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Synthesis and Biological activity of new hydrazone\Oxadiazole derivatives based on 2-Indole Carboxylic acid

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ABSTRACT

A two-step reaction procedure was used to develop and synthesis a three of new oxadiazole derivatives that have a 2-indole carboxylate scaffold. Initially, 5-Bromo indole-2-carbohydrazide were condensed with three different heteroaromatic aldehydes (furan-2-carbaldehyde, 5-methylfuran-2-carbaldehyde, and oxazole-2-carbaldehyde), to produce the required hydrazone intermediate (Hn1, Hn2, and Hn3). Following cyclization in DMSO with iodine and potassium carbonate, the desired 1,3,4-oxadiazole derivatives (CHn1, CHn2, and CHn3), were produced in high yield. The synthesized derivatives were characterized and their structures were confirmed using FT-IR, ^{1}H NMR, and ^{13}C NMR techniques. The antibacterial activity of the produced compounds was tested on a panel of Gram-positive and Gram-negative bacterial strains using the agar diffusion technique. The results showed that oxadiazole derivatives had much higher antibacterial activity than their comparable hydrazone predecessors. The synthesized compounds showed significant antibacterial effect was observed against (*Escherichia coli* and *Pseudomonas aeruginosa*, *Proteus, Klebsiella pneumoniae and Staphylococcus aureus*), with the oxadiazole series showing improved efficacy compared to hydrazone analogs; notably, CHn3 showed the highest broad-spectrum activity, and in some cases was comparable to or exceeding that of amoxicillin.

Keywords: ***Pseudomonas aeruginosa, Proteus, Klebsiella pneumoniae*, hydrazone, indole.**

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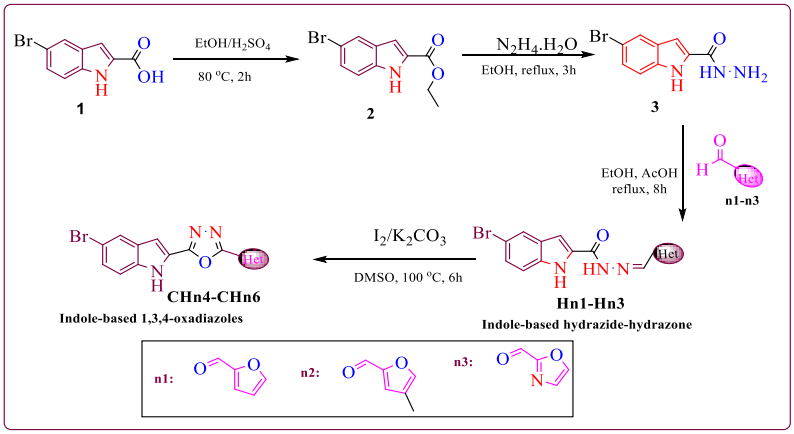
1. Introduction

Antimicrobial resistance among pathogenic bacteria is an ongoing and serious global health threat, reflecting the critical need for innovative and effective antibacterial drug discovery [1],[2]. Heterocyclic compounds have attracted great attention in medicinal chemistry due to their diverse biological activity and structurally diverse nature [3], [4], [5]. Indole derivatives stand out as well-established scaffolds for drug development, and possess a variety in their pharmacological properties including antibacterial, antifungal, anticancer, and anti-inflammatory activity [6],[7],[8]. Indole-2-carboxylate and indole-2-carboxamide derivatives have in particular shown significant biological potential given their ability to respond to a wide range of drug receptors [9][10],[11]. However, 1,3,4-oxadiazole is a significant Quintet heterocyclic ring widely used in medicinal chemistry as a bioisosteric substitute for amide and ester functionalities [12]. Oxadiazole compounds are recognized for possessing various biological activities, including antibacterial effects, antitubercular, anticancer, and anti-inflammatory features [13], [14], [15]. The addition of the oxadiazole moiety frequently improves the metabolic stability [16], lipophilicity [17], and binding affinity of pharmaceutical candidates [18], [19], [20]. Given these conditions, the current study aims to combine the physiologically active indole nucleus and the 1,3,4-oxadiazole pharmacophore in a single molecular framework. We present a new series of oxadiazole derivatives based on 2-indole carboxylate via hydrazone production followed by oxidative cyclization. Furthermore, the antibacterial activity of these synthetic compounds was tested on selected Gram-positive and Gram-negative strains to learn their possibilities as new antibacterial agents. This work aims to prepare a group of cyclic compounds new hydrazone\Oxadiazole, based on 2-Indole Carboxylic acid, were prepared, and their activity against bacteria was studied and compared.



Scheme1. Synthesis of indole-based oxadiazoles

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2. Experimental

2.1. Materials and Instruments

All chemicals used in this study, including indole derivatives, heterocyclic aromatic aldehydes, hydrazine hydrate (80%), iodine, potassium carbonate, and different solvents, were analytical grade and obtained from renowned vendors such as Sigma Aldrich and Fluka. The melting points were determined with a Gallenkamp MFB-600 melting point equipment. FT-IR spectra were obtained using a Shimadzu FT-IRAffinity-1S instrument. TLC was used to monitor the reaction's progress using silica-gel SILG/UV 254 plates, and 1H and 13C NMR spectroscopy was performed using a Bruker AC 400 NMR spectrometer at a frequency of 400 MHz.

2.1.1. Synthesis of compound ethyl 5-bromo-1H-indole-2-carboxylate (2) [20].

A solution of (5g, 20 mmol) of 1H-indole-2-carboxylic acids **(1),** 25 mL ethanol was treated with 0.5 mL of H_2SO_4 and agitated at heating (8 ^oC) for 16 hours. After TLC monitoring, the reaction was stopped with a saturated $NaHCO_3$ hydrate solution and extracted three times with EtOAc (3 × 30 mL). The mixed organic phase was dried over anhydrous Sodium sulfate before vacuum suction filtering. The solvent was evaporated and the produced was filtered, and dried, recrystallized from hot ethanol, to afford 4.2 g of a **(2)** as white brownish solid in 75% yield.

2.1.2. 5-bromo-*1H*-indole-2-carbohydrazide (3) [21].

Hydrazine hydrate 80%, (2 mL) was added dropwise to a solution of ethyl 5-bromo-1H-indole-2-carboxylate 2 (2.5 g, 10 mmol) in 20 mL of EtOH and refluxed for 12 hrs. until no ester spot has been shown in TLC plate. Following this time span, the mixture was allowed to cool at room temperature. The resulting solid product underwent recrystallization in ethanol, yielding pure white brownish product of compound **(3)** in 99 % yield.

2.1.3. General procedure of hydrazone derivatives (Hn1-Hn3) [22].

In a solution of indole carbohydrazide (3), (1 mmol) and heterocyclic aromatic aldehydes (1mmole) in EtOH (10 mL), 3 drops of AcOH were added and agitated under refluxed conditions for 5 hours. TLC analysis revealed that the reaction was complete, thus the precipitate was filtered and washed numerous times with hot ethanol. The residue was collected and purified by recrystallization in ethanol, yielding pure hydrazone products (Hn1-Hn2) that were then studied by FTFT-IR, 1H, and 13C NMR spectroscopy.

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2.2.3.1. Spectral data of indole-linked hydrazide-hydrazone (Hn1-Hn3)

5-bromo-*N'*-(furan-2-ylmethylene)-*1H*-indole-2-carbohydrazide (Hn1)

Brownish-weight, yield = 78 %, m.p. = 233-235°C., *Rf* = 0.54 (ethyl acetate, 100%), FT-FT-IR (υ/cm^{-1}): 3417, 3339, (N-H), 3056 (Csp^2-H), 1631 (C=O), 1636 (C=N), 1518 (C=C).

HNMR: ^{1}H NMR (300 MHz, DMSO) δ 12.10 (s, 1H), 12.02 (s, 1H), 8.71 (s, 1H), 7.99 (d, *J* = 1.9 Hz, 1H), 7.75 (d, *J* = 5.0 Hz, 1H), 7.56 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.43 – 7.30 (m, 2H), 7.21 (dd, *J* = 5.0, 3.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ 157.12, 142.63, 139.05, 135.46, 131.36, 131.20, 129.11, 128.79, 127.98, 126.47, 124.00, 114.45, 112.47, 102.98, 40.35, 40.07, 39.80, 39.52, 39.24, 38.96, 38.69.

5-bromo-*N'*-((4-methylfuran-2-yl)methylene)-*1H*-indole-2-carbohydrazide (Hn2)

yellow, yield = 88 %, m.p. = 213-215°C., *Rf* = 0.59 (ethyl acetate, 100%), FT-IR (υ/cm^{-1}): 3274 (N-H), 1635 (C=O), 1592 (C=N), 1573 (C=C). ^{1}H NMR (300 MHz, DMSO) δ 11.99 (s, 1H), 11.82 (s, 1H), 8.66 (s, 1H), 7.88 (d, *J* = 1.9 Hz, 1H), 7.54 (d, *J* = 5.0 Hz, 1H), 7.41 – 7.17 (m, 3H), 6.93 (d, *J* = 5.1 Hz, 1H), 2.29 (s, 3H). C: ^{13}C NMR (75 MHz, DMSO) δ 157.37, 142.14, 140.64, 135.87, 132.88, 131.89, 131.41, 129.25, 128.57, 126.87, 124.41, 114.88, 112.91, 103.15, 40.78, 40.50, 40.23, 39.95, 39.67, 39.39, 39.11, 14.10.

5-bromo-*N'*-(oxazol-2-ylmethylene)-*1H*-indole-2-carbohydrazide (Hn3)

Light brown, yield = 82 %, m.p. = 119-201°C., *Rf* = 0.49 (ethyl acetate, 100%). FT-IR (υ/cm^{-1}): 3370 (N-H), 1667 (C=O), 1570 (C=N), 1547 (C=C). ^{1}H NMR (300 MHz, DMSO) δ 12.28 (s, 1H), 11.97 (s, 1H), 8.73 (s, 1H), 7.99 (s, 1H), 7.86 (d, *J* = 3.2 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.47 (m, 1H), 7.39 (s, 1H), 7.34 – 7.18 (m, 1H), 7.13 (d, *J* = 5.9 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ 164.77, 158.03, 144.74, 142.43, 136.26, 131.49, 129.42, 129.33, 127.66, 127.44, 124.78, 122.73, 115.24, 115.14, 113.23, 104.30, 40.95, 40.68, 40.40, 40.12, 39.84, 39.56, 39.29.

2.2.4. General procedure of oxadiazole derivatives (Cn1-CHn3) [23].

In different reaction flasks (1 mmole) of indole hydrazide-hydrazone **(Hn1-Hn3)** in 10 mL of DMSO, 3 mmol of K_2CO_3 and 1.2 mmol of I_2 was introduced into the reaction, followed by stirring at 100 °C for 6 hours. When the reaction reached completion, as confirmed by TLC analysis, the mixture was poured in ice-water. The resulting residue was collected and washed with water and EtOAc. The solid product was more purified through recrystallization in ethanol, yielding pure products **(Hn1-Hn3)**.

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2.2.4.1. Spectral data of indole-linked hydrazide-hydrazone (CHn1-CHn3)

2-(5-bromo-1H-indol-2-yl)-5-(furan-2-yl)-1,3,4-oxadiazole (CHn1)

Light yellow, yield = 80 %, m.p. = 201-204°C., *Rf* = 0.56 (ethyl acetate, 100%). FT-IR (υ/cm^{-1}): 3417, 3282 (N-H), 1630 (C=N), 1536 (C=C), 1250 (Csp^2-O). ^{1}H NMR (300 MHz, DMSO) δ 12.04 (s, 1H), 8.61 (s, 1H), 7.70 (d, *J* = 5.3 Hz, 1H), 7.55 – 7.40 (m, 3H), 7.38 – 7.03 (m, 3H). C: ^{13}C NMR (75 MHz, DMSO) δ 157.98, 143.31, 139.37, 136.73, 131.92, 131.77, 130.65, 129.71, 128.43, 125.31, 122.18, 121.48, 113.13, 40.79, 40.51, 40.23, 39.96, 39.68, 39.40, 39.12.

2-(5-bromo-1H-indol-2-yl)-5-(4-methylfuran-2-yl)-1,3,4-oxadiazole (CHn2)

Greenish yellow, yield = 72 %, m.p. = 212-214°C., *Rf* = 0.64 (ethyl acetate, 100%). FT-IR (υ/cm^{-1}): 3245 (N-H), 1621 (C=N), 1536 (C=C), 1248 (Csp^2-O). ^{1}H NMR (300 MHz, DMSO) δ 12.22 (s, 1H), 8.74 (s, 1H), 7.61 (s, 1H), 7.50 (dd, J = 14.3, 8.1 Hz, 2H), 7.41 – 7.20 (m, 2H), 7.02 (t, J = 5.2 Hz, 1H), 2.35 (s, 3H). C: ^{13}C NMR (75 MHz, DMSO) δ 157.84, 142.37, 140.62, 136.83, 132.90, 131.79, 131.40, 130.74, 128.62, 125.21, 122.14, 121.37, 113.17, 112.90, 40.79, 40.51, 40.24, 39.96, 39.68, 39.40, 39.12, 14.08.

2-(5-bromo-1H-indol-2-yl)-5-(oxazol-2-yl)-1,3,4-oxadiazole (CHn3)

Greenish yellow, yield = 72 %, m.p. = 212-214°C., *Rf* = 0.64 (ethyl acetate, 100%). FT-IR (υ/cm^{-1}): 3188 (N-H), 1643 (C=N), 1552 (C=C), 1264 (Csp^2-O). ^{1}H NMR (300 MHz, DMSO) δ 12.27 (s, 1H), 8.63 (s, 1H), 8.01 (d, *J* = 3.2 Hz, 1H), 7.92 – 7.84 (m, 1H), 7.49 (dd, *J* = 16.1, 8.1 Hz, 2H), 7.40 – 7.16 (m, 2H). ^{13}C NMR (75 MHz, DMSO) δ 164.73, 164.40, 144.60, 142.47, 136.85, 131.27, 130.66, 125.64, 122.77, 122.35, 121.64, 120.65, 113.20, 112.99, 40.78, 40.50, 40.22, 39.94, 39.67, 39.39, 39.11.

2.3. Antibacterial Activity

The minimum inhibitory concentration (MIC) values of hydrazones and oxadiazole derivatives were tested against *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus*, *Klebsiella pneumoniae*, *and Staphylococcus aureus*, according to protocols approved by the Institute for Clinical and Laboratory Standards. Samples were prepared in dimethyl sulfoxide (DMSO) at concentrations ranging from 2 × 10^{-3} to 5 mM, with 100 µL of each sample added to a 96-well plate. The McFarland semi-standard was used to prepare a bacterial suspension (18–20 h) in normal saline, which was then diluted 1:100 using Mueller-Hinton broth. Subsequently, 100 µL of this suspension was added to each well, resulting in final concentrations ranging from 1 × 10^{-3} to 2.5 mM after inoculation with 0.5–1 × 10^6 CFU/mL of bacteria. The minimum inhibitory concentration was determined after a 22-hour incubation at 37°C.

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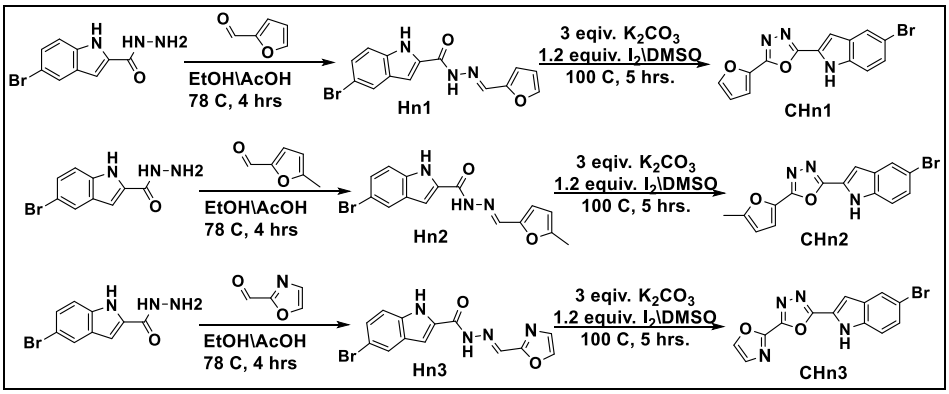
3. Results and discussion

3.1. Preparation of Hn1-Hn3 and CHn1-CHn3

The synthetic pathway for synthesizing synthesized derivatives is shown in Scheme 2. The products ethyl 1*H*-indole-2-carboxylates **2** were obtained from the reaction of 1*H*-indole-2-carboxylic acids **1** in the presence of sulfuric acid under reflux conditions in EtOH. The treatment of ester derivative **2** with hydrazine leads to the synthesis of indole carbohydrazide **3**, which are by reacting with heterocyclic aromatic aldehydes **n1-n3**, led to indole-based hydrazones **Hn1-Hn3**. Intramolecular cyclization reaction of hydrazide-hydrazone derivatives **Hn1-Hn3** in the presence of molecular iodine and potassium carbonate in DMSO at 100 ^{o}C for 6h afforded to the C**Hn1-CHn3.**



Scheme 2. The synthetic route of Hn1, Hn2, Hn3, CHn1, CHn2, and CHn3

The structures of all synthesized products were deduced from their FT-IR, ^{1}H, and ^{13}C NMR. The infra-red spectrum of all preparation compound showed that a medium band observed at 3400–3200 cm^{-1} is attributed to the N–H stretching vibration of the indole moiety. Aromatic C–H stretching vibrations appeared in the region 3100–3000 cm^{-1}. A strong band at 1670–1580 cm^{-1} corresponds to the C=N of the imine groups stretching vibration, and the shifting of these bands indicates the successful cyclization 1,3,4-oxadiazole ring, confirming. Multiple bands in the region 1600–1450 cm^{-1} are assigned to aromatic C=C stretching vibrations. Strong absorptions at 1300–1200 cm^{-1} are due to C–O–C stretching vibrations of the oxadiazole and furan rings. Additionally, a band observed at 650–500 cm^{-1} corresponds to the C–Br stretching vibration. The deficiency of a carbonyl absorption band near 1690 cm^{-1} confirms the formation of the oxadiazole ring. The proton NMR spectrum of the hydrazone derivatives in dimthylsolfoxide-d_6 at 25°C displays a broad characteristic signal at around (12.02- 11.88) pp for the NH groups and the indole ring. And that of amido groups appeared at the range of (12.28-11.98) ppm. The disappearance of these signals confirms the formation of the oxadiazole ring successfully.

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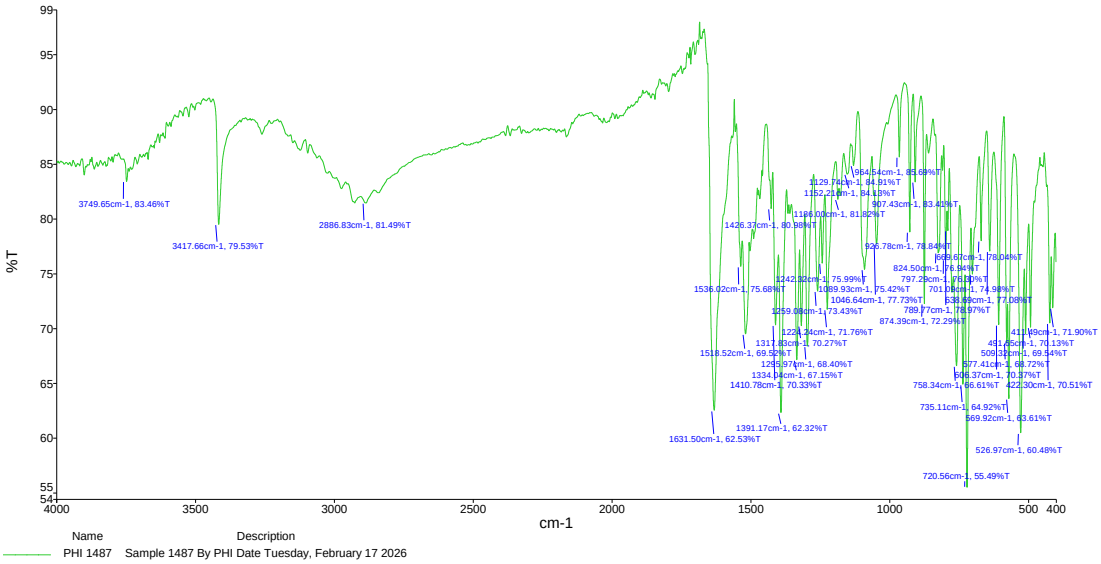

Figure 1. FT-IR spectrum of compound (Hn1)

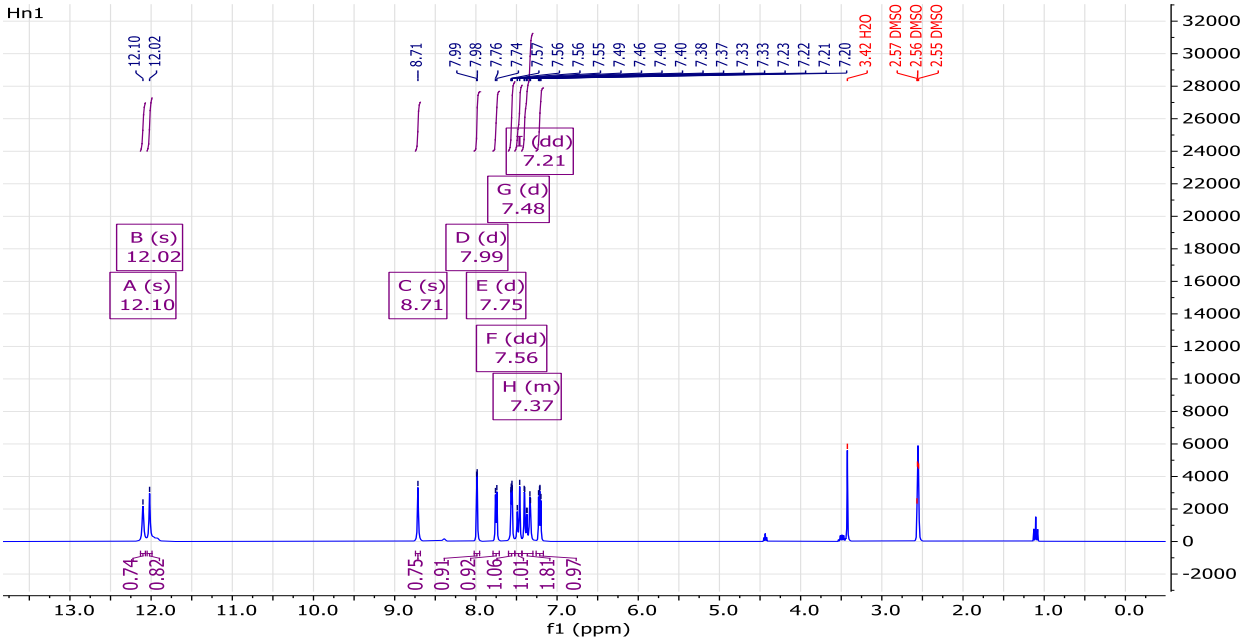

Figure 2. ^{1}H-NMR spectrum of compound (Hn1)

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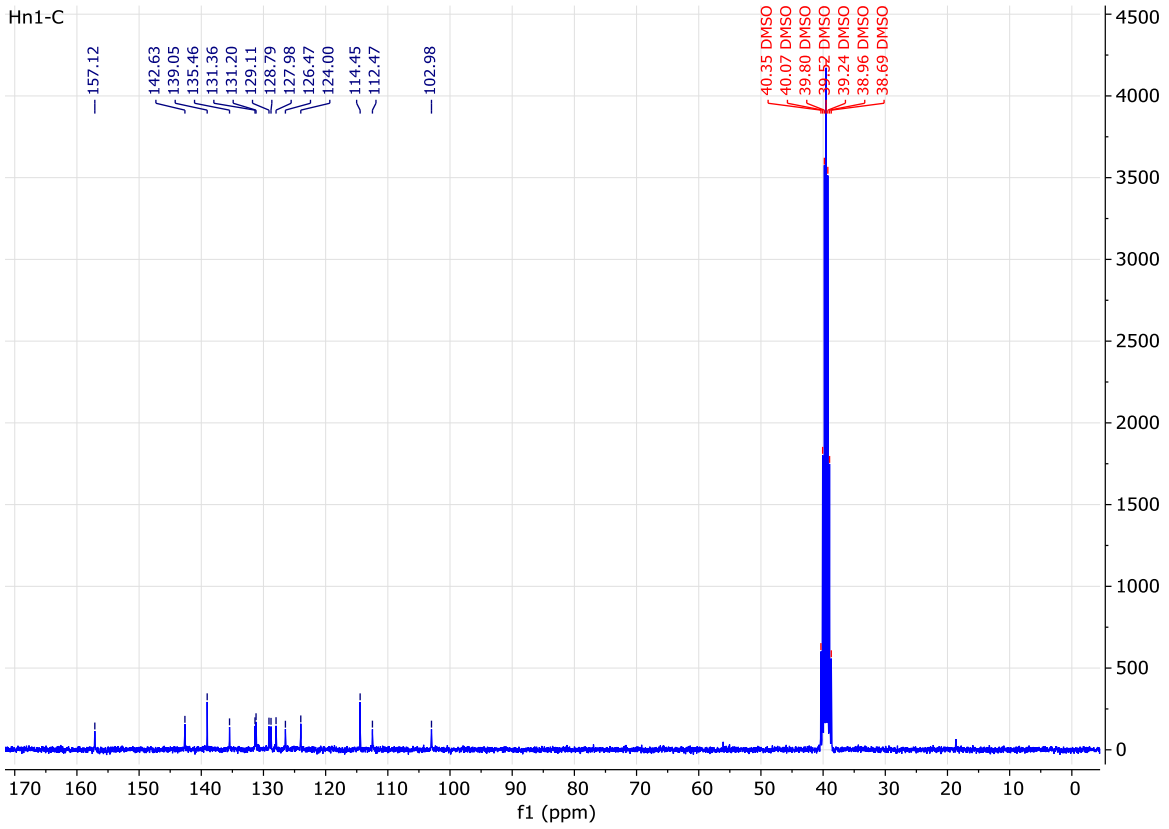

Figure 3. ^{13}**C-NMR spectrum of compound(Hn1)**

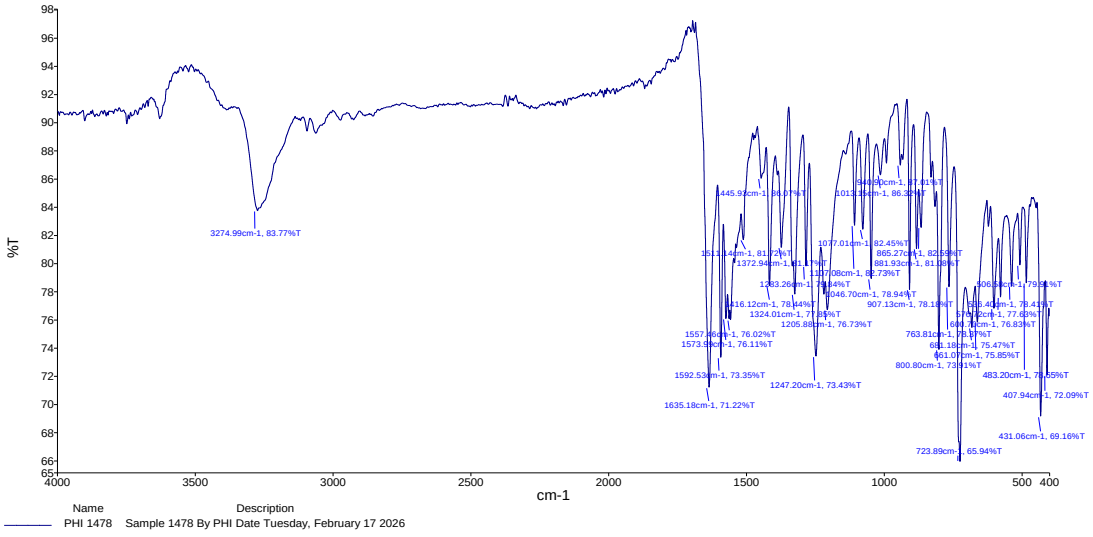

Figure 4. FT-IR spectrum of compound (Hn2)

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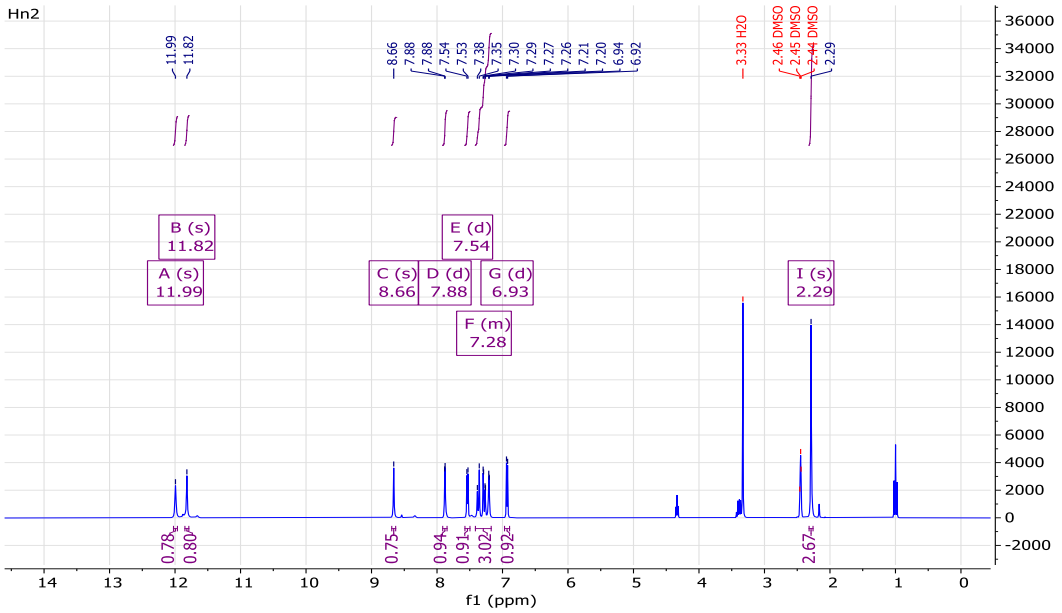

Figure 5. ^{1}H NMR spectrum of compound(Hn2)

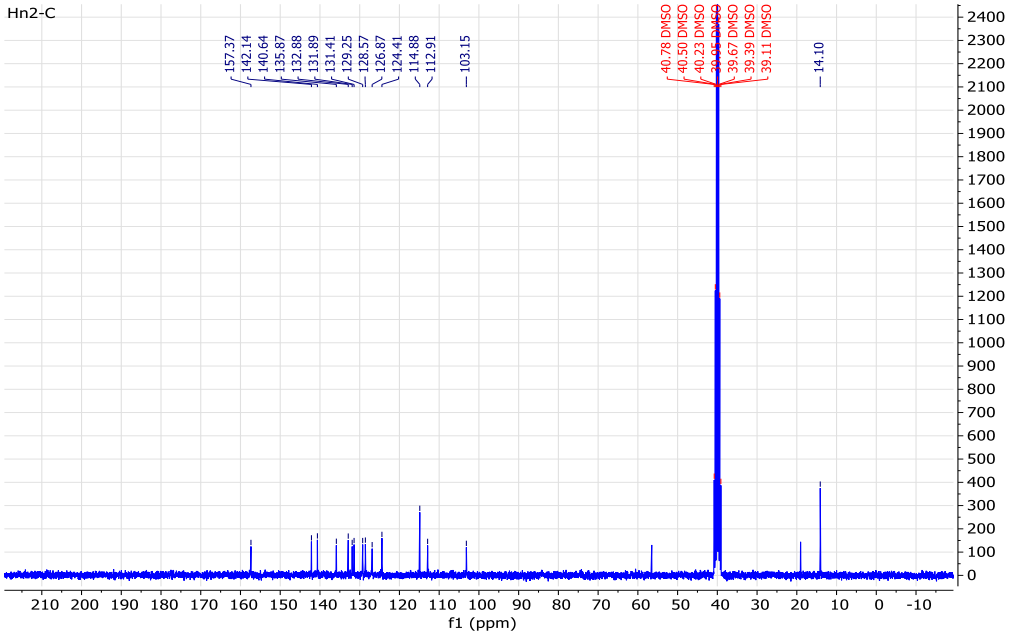

Figure 6. ^{13}CNMR spectrum of compound(Hn2)

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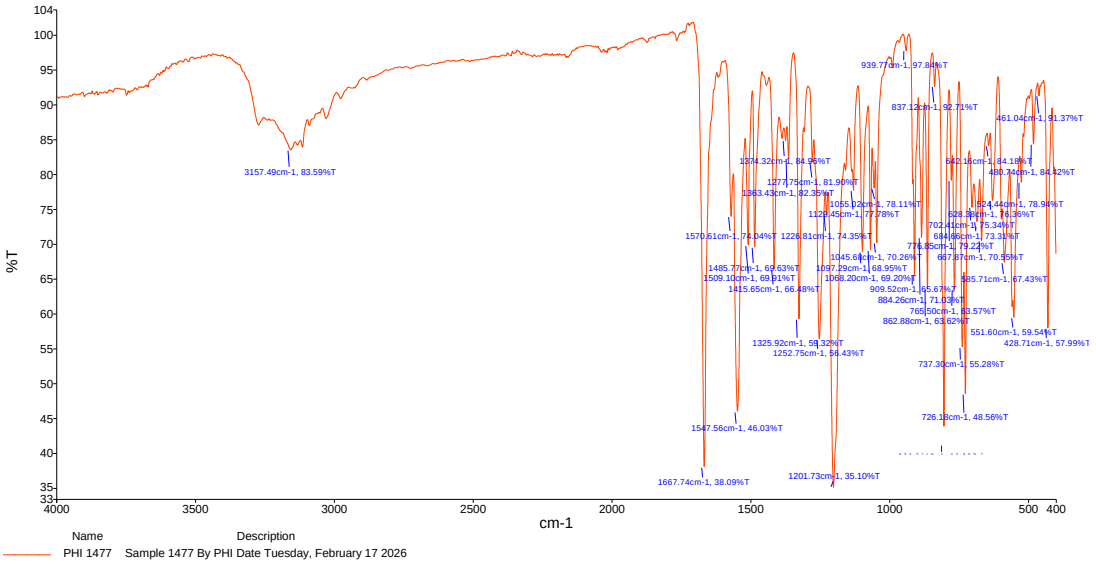

Figure 7. FT-IR spectrum of compound (Hn3)

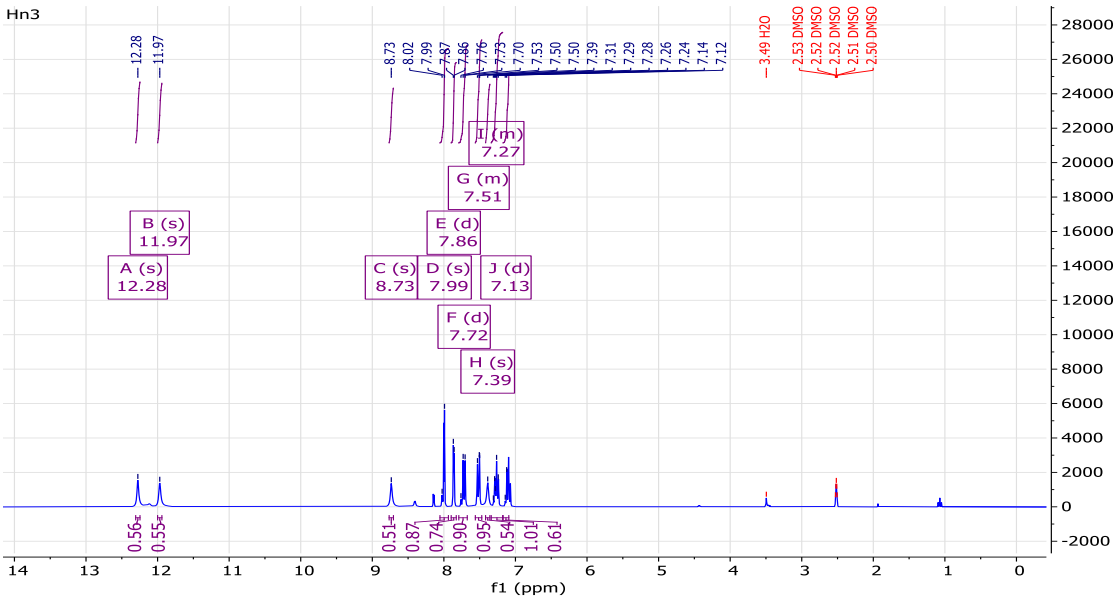

Figure 8. ^{1}H NMR spectrum of compound(Hn3)

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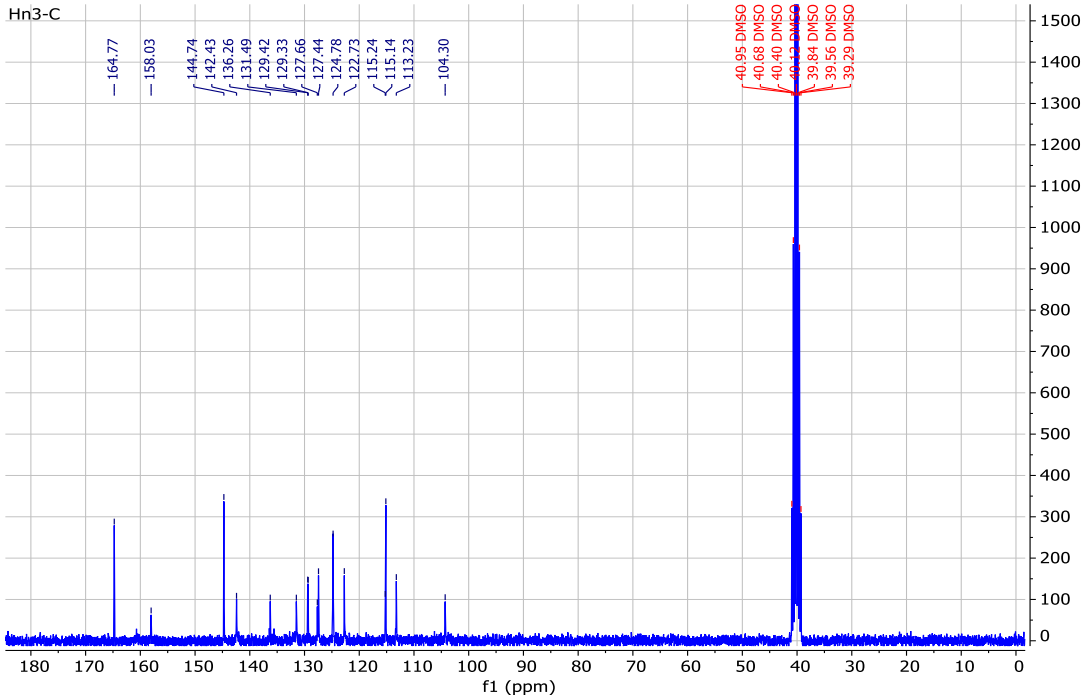

Figure 9. ^{13}C NMR spectrum of compound(Hn3)

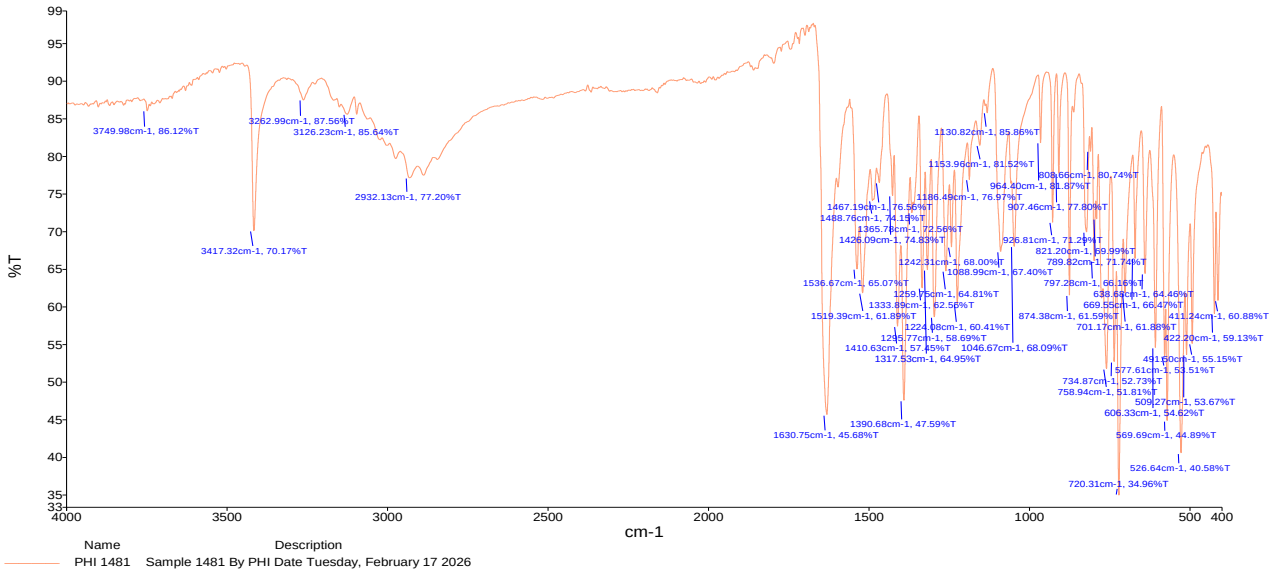

Figure 10. FT-IR spectrum of compound (CHn1)

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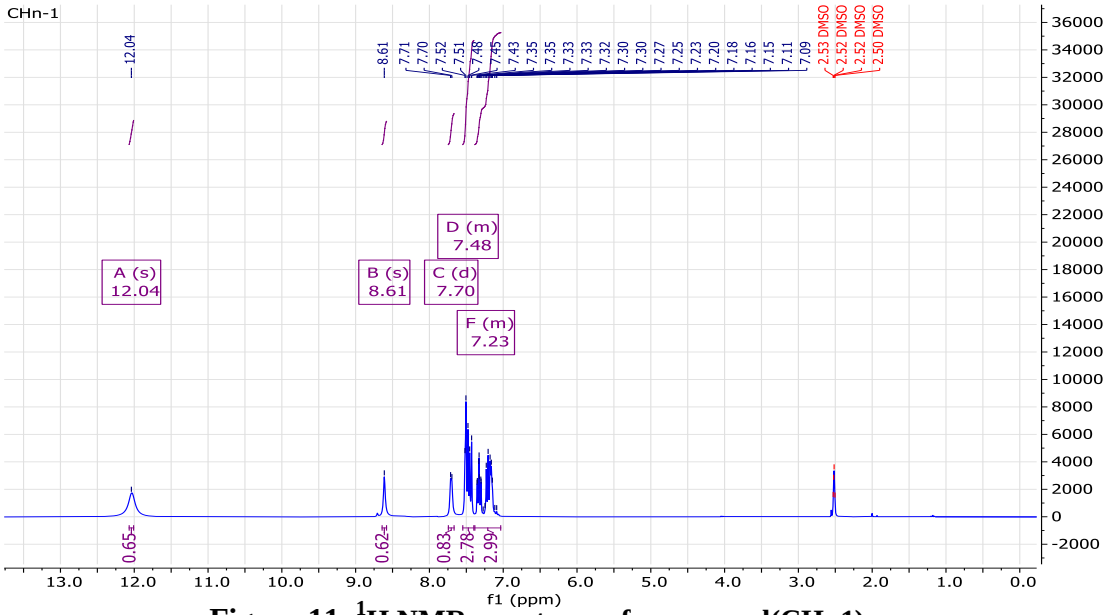

Figure 11. ^{1}H NMR spectrum of compound(CHn1)

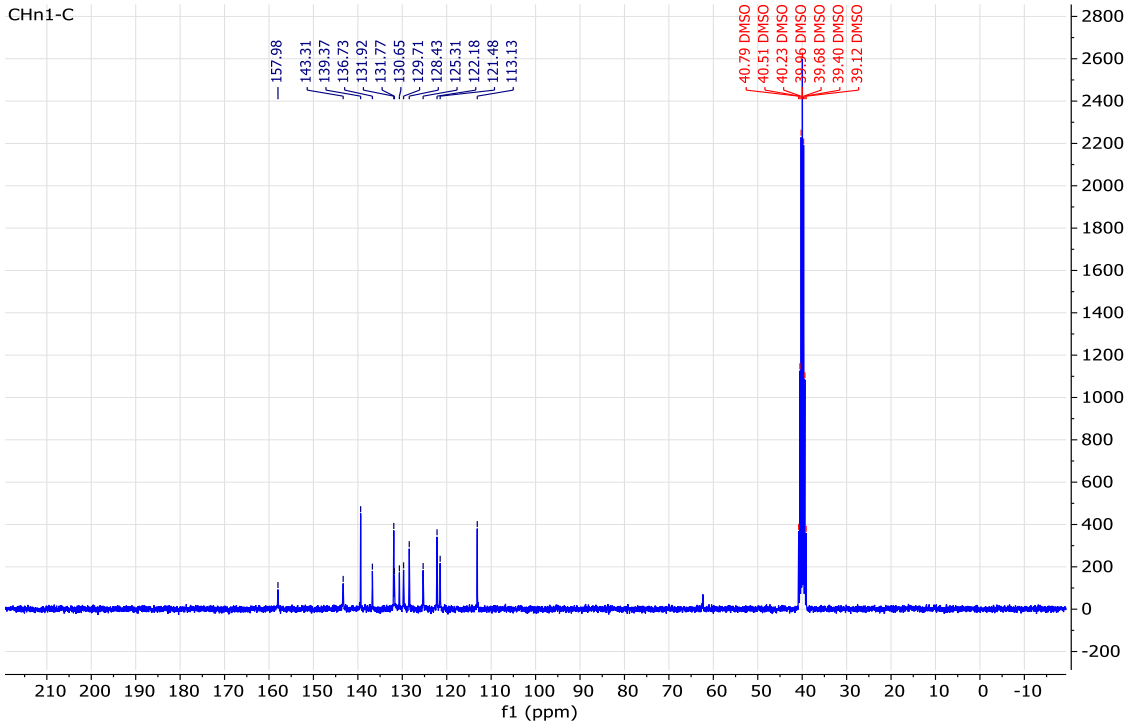

Figure 12. ^{13}C NMR spectrum of compound(CHn1)

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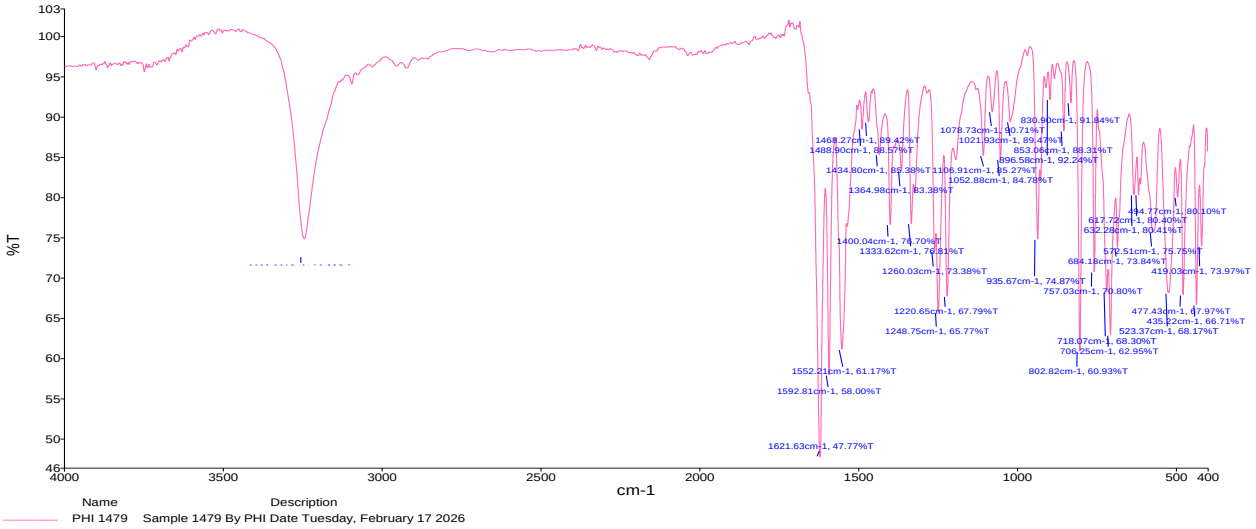

Figure 13. FT-IR spectrum of compound (CHn2)

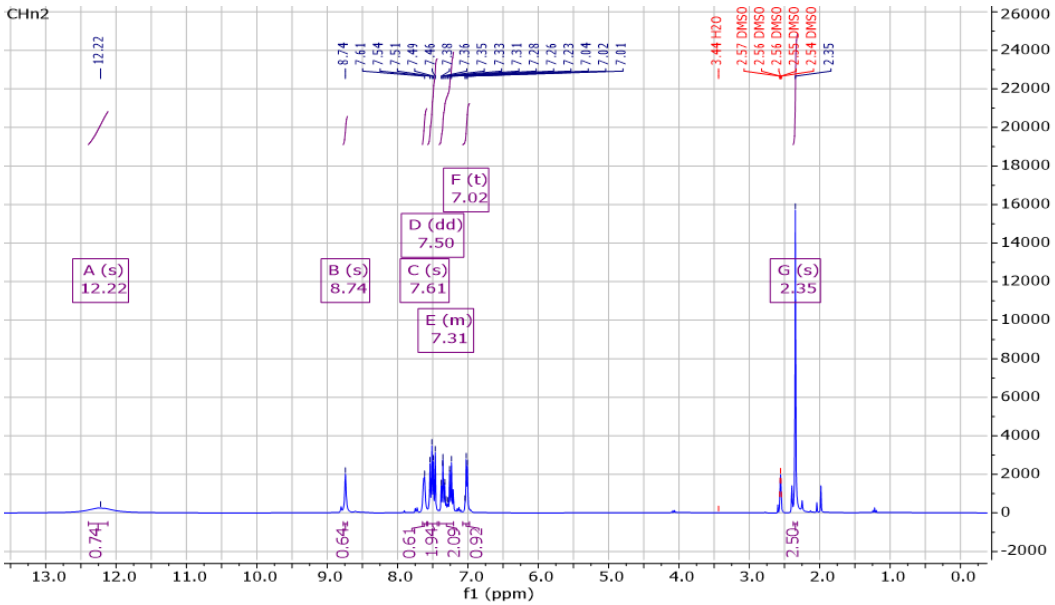

Figure 14. ^{1}H-NMR spectrum of compound(CHn2)

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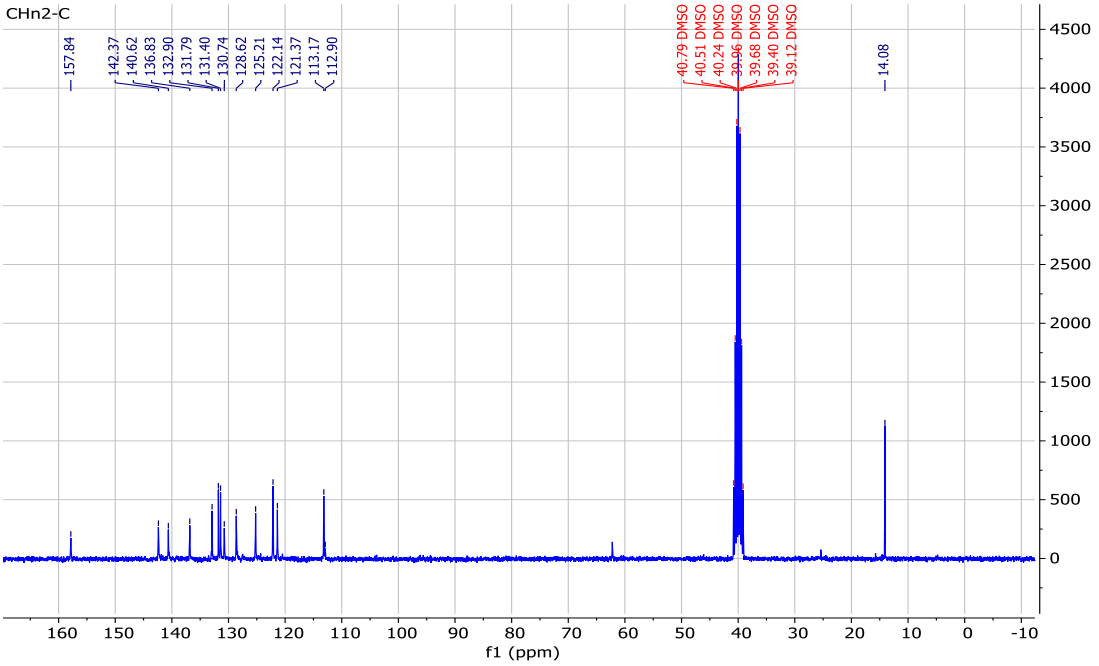

Figure 15. ^{13}C NMR spectrum of compound(CHn2)

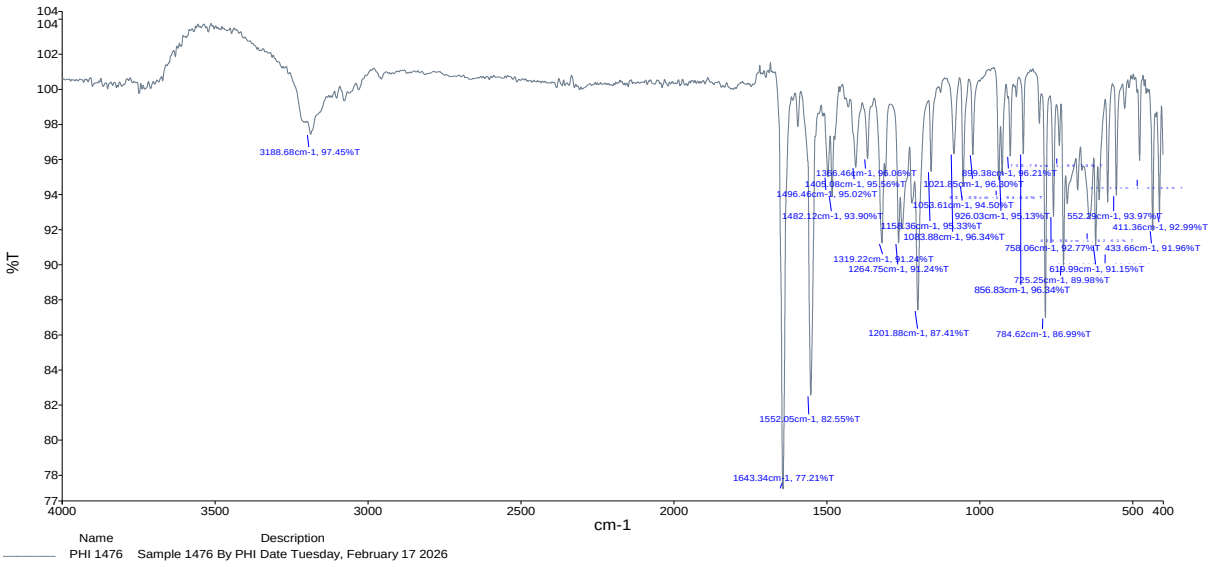

Figure 16. FT-IR spectrum of compound (CHn3)

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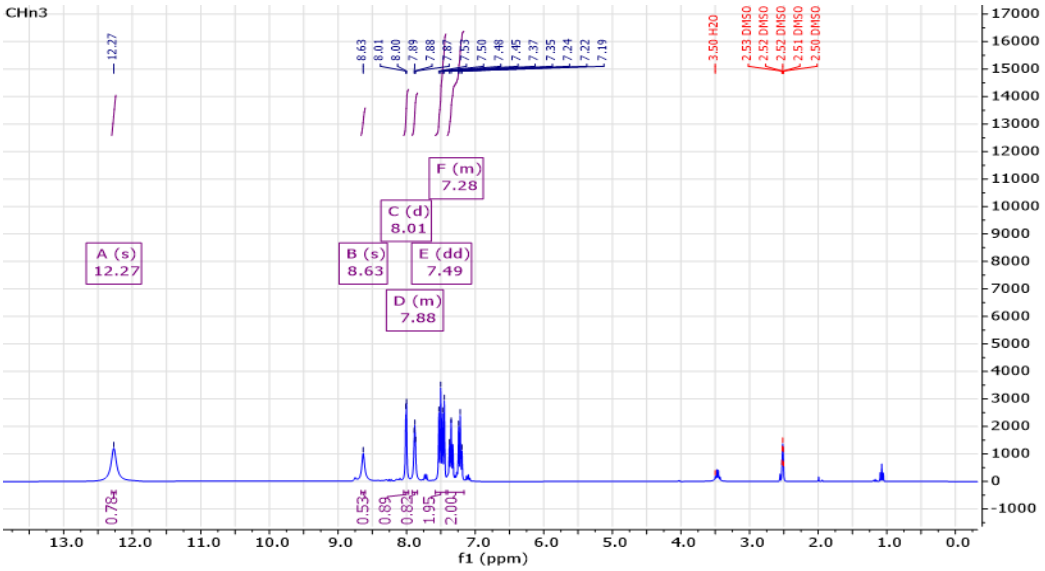

Figure 17. ^{1}H NMR spectrum of compound(CHn3)

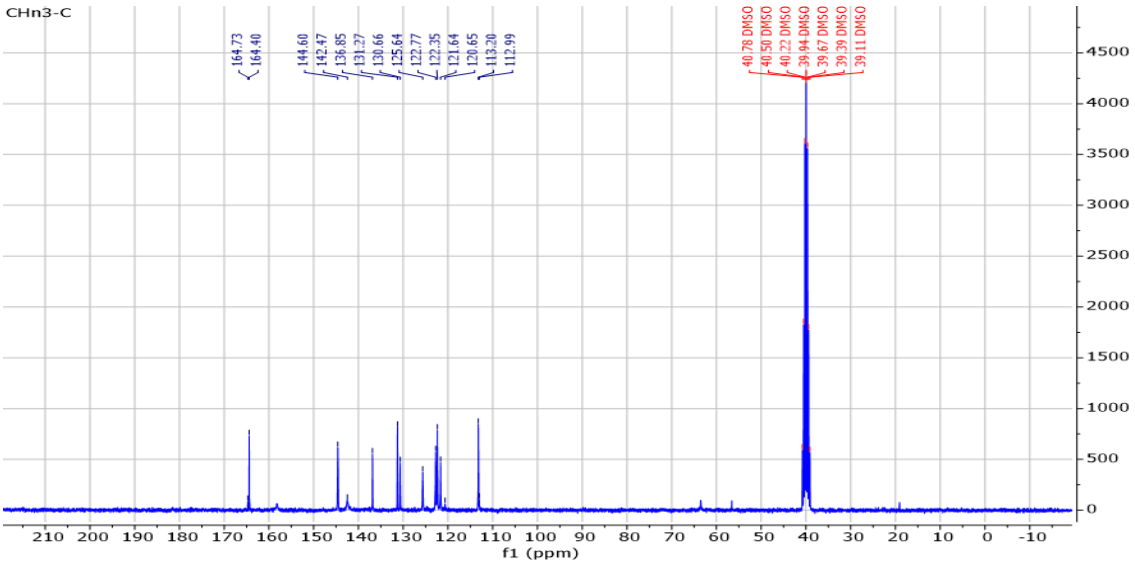

Figure 18. ^{13}C NMR spectrum of compound(CHn3)

3.2. The antibacterial activity

The antibacterial activity of the synthesized indole derivatives (Hn1–Hn3 and CHn1–CHn3) was evaluated using the minimum inhibitory concentration (MIC) method against five bacterial strains, including Gram-negative bacteria (Escherichia coli, Pseudomonas aeruginosa, Proteus, and Klebsiella pneumoniae) and Gram-positive bacteria (Staphylococcus aureus). The results were compared to the

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reference antibiotic amoxicillin, and the obtained MIC values are summarized in Table 1. The hydrazone derivatives (Hn1–Hn3) exhibited moderate antibacterial activity, with MIC values generally ranging between 3.000 and 3.500. Of these derivatives, Hn3 exhibited slightly greater activity against Escherichia coli and Staphylococcus aureus (MIC) 3.000, whereas Hn2 exhibited somewhat better inhibition against Staphylococcus aureus (MIC 3.000). Overall activity of the hydrazone chain was still moderate compared to the reference drug. Notably, this modified hydrazone moiety was converted to a 1,3,4-oxadiazole moiety to significantly increase antibacterial activity. The oxadiazole derivatives CHn1–CHn3 had enhanced activity, especially against Gram-negative bacteria. Of these compounds, the antimicrobial activity of CHn3 was highest compared to other compounds, with very low MIC values of 0.450 against Escherichia coli, 0.300 against Pseudomonas aeruginosa, 0.350 against Staphylococcus aureus. It was then deduced that the 1,3,4-oxadiazole ring heterocyclic are involved in the activity enhancement for biological functions such as that in structural rigidity, lipophilicity and interaction to bacterial targets, thus this was the key element in that. There is a very well-defined relation between structure and activity in the oxadiazole chain. It is evident that the replacement of a furan group (CHn1) with the 5-methylfuran group (CHn2), with increased activity against Escherichia coli and Pseudomonas aeruginosa indicate that the methyl group might be adding lipophilicity and membrane permeabilities. Nevertheless, the most remarkable improvement was reported with respect to the oxadiazole derivative of CHn3 which demonstrated the least minimum inhibitory concentration (MIC) values of all compounds synthesized. The addition of oxadiazole ring may further improve electronic interactions to stronger binding to bacterial biomolecule targets. CHn3 showed comparable activity against some bacterial strains, indicating that the indole-based oxadiazole derivatives may represent potential targets for antibacterial architecture. These results indicate that antibacterial activity increases with decreasing minimum inhibitory concentration (MIC) and the structural modification of indole hydrazone framework to 1,3,4-oxadiazole derivatives considerably enhances bioactivity. There are several insights provided by these results which will be useful for the development of novel (indole-based) potent antimicrobial agents.

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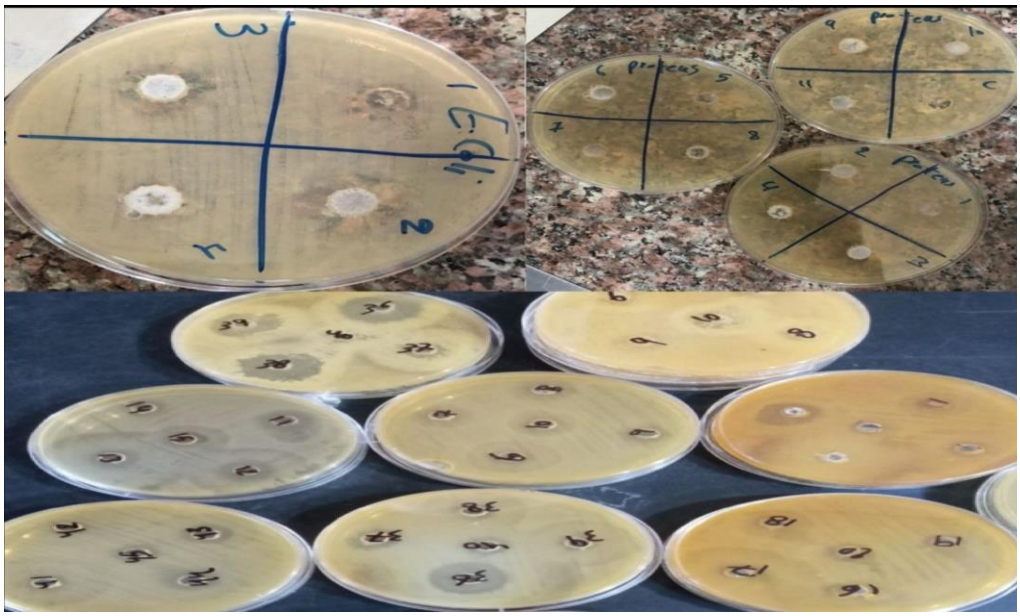

Figure 19. The analysis of cell dimension .

Table 1: The anti-bacterial effect of the synthesized derivatives [a]

Entry	Sample	*E. coli*	*P. aeruginosa*	*Proteus*	*K. pneumoniae*	*S. aureus*
1	Hn1	3.250	3.250	3.500	3.25	3.500
2	Hn2	3.250	3.250	3.150	3.500	3.000
3	Hn3	3.000	3.250	3.150	3.250	3.000
4	CHn1	1.500	3.500	3.150	3.125	3.125
5	CHn2	1.250	1.00	2.500	3.250	1.250
6	CHn3	0.450	0.300	1.500	3.000	0.350
7	Amoxicillin	0.1250	0.100	1.120	0.856	0.220

[a] Values as mM.

4. Conclusion.

We created a unique series of oxadiazole derivatives by preparing indole carbohydrazide, which were subsequently reacted with heterocyclic aromatic aldehydes to produce the matching indole-containing hydrazide-hydrazones. This was followed by heating in DMSO at 100°C with molecular iodine and potassium carbonate. The structure of the produced compounds was confirmed using FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. The antibacterial activity of the examined substances was assessed against various microorganisms. In contrast to hydrazones,

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the data showed that all oxadiazole derivatives had the greatest effect on all tested microorganisms. Compound CHn3, in particular, had the highest antibacterial activity against S. aureus.

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