by FT-IR, 13C-NMR,1H NMR techniques. And all the compounds were tested for antibacterial activity. The complexes showed low antibacterial activity.

Keywords: Thiophene; Antibacterial; Antifungal; Synthesis; Characterization

1. Introduction

Cyclic compounds with a ring containing an element other than a carbon atom are called heterocyclic compounds [1]. The next most common heteroatoms are oxygen, nitrogen, and sulfur, and many heterocyclic rings with other heteroatoms are also known. Many organic compounds form a heterocyclic compound.

To this day, a large number of heterocyclic groups are known, the number of which is increasing rapidly every day [2]. Most drugs on the market consist of a heterocyclic group. In the metabolism of living cells, this compound plays a major role, and they are also very important for life. Heterocyclic compounds play an important role in synthetic chemistry, medicinal chemistry, pharmaceutical chemistry, coordination chemistry, biochemistry, and also in other scientific fields [3]. These compounds can be found either naturally or synthetically. They have a wide range of different biological activities [4], such as antimicrobial [5-8], anti-inflammatory [9], antiviral [10], antitumor drugs [11-12] and antioxidant [13-14], anti-aging [15]. , with their numerous biological applications.

Heterocyclic compounds are widely distributed in nature and have versatile synthetic applications and biological activity, which have helped them in medicinal chemistry to plan organic substances and implement new approaches to new drug discovery [16]. Heterocyclic compounds are very important in our daily life. Heterocyclic compounds have one or more heteroatoms in their structure. They can be cyclical or non-cyclical in nature. They are most often used as medicines, as agrochemicals and as veterinary products. They are also used as a vehicle in the synthesis of other organic compounds [17].

Thiophene belongs to a class of heterocyclic compounds containing 5-membered rings formed by one sulfur as a heteroatom with the formula C_4H_4S. Sulfur containing heterocycle has found a way for active research in pharmaceutical chemistry, pharmaceutical applications such as anti-allergic, analgesic, anti-inflammatory. Thiophene is the most important aromatic heterocyclic derivative. Indeed, many molecules that construct the thiophene core have shown important pharmacological activity, with the thiophene derivative finding great use in materials science and coordination chemistry and as an intermediate in organic synthesis [18-21].

* Corresponding author: Madavi Sunitha

In this review, we highlight some recently developed efficient and selective syntheses of thiophene derivatives by cyclization of readily available S-containing alkyne substrates. As will be seen, many of these cyclization reactions leading to thiophene have been carried out under mild conditions (even at room temperature, especially with iodocyclization) in classical organic solvents, either dipolar aprotic (such as N,N-dimethylacetamide (DMA) dimethylsulfoxide (DMSO) or MeCN), polar or slightly polar (such as toluene, THF or CH2Cl2) or protic (such as MeOH) [22].

The activity of a compound strongly depends on the nature of the heteroatom ring and the position of attachment to the ring. these are extensively studied due to their flexibility, their selectivity and sensitivity to the central metal atom, structure and similarity to natural biological activities [23]. Classical approaches to substituted thiophene are mainly based on a condensation-like reaction or subsequent functionalization of the thiophene ring [24-34]. During the last year, however, innovative approaches have been developed for the regioselective synthesis of substituted thiophene starting from acyclic precursors, mainly based on the heterocyclization of functionalized alkynes [35].

Substituted thiophenes have been synthesized by various methodologies and investigated for various pharmacological activities, including the antiallergic agent, metaphenylin, the anticonvulsant tiagabine, and biotin, which is used to prevent and treat pregnancy-associated biotin deficiency [36]. Thus, this available literature encouraged us to synthesis the thiophene derivatives. As per our knowledge the prepared 2-acetyl thiophene derivatives are less studied. It promoted us to synthesize the thiophene derivatives.

2. Materials and Methods

All the solvents and reagents were purchased from Sigma–Aldrich. All reactions were performed under ambient conditions. Absorption spectra were recorded on a Shimadzu UV-1800 spectrophotometer, and FT-IR spectra were measured on a PerkinElmer instrument with solid samples using a Golden Gate ATR accessory, and ^{1}H and ^{13}C NMR spectra were obtained at 400 MHz and 100 MHz.All other chemicals used were of analytical grade. Microorganism such as both Gram+ and –ve bacterial strains were purchased from National Chemical Laboratory (NCL), PUNE. These strains were maintained on nutrient agar slant at 4 ◦ C. The microorganisms used in this study Escherichia coli (E. coli) [NCIM-5051] and Staphylococcus aureus (S. aureus) [NCIM-5022] as pathogenic bacterial strains.

2.1. General procedure for the synthesis of Thiophene Derivatives

2-acetylthiophene (2eq, 1.518g, 0.01203mmol) is dissolved in 25 ml of methanol solvent was taken in a three necked round bottom flask to this KOH pellets (0.675g ,0.01203mmol) and three drops of water added, the mixture was stirred for 20 minutes. Then corresponding aldehyde (1eq, 1g, 0.006017mmol) dissolved in methanol was slowly added to the content of the round bottom flask. Then the reaction mixture was stirred well for 30 minutes, after 30 minutes liquor ammonia (3ml) was added continue further stirred for 8 hours, after 8 hours of stirring yellowish solid obtained, which was collected by simple filtration using Whatman filter paper. Then the product was washed with 10 ml of methanol and then with 5 ml of the diethyl ether and finally dried the compound. The collected product was recrystallized from methanol and chloroform mixture.

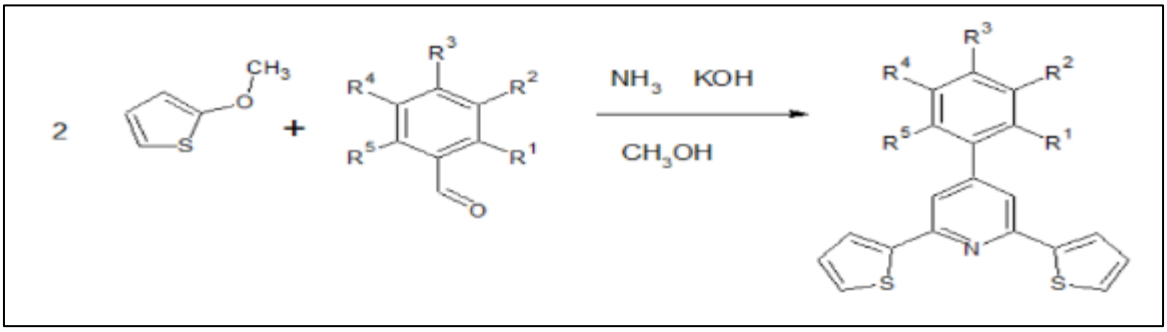


Table 1 Aldehyde used to synthesize Thiophene Derivatives D1 to D4

Thiophene Derivatives	**R_1**	**R_2**	**R_3**	**R_4**	**R_5**
D_1	-OMe	H	-OMe	H	H
D_2	-OMe	-OMe	H	H	H

D_3	H	-OMe	H	-OMe	-OMe
D_4	H	H	-OMe	-OMe	-OMe

2.2. Antibacterial and antifungal assay:

Antibacterial activity of thiophene derivatives D_1-D_4 against pathogenic bacterial strains namely Gram-positive bacteria Staphylococcus aureus and Gram-negative bacterial strains Escherichia coli by Agar well diffusion method [40]. Nutrient Agar plates were prepared and swabbed using Sterile L-shaped glass rod with 100 µl of 24h mature broth culture of individual bacterial strains. The well was made by using sterile cork borer 6mm wells was created into each Petri-plate. Various concentrations of Heterocyclic derivatives (250µg and 500µg/well) were used to assess the activity of the compounds. The compounds were prepared in sterile water added into the wells by using sterile micropipettes. Simultaneously the standard antibiotics Ciprofloxacin (Hi Media, Mumbai, India) (as positive control) were tested against the pathogens. The plates were inculcated by the bacteria incubated for 36 h at 37°C for bacteria. After the incubation period, the zone of inhibition of each well was measured and the values were noted. Triplicates were maintained in each compound and the average values were calculated for the ultimate bactericidal activity.

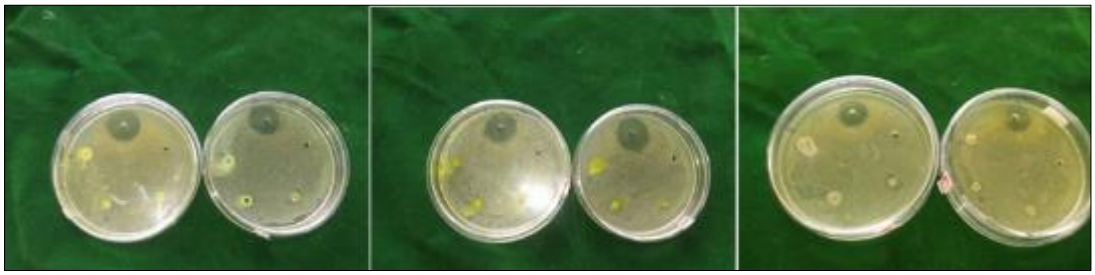


Figure 1 Petri-plates showing bacterial growth

Table 2 Antimicrobial data of synthesized compounds

Compounds	**Treatment**	**Pathogenicmicrobial strains**	
		S. aureus	**E. coli**
Ciprofloxacin	5μg/50μg	14.00	13.67
D_1	25 μg/250 μg	-	-
	50 μg/500 μg	-	-
D_2	25 μg/250 μg	-	-
	50 μg/500 μg	-	-
D_3	25 μg/250 μg	-	-
	50 μg/500 μg	-	-
D_4	25 μg/250 μg	-	-
	50 μg/500 μg	-	-

3. Results and discussion

The newly synthesized Thiophene Derivatives are colored solids, stable at room temperature and possess high melting point. The Thiophene derivatives are soluble in $CDCl_3$.elemental analysis and analytical data agree well with the proposed composition of Thiophene Derivatives.

The structures of the newly synthesized molecules were characterized by spectral methods like ^{13}C-NMR, IR, ^{1}H–NMR and Mass spectra. Data obtained from spectroscopic characterization are in good correlation with the expected. Hence all the synthesized Thiophene Derivatives were confirmed by the assigned structure.

3.1. Physical Characterization data of synthesized compounds

All the synthesized Thiophene Derivatives are colored solid and amorphous

Table 3 Physical data of synthesized compounds

Ligand	Mol. Formula	Color/Nature	Yield (%)	Melting-point (^{0}C)
D_1	$C_{21}H_{17}NO_2S_2$	Yellow solid	80	95-100
D_2	$C_{21}H_{17}NO_2S_2$	Light-Brown Solid	85	98-102
D_3	$C_{22}H_{19}NO_3S_2$	Yellow Solid	83	150-160
D_4	$C_{22}H_{19}NO_3S_2$	Pale-Yellow Solid	74	153-164

3.2. Spectral interpretation

3.2.1. Infrared Spectrum

The FTIR spectrum of 4- (2, 4 dimethoxyphenyl)-2, 6-di(thiophen-2-yl) pyridine show bands a 1585-1536 cm^{-1}, 1466-1427 cm^{-1} corresponds to C=N and C=C respectively due to stretching vibration. A weak band observed at 3066 cm^{-1} due to aromatic stretching and another band at 794 cm^{-1} represents out of plane bending vibration of the C-H bond. A band at 764 cm^{-1} is due to the C-S Stretching vibrations. Bands observed in the range of 1323 cm^{-1} to 1044 cm^{-1} are to the C-O Stretching frequency [37].

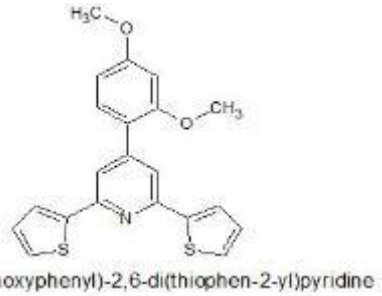
3.2.2. ^{1}H NMR

In all the synthesized Heterocyclic derivatives, a singlet observed at δ 8.400 represents the presence of –CH proton of the pyridine ring, a doublet at δ 7.927-7.935 (J = 3.2 Hz) corresponds to –CH proton of the thiophene ring [38], a doublet at δ 7.462-7.469 (J = 2.8 Hz) corresponds to –CH proton of the thiophene ring near to sulfur atom. A triplet observed at δ 7.126-7.166 (J = 7 Hz) represents the presence of aromatic proton. A doublet observed at δ 6.994-7.018 due to aromatic proton (ArH) [39].

3.2.3. ^{13}C NMR (100 MHz, δ ppm)

In all the synthesized Heterocyclic derivatives Methoxy group (C_{20} ,C_{21} ,C_{22}) 55.15-56.46, C-O at 139.7-162.9,chemically equivalent pyridine carbon (C_5,C_{15}) 152.4,(C_6,C_{14}) 118,Thiophene carbon(C_1,C_2,C_3,C_{17},C_{18},C_{19}) 127.6-128,(C_4,C_{16}) chemically equivalent carbon 142.4,Benzene carbon (C_8)128.1,(C_9) 122.6,(C_{10}) 122.5 ,(C_7) 152.0

3.3. ^{1}H NMR, FTIR &^{13}C NMR of D_1: 4-(2,4-dimethoxyphenyl)-2,6-di(thiophen-2-yl) pyridine

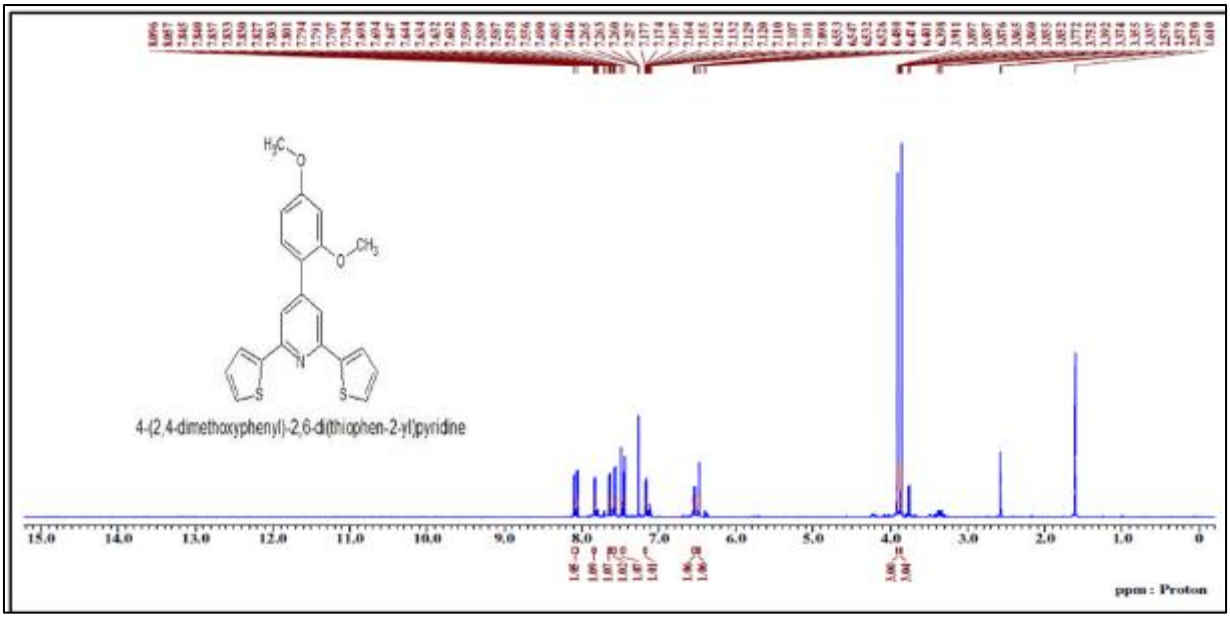


4-(2,4-dimethoxyphenyl)-2,6-di(thiophen-2-yl)pyridine

Chemical formula:$C_{21}H_{17}NO_2S_2$
Molecular Weight: 379.495

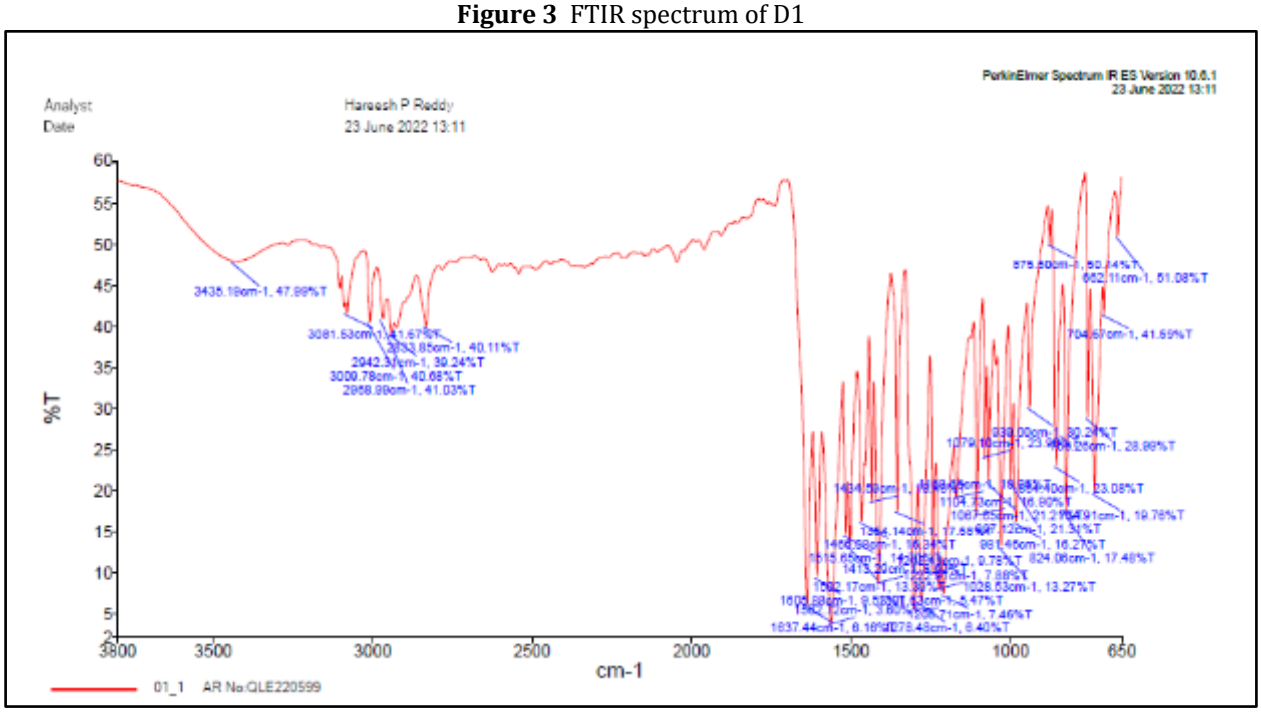
^{1}HNMR(δ) of D1:3.8762(S,2H,OMe),3.772(s,3H,OMe),6.553-6.526(d,2H,Ar H), 7.794(S,1H,CH), 8.096-8.057(d,2H,py-CH) 7.446-7.490(d,2H,Th-CH), 7.177(d,2H,Th CH)7.644-7.698(d,2H,Th-CH).

Figure 2 ^{1}HNMR spectrum of D1



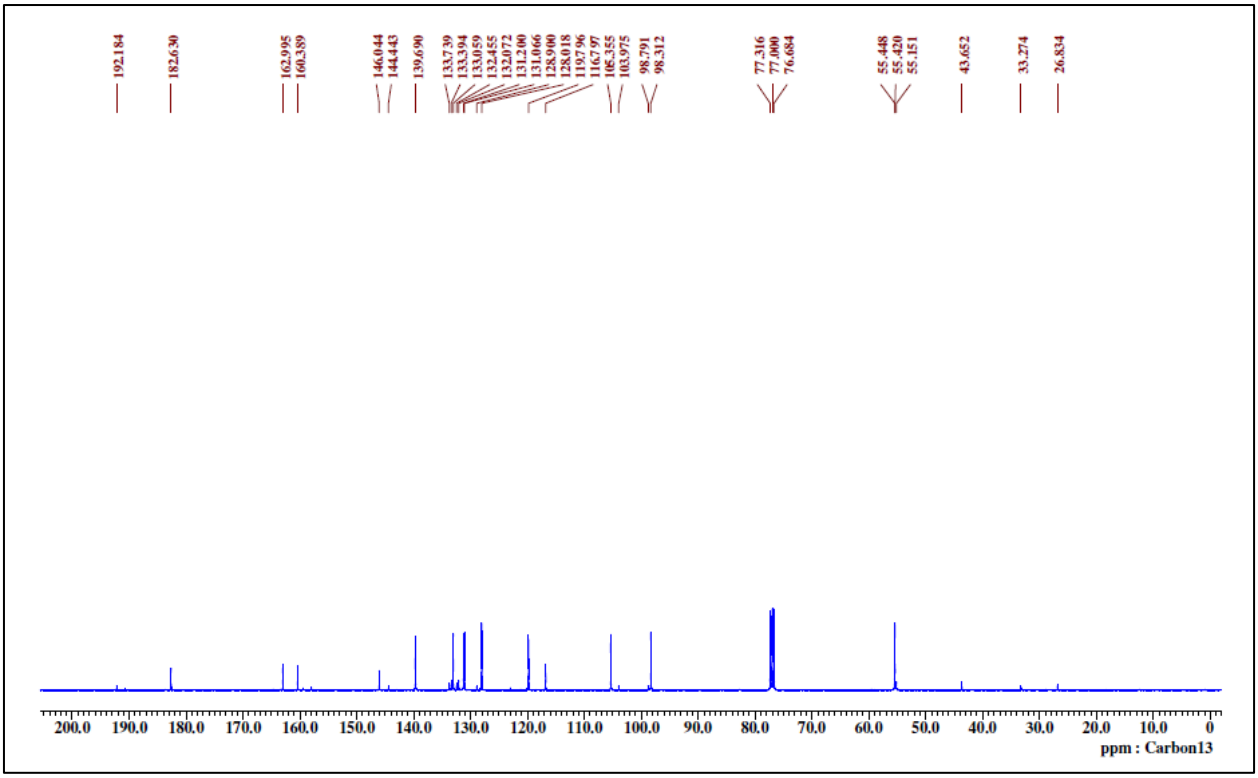
FTIR(ϑ ,cm^{-1}) of D1:1605.88-1515(C=N),1466-1413.29(C=C),1278.48-1067.65(C-O),3081.53(Ar-streching)824.06(C-H), 756.26(C-S)

Figure 3 FTIR spectrum of D1

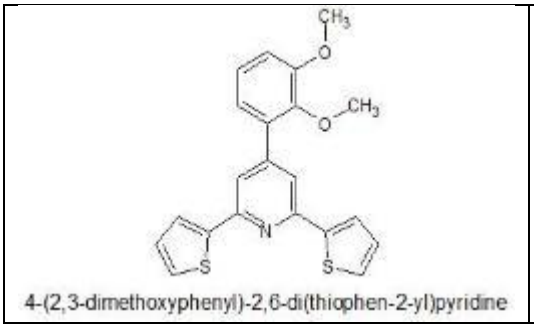


^{13}C NMR(δppm) of D1: 55.151(OMe),55.448(OMe),162.9(C-O),160.38(Ar-C),
105.355(CH_2,ArC),128.9(CH_2,ArC),128.0(CH,ArC), 98.8(C,Ar C),146.04(C, py), 119.79(2C, Py),144.44(2C, Th), 128-128.90(C Th).

Figure 4 ^{13}CNMR spectrum of D1



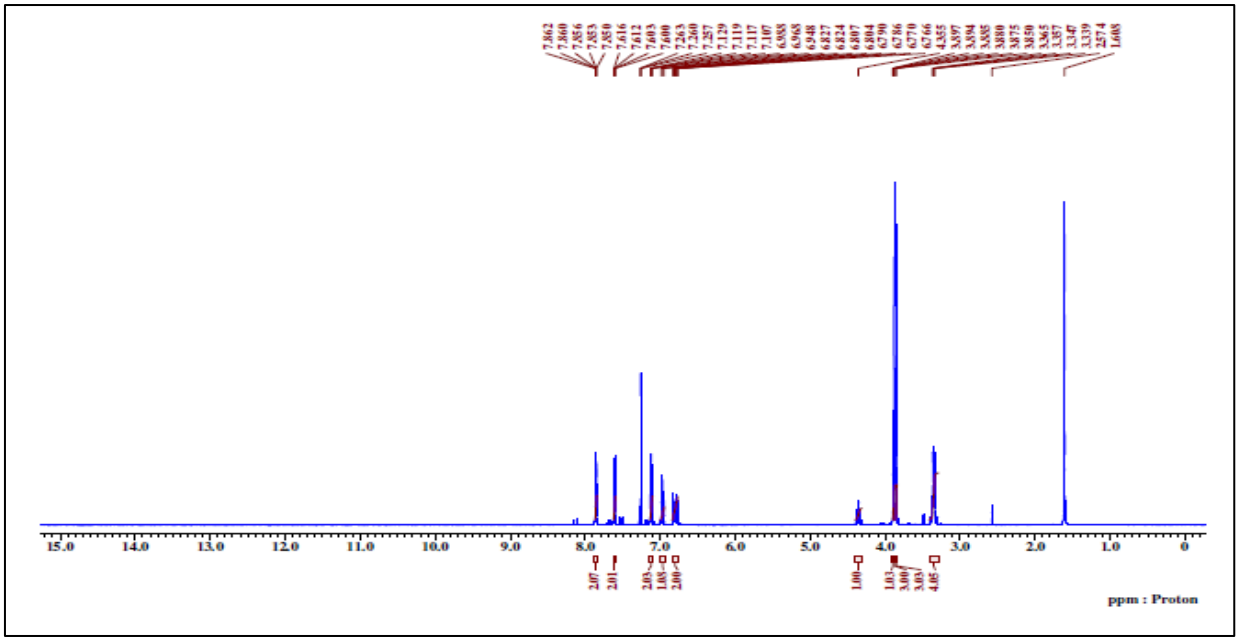
^{1}H NMR, IR &^{13}C NMR of D_2: 4-(2,3-dimethoxyphenyl)-2,6-di(thiophen-2-yl) pyridine



Chemical formula: $C_{21}H_{17}NO_2S_2$
Molecular Weight: 379.495

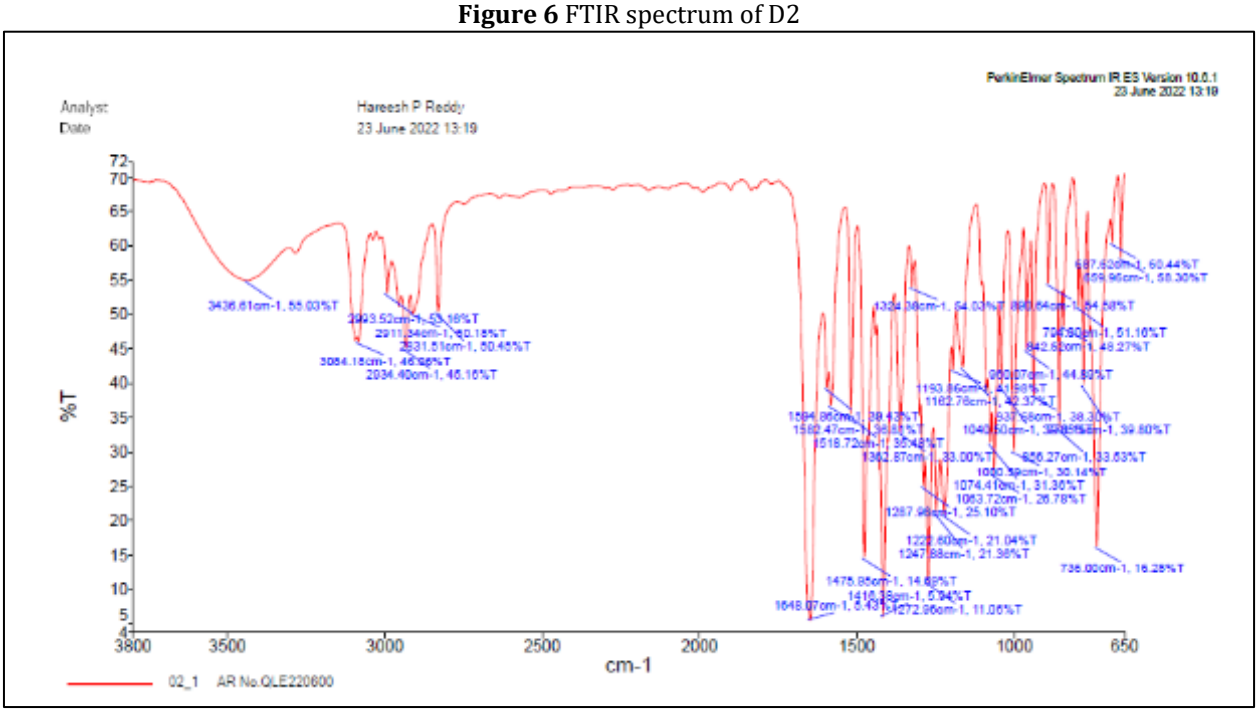
^{1}HNMR(δ) of D2 :3.850-3.880(s,3H,OMe),3.885-3.897(s,3H,OMe), 7.107(S,1H,Ar-H),7.129(t,3H,Ar-H),7.61(d,CH, Ar-H), 8.22(s,2H,py),7.60-7.61(d-d, 6H, Th-CH).

Figure 5 ^{1}HNMR spectrum of D2



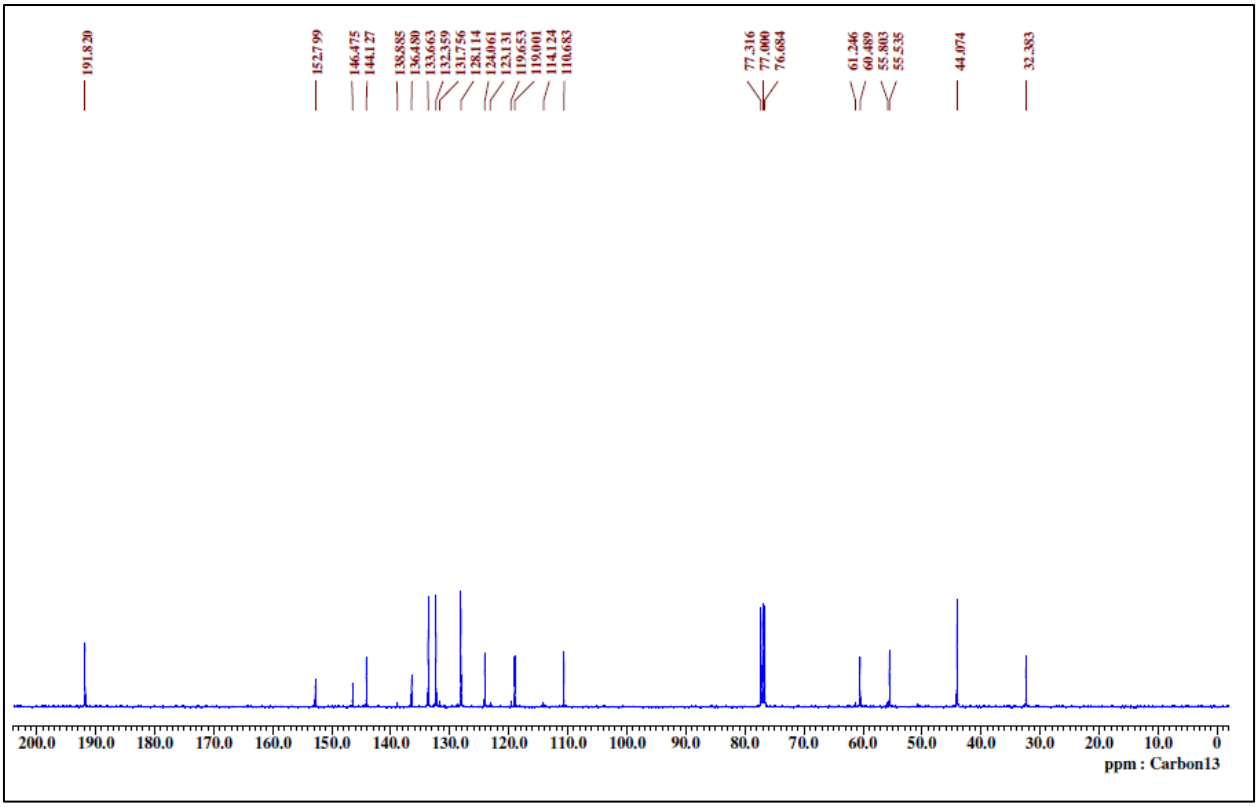
FTIR(ϑ cm^{-1}) of D2 :3084.18(Ar),1594.86-1515(C=N),1475.95-1416.38(C=C),1324-1063.72(C-O),794.00(C-H),778.15(C-S)

Figure 6 FTIR spectrum of D2

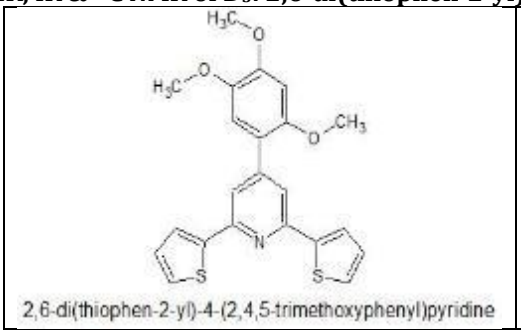


^{13}CNMR(δppm) of D2 :55.53(OMe),55.80(OMe),114.12(CH_2,ArC),123.13(1C,Ar), 124.061(1C,Ar-C), 128.114(1C,Ar-C), 152.79(C-O),119.0(2C,py),144.127(Th-C),128.11(Th-C).

Figure 7 ^{13}C NMR spectrum of D2



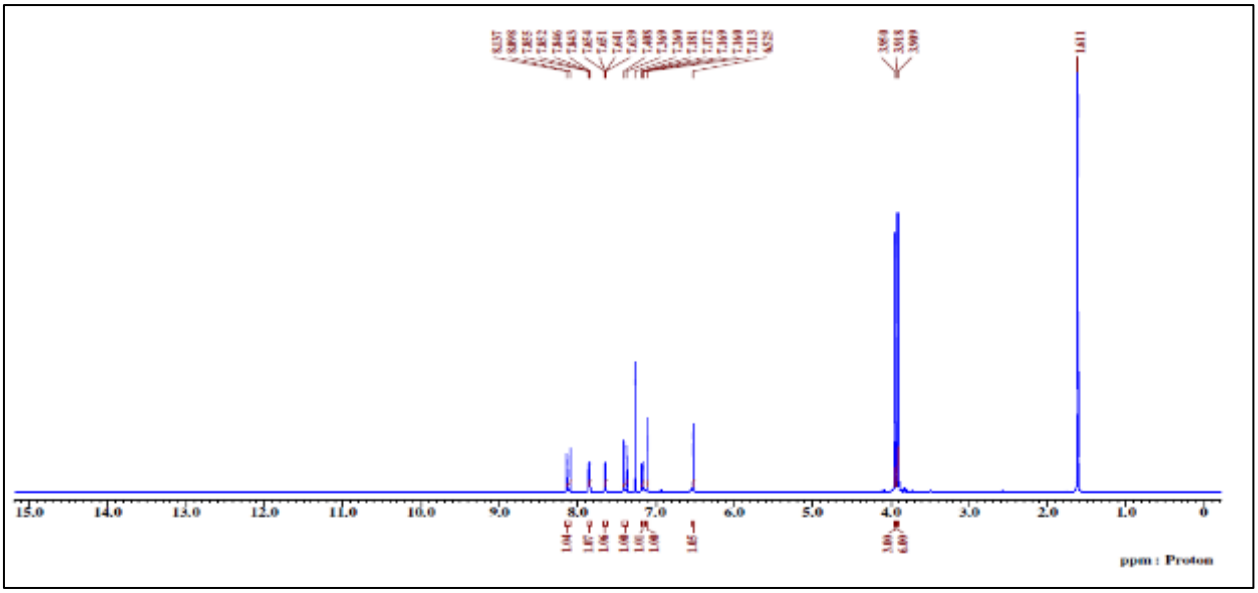
^{1}H NMR, IR &^{13}C NMR of D$_3$: 2,6-di(thiophen-2-yl)-4-(2,4,5-trimethoxyphenyl) pyridine



Chemical formula: $C_{22}H_{19}NO_3S_2$
Molecular Weight: 409.52116

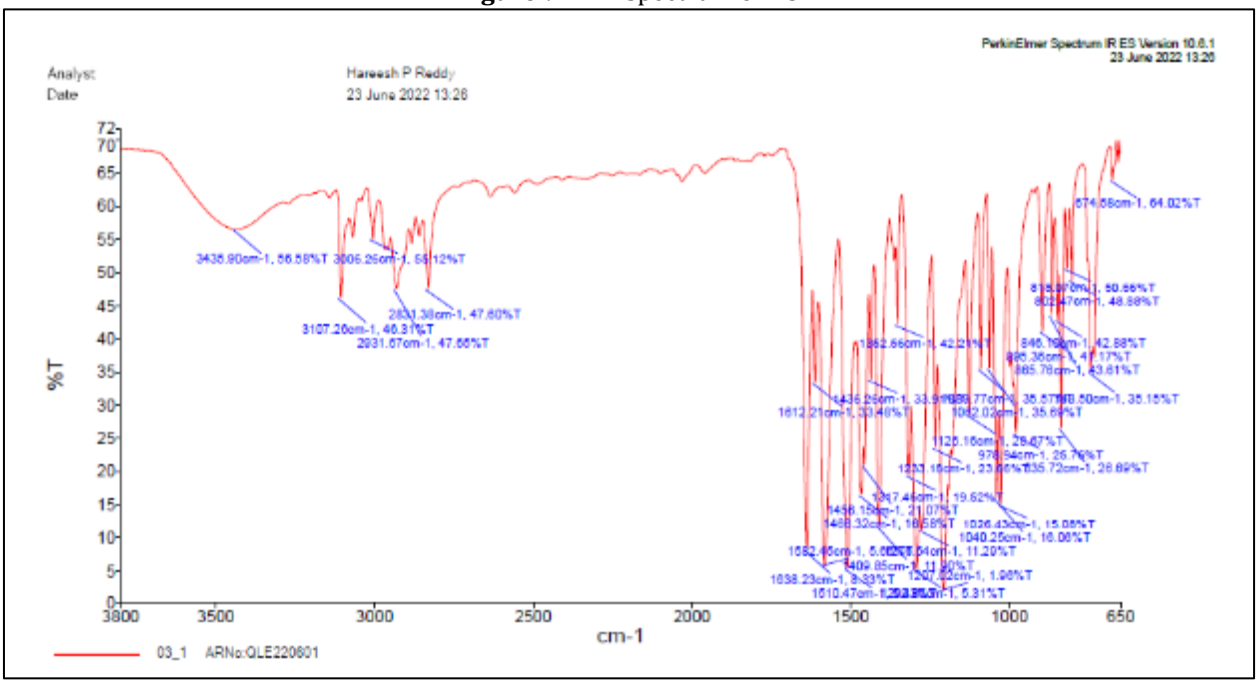
^{1}HNMR(δ) of D3 :3.909(s,3H,OMe),3.918(s,3H,OMe),3.950(s,3H,OMe),6.525(s,Ar-H), 7.260(s,Ar-H),8.137(s,py,2H),7.36-7.408(d,2H,Th-H),7.18(t,3H,Th-N),7.651-7.654(d,2H,Th-H).

Figure 8 ^{1}HNMR spectrum of D3



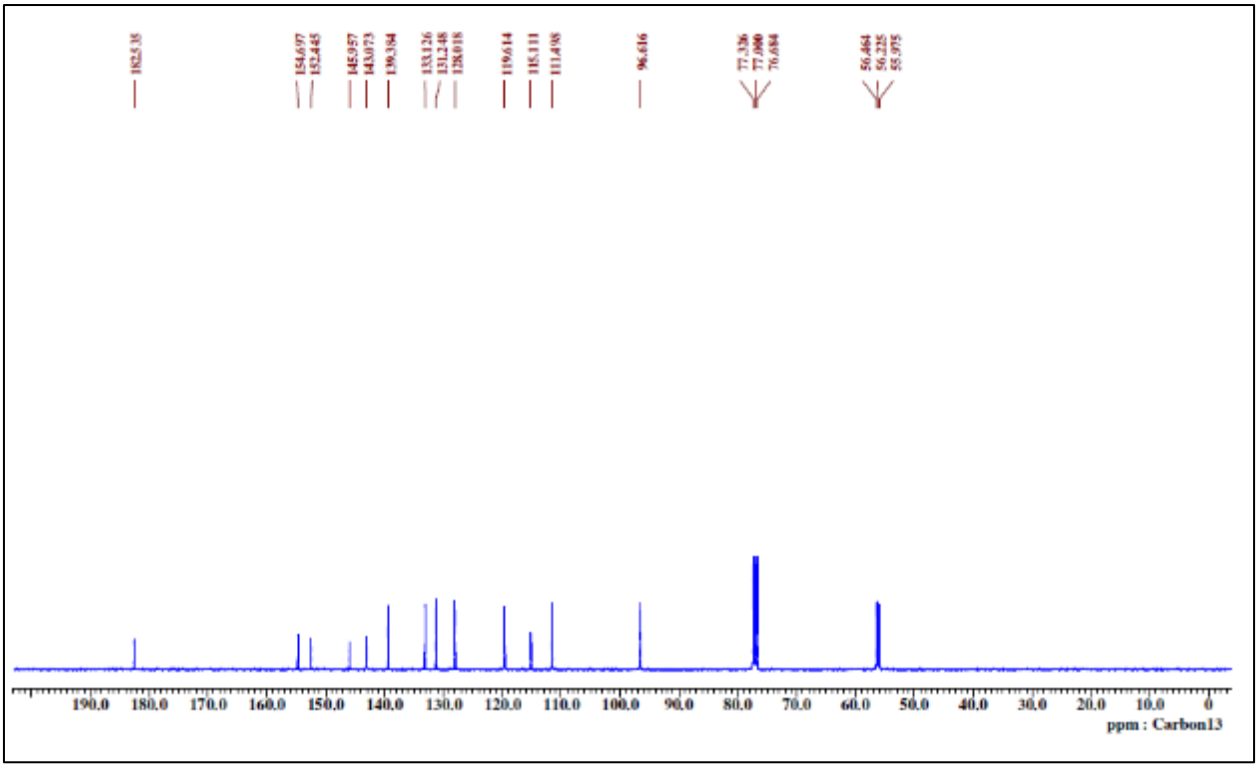
FTIR(ϑ,cm^{-1}) **of D3**:3107.26(Ar),1612-1510.47(C=N),1466-1436.26(C=C),1317-1040(C-O),802.47(C-H),743.50(C-S).

Figure 9 FTIR spectrum of D3

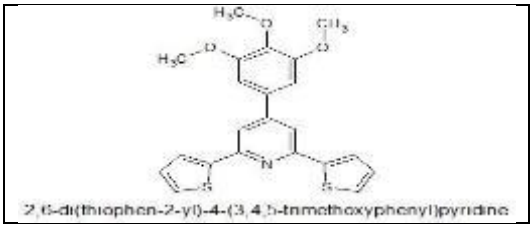


^{13}CNMR(δ ppm) of D3:55.975(OMe),56.25(OMe),56.464(OMe),139.7(C-O),154.69(2C,C-O),1111.49(2C,ArC),133.126(C,Arpy),152.44(3C,py),119.61(2C,py),128.018(3C,Th),143.07(2C,Th).

Figure 10 ^{13}CNMR spectrum of D3



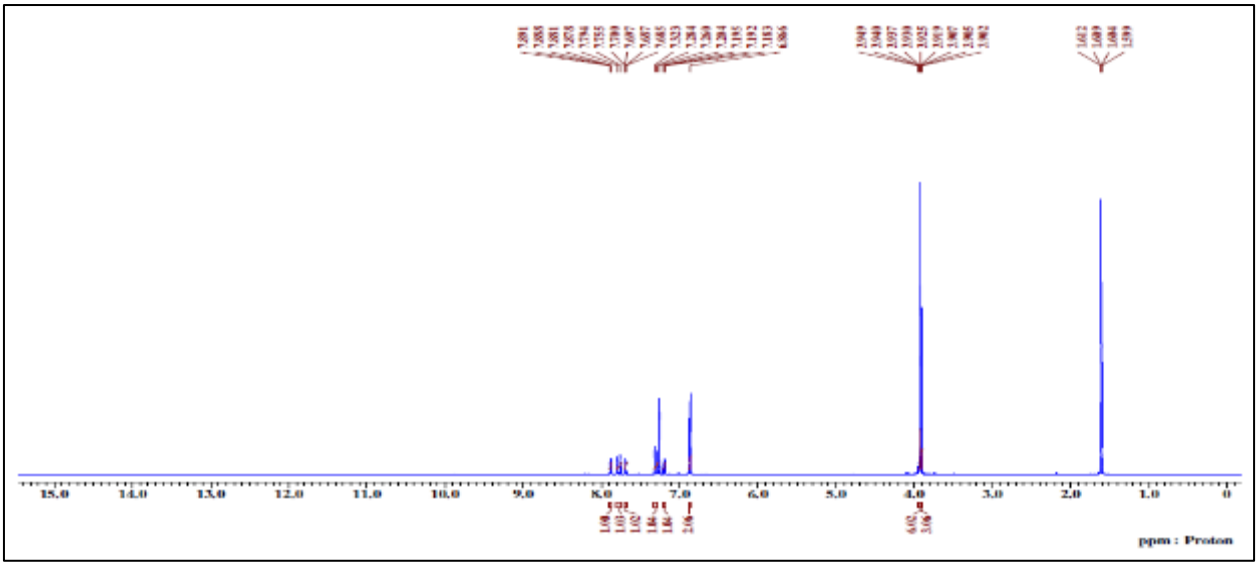
^{1}H NMR, IR &^{13}C NMR of D$_4$: 2,6-di(thiophen-2-yl)-4-(3,4,5-trimethoxyphenyl) pyridine



Chemical formula: $C_{22}H_{19}NO_3S_2$
Molecular Weight: 409.52116

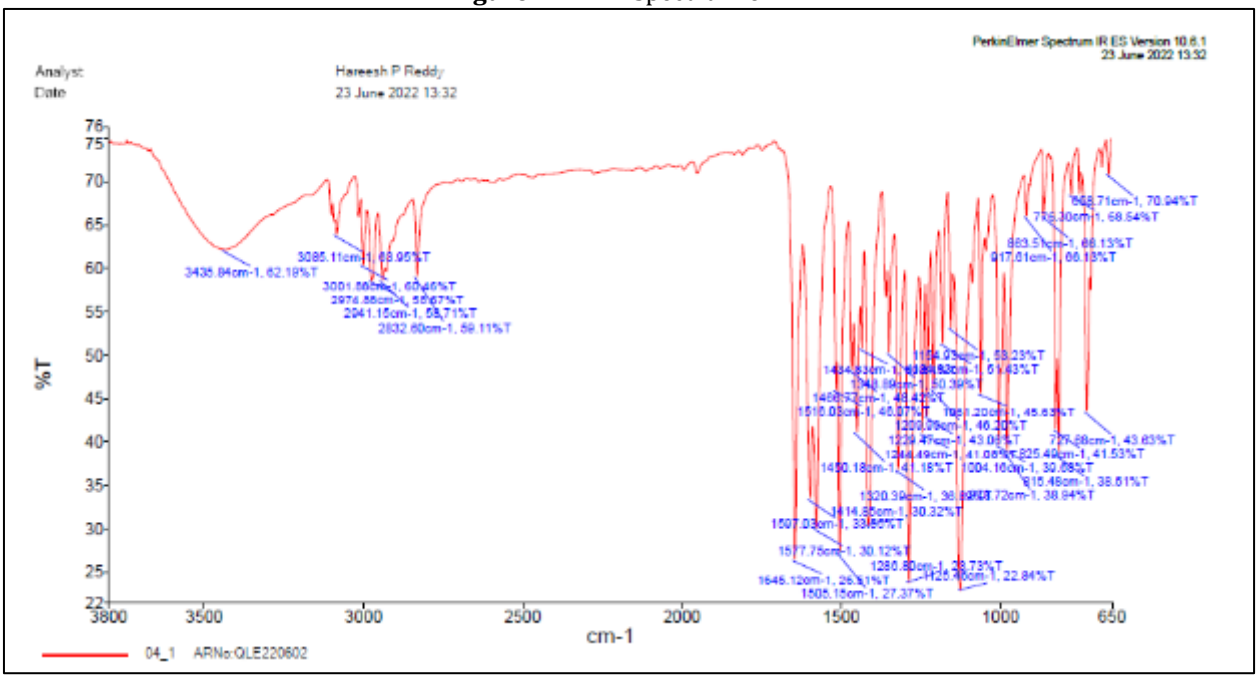
^{1}H NMR(δ) of D$_4$:3.902-3.907(s,3H,OMe), 3.925-3.930(s,3H,OMe),3.937-3.949(s,3H,OMe), 6.866(s,2H,Ar-H),8.2(s,2H,py), 7.195(t,3H,Th),7.690(d,Th).

Figure 11 ^{1}HNMR spectrum of D4



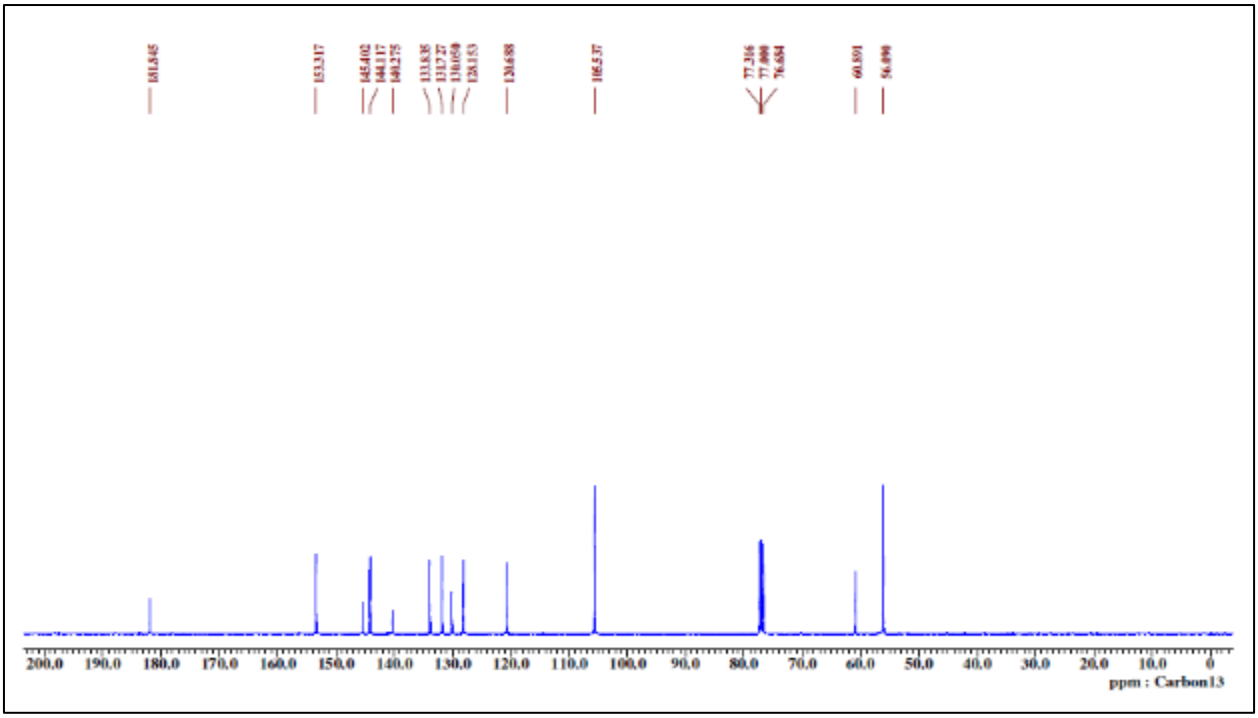
FTIR(ϑ,cm^{-1}) of D$_4$:3085.11(Ar),1597-1516(C=N),1320-1061(C-O),815(C-H),776.30(C-S).

Figure 12 FTIR spectrum of D4



^{13}CNMR(δppm) of D$_4$:76.684(OMe),77.00(OMe),77.316(OMe),153.317(C-O,Ar),133.835(C-O),131.72(Ar C),105.53(2C,Ar),120.68(py,2C), 128.15(3C,Th), 144(1C,Th).

Figure 13 ^{13}CNMR spectrum of D4



3.4. Antimicrobial activity

The antibacterial properties of Thiophene derivatives were evaluated against two pathogenic bacterial strains namely Gram +ve bacteria S. aureus and Gram-ve bacteria E. coli by agar well diffusion method [41]. In agar well, diffusion method the Thiophene derivatives didn't show antibacterial activity on pathogenic bacterial strains.

By considering all above observations we can conclude that our synthesized compounds doesn't show any significant inhibition of bacterial strain. Therefore the compounds do not possess antibacterial activity.

Table 4 Antimicrobial data

Compounds	**Treatment**	**Pathogenicmicrobial strains**	
		S. aureus	**E. coli**
Ciprofloxacin	5μg/50μg	14.00	13.67
D_1	25 μg/250 μg	-	-
	50 μg/500 μg	-	-
D_2	25 μg/250 μg	-	-
	50 μg/500 μg	-	-
D_3	25 μg/250 μg	-	-
	50 μg/500 μg	-	-
D_4	25 μg/250 μg	-	-
	50 μg/500 μg	-	-

4. Conclusion

The Thiophene derivatives D_1-D_4 synthesized in good yield and characterized and confirmed by using spectroscopic techniques like ^{1}H NMR and ^{13}C NMR, FT-IR. Physical and analytical data found was in good correlation with the expected values. Hence, assigned structures were confirmed. All the synthesized compounds were screened for antibacterial activity and it shows very low antibacterial activity with respect to standard.

Compliance with ethical standards

Acknowledgments

The authors are thankful to Dr. Raghavendra Kumar for providing lab facility. Also, the authors are grateful Dr.Devaraja, Department of Biochemistry for providing lab facility and support to study bacterial, fungal, and antioxidant activities.

Disclosure of conflict of interest

The authors declared no potential conflict of interest with respect to the authorship and publication.

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