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SYNTHESIS OF SOME NEW OXADIAZOLINE DERIVATIVES FROM 6-METHYL NICOTINATE

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Abstract: Background: Heterocyclic compounds have attracted considerable research due to their critical applications in biology and medicine.

Methods: The synthesis involved the production of four derivatives of the 1,3,4-oxadiazoline compound. The process commenced with converting 6-methyl nicotinate to 6-methyl nicotinic acid hydrazide through a reaction with (99%) hydrazine hydrate. Subsequently, the hydrazone was synthesized by reacting to 6-methyl nicotinic acid hydrazide with various aromatic aldehydes. Finally, oxadiazole derivatives were generated through a cyclization reaction between the hydrazone and acetic anhydride.

Results: The FT-IR, 1H-NMR, and 13C-NMR techniques were used to confirm the structure of the produced compounds.

Conclusion: Successful 13C-NMR, 1H-NMR, and FTIR data analysis support the compound's synthesis.

Keywords: 1, 3, 4-oxadiazoline, Heterocyclic, hydrazone compounds, 6-Methyl nicotinate.

2. Introduction

Heterocyclic compounds are ring structures consisting of carbon atoms and at least one heteroatom, commonly nitrogen, oxygen, or sulfur. These compounds have garnered significant attention from researchers due to their paramount importance in the pharmaceutical and medical industries. Over 90% of innovative medications incorporate heterocyclic compounds, serving as vital connectors between chemistry and biology and thereby constituting a focal point for extensive scientific research and practical applications.[1], [2]

The use of heterocyclic compounds in veterinary medications and pharmaceuticals is extensive. Numerous heterocyclic substances are highly beneficial and necessary for human survival. Hormones, antibiotics, alkaloids, vital amino acids, vitamins, hemoglobin, pigments, and dyes are only a few examples of the many chemicals that contain heterocyclic structures. With its antifungal, antibacterial [3], anti-allergic [4], anti-inflammatory [5], antioxidant [6], anti-convulsant [7], enzyme-inhibiting [8], herbicidal [9], anti-HIV [10], anti-cancer [11], antidiabetic [12], and insecticide properties [13], heterocycles have become significant structures in medicinal chemistry [14], [15].

Oxadiazole and 1,3,4-oxadiazoline (2,3-dihydro-1,3,4-oxadiazole) derivatives are the essential types of heterocyclic compounds as shown in (**Figure 1**) with different biological activity[16].

1,3,4-oxadiazoline ring (1) 1,3,4-oxadiazole ring (2)

Figure 1: The structure of 1,3,4-oxadiazole and 1,3,4-oxadiazoline

The oxadiazoline compound contains a five-membered heterocyclic ring with one oxygen atom, two nitrogen atoms, two carbons, and one double bond. They are produced by substituting two nitrogen atoms for two methylene groups (=CH) in furan with one double bond [17].

Oxadiazoline derivatives have different biological activities, including antibacterial, antifungal, anti-inflammatory, antiviral, anticancer, anti-tubercular, and antihypertensive activities. 1,3,4-Oxadiazoline derivatives probably demonstrate different biological activity due to the presence of an N=C-O linkage [18].

3. MATERIALS and METHODS

3.1. Chemicals and Instruments

The synthesis of 1,3,4-oxadiazoline involved materials sourced from various reputable suppliers. Baoji Guokang Biotech Company provided the 6-methyl nicotinate, while Central Drug House supplied the 99% hydrazine hydrate. Additionally, solvents from Sigma-Aldrich Company and Alpha Lab were utilized in the process. The aldehydes used were also procured from Sigma-Aldrich.

To determine the melting point of the synthesized product, the STUART melting points SMP30 device was employed in an open capillary tube. The reaction was monitored using thin-layer chromatography (TLC) on 0.5 mm thick silica gel sheets (Merck, 60, F254). The spectral analysis of the synthesized compounds was carried out using the FT-IR 8400s SHIMADZU for measuring the spectra, ^{1}H-NMR spectra on the INOVA BRUKER 400MHz using deuterated DMSO as a solvent, and ^{13}C-NMR spectra on the INOVA 100MHz using deuterated DMSO as a solvent. Tetramethyl silane (TMS) served as the internal standard for both NMR analyses.

3.2. Methods

3.2.1. Synthesis of 6-methyl nicotinoyl hydrazide:

In a round-bottom flask (150ml), a mixture of 0.01 mol of 6-methyl-nicotinate (**1**) and 0.02 mole of hydrazine hydrate 99% was refluxed in absolute ethanol (20 ml) for 5 hours with stirring. The mixture of the reaction was cooled using an ice-water bath. The desired 6-methyl-nicotinoyl hydrazide **(2)** was filtrated and dried as a white precipitate. Yield = 60%, melting point = 136-137 ˚C **Scheme 1** [19].

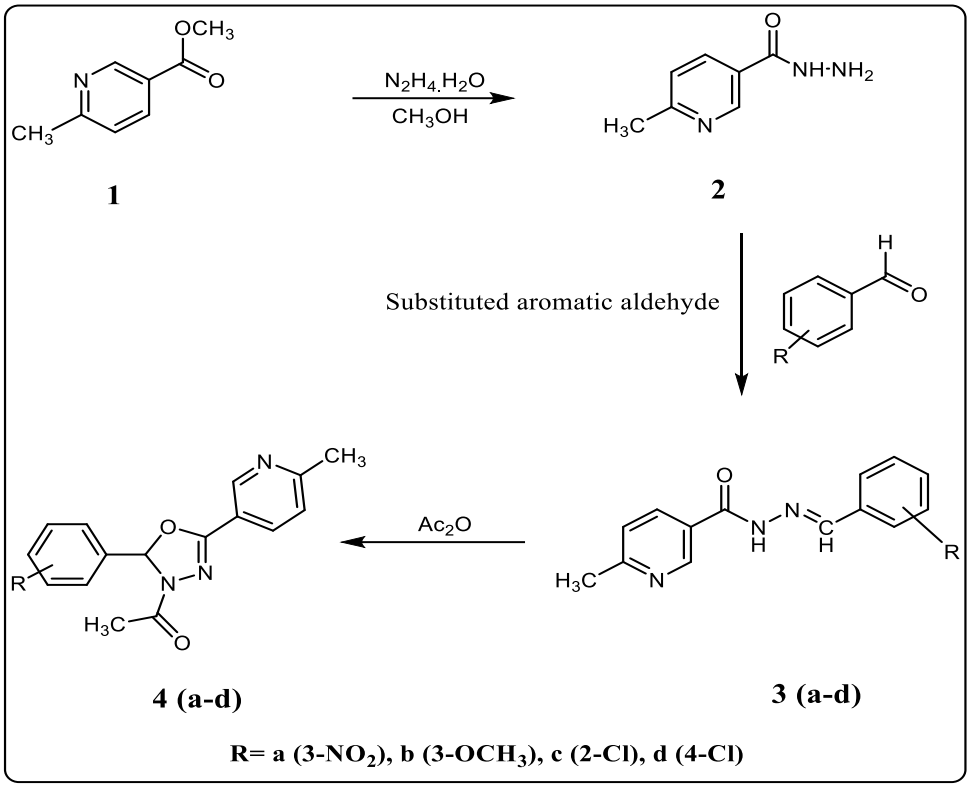
3.2.2. General procedure to Synthesis 6-methyl-nicotinc acid hydrazone (3a-3d):

In the round bottom flask (150 ml), 0.01 mol of 6-methyl-nicotinoyl hydrazide and 0.01 mole of substituted aromatic aldehydes have been refluxed in 20 ml of absolute ethanol in the presence of 5 drops of glacial acetic acid as a catalyst for 6.5 hours. The reaction progress was continuously monitored using thin-layer chromatography (TLC) with a hexane-ethyl acetate (3:2) as an eluent. The desired product was filtrated and recrystallized by using a mixture of ethanol and water (3:1)[20].

3.2.3. General procedure for the synthesis of oxadiazole compounds (4a-4d):

In a 150 ml round bottom flask, 1 g of compound **3a-3d** was refluxed in 10 ml of acetic anhydride for an appropriate time. The reaction was monitored by thin-layer chromatography (TLC) with ethyl acetate—n-

hexane (1:1) as eluent. At the end of the reaction, the mixture was poured into 250 ml of ice water with vigorous stirring. The solid precipitate product was filtered and recrystallized using a mixture of ethanol and water (3:1)[21].



Scheme 1: Synthesis pathway for 1,3,4-oxadiazolines compounds.

Table (1): The physical properties of synthesized compound.

Compounds.	Molecular weights	Melting point (°C)	Appearance	Yield (%)
3 a	284	219-222	Yellow crystals	67
3 b	269	195-197	Yellow crystals	58
3 c	273	180-183	Yellow crystals	65
3 d	273	215-218	White crystals	61
4 a	326	126-128	Yellow crystals	60
4 b	311	117-119	White crystals	57
4 c	315	120-123	Yellow crystals	53
4 d	315	119-122	Yellow crystals	46

4. RESULT AND DISCUSSION

The newly synthesized compounds undergo a process of converting 6-methyl-nicotinate hydrazone into 1,3,4-oxadiazoline. Subsequently, they are subjected to characterization utilizing FT-IR, ^{1}H-NMR, and ^{13}C-NMR techniques to ascertain and validate their chemical structures.

4.1. FT-IR Spectra

The newly synthesized oxadiazoline compound underwent analysis using FTIR and was detailed in (**Figure 2**) to (**Figure 5**), with the presentation of results in (**Table 2**).

The FT-IR spectra all demonstrate the absence of the stretching vibration related to the N-H bond of the acyl hydrazone derivatives within the 3429-3139 cm^{-1} range. [22]

The FT-IR spectra of oxadiazoline reveals a new stretching vibration within the 1600-1631 cm^{-1} range, indicating the presence of C=N [23][24]. The spectral range of 3006-3090 cm^{-1} exhibited the presence of the stretching vibration associated with the aromatic C-H bond [25].

Upon analyzing the IR spectra, absorption bands were identified in the range of 2922-2965 cm^{-1}, indicative of the stretching vibration of the aliphatic C-H bond. [26].

The FT-IR spectra of all samples displayed bands ranging from 1654-1666 cm^{-1}, which can be associated with the stretching vibration of the C=O bond in the acetyl groups. [27].

The oxadiazoline compound exhibits absorption bands in the spectral ranges of (1441-1442 cm^{-1}) and (1531-1600 cm^{-1}), which are characteristic of the presence of the aromatic C=C bond [28].

The FT-IR spectroscopic analysis of compound (4a) detected two distinct stretching vibrations at wavenumbers of 1354 cm^{-1} and 1531.53 cm^{-1}. These vibrations are associated with the symmetric and asymmetric NO2 groups, respectively [29].

Table (2): IR characteristics bands of the synthesized oxadiazoline compounds

Compd.	C-H aromatic	C-H aliphatic	C=O	C=N	C=C aromatic	C-N
4 a	3090	2922	1662	1600	1531 1442	1311.64
4 b	3006	2965	1654	1625	1599 1441	1327.64
4 c	3045	2957	1666	1627	1588 1441	1320
4 d	3034	2927	1664	1631	1600 1442	1317.38

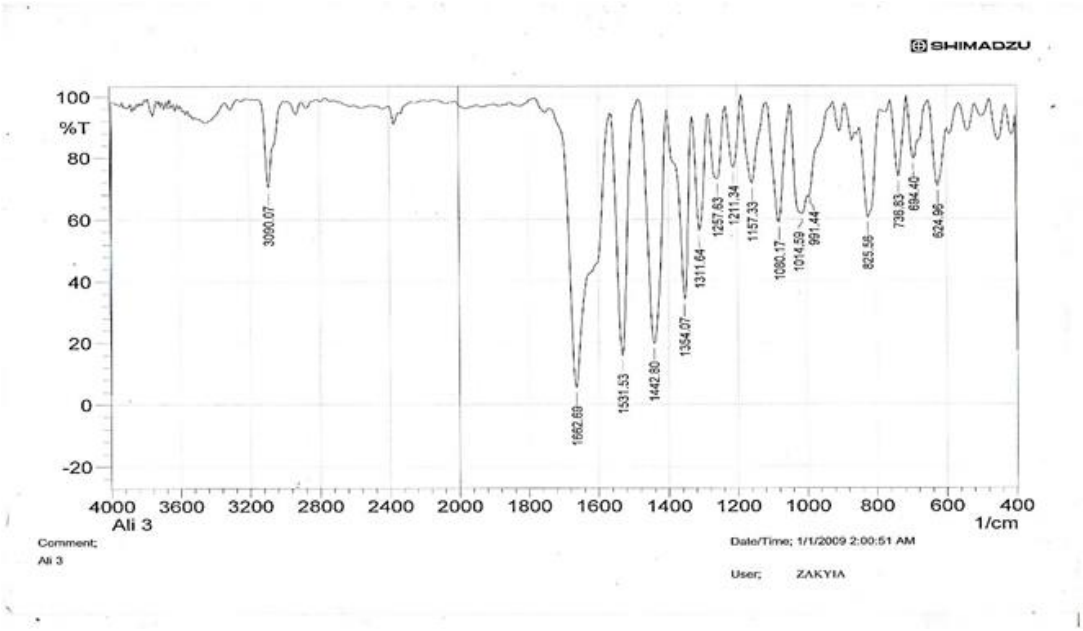


Figure 2: FT-IR spectrum of compound 4a

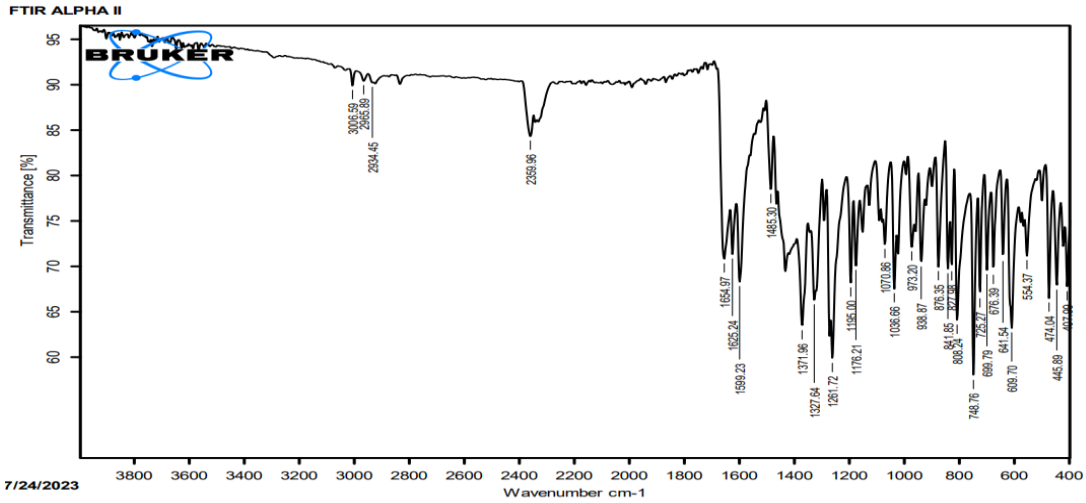


Figure 3: FT-IR spectrum of compound 4b

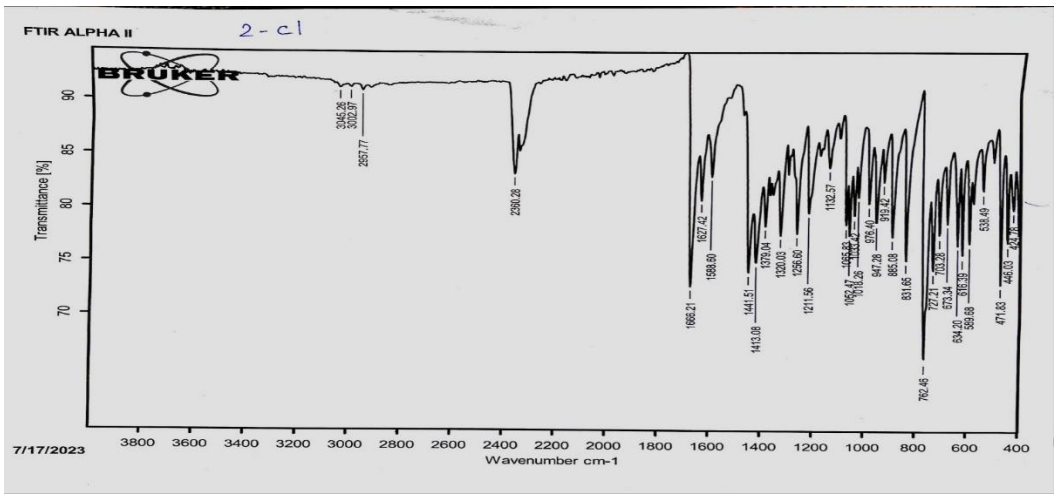


Figure 4: FT-IR spectrum of compound 4c

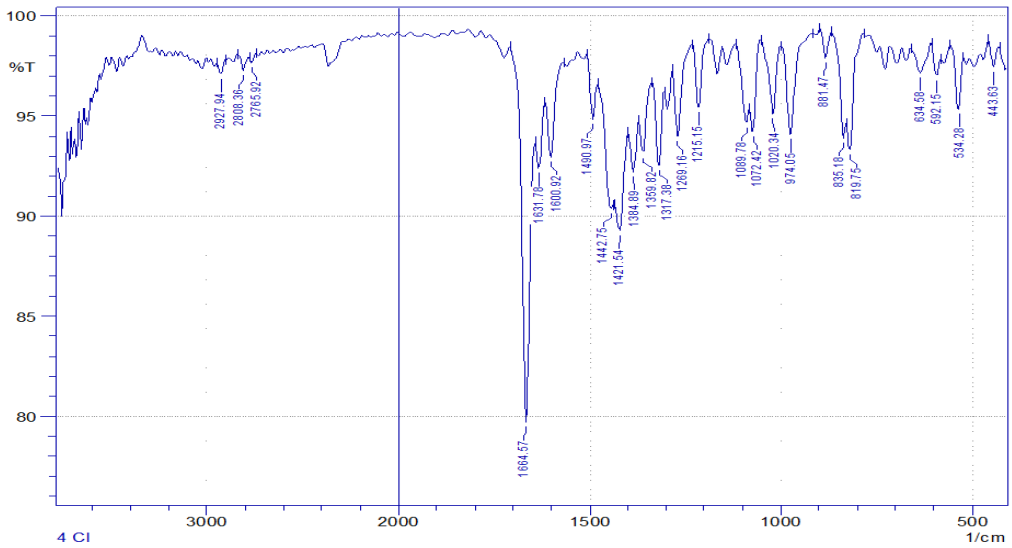


Figure 5: FT-IR spectrum of compound 4d

4.2. ^{1}H-NMR spectra

The oxadiazoline compounds produced in this process are identified using ^{1}H-NMR spectroscopy. The signals present in all spectra at (2.5 ppm) and (3.3 ppm) correspond to DMSO and H_2O, respectively [30]. The details of each compound were recorded in **Table 3**, accompanied by the corresponding spectra displayed in **Figures 7 to 10**. The ^{1}H-NMR spectra exhibit singlet signals within the 2.268-2.297 ppm range, attributable to the protons of the acetyl group [31]. The singlet signals observed in the chemical shift range of 2.508-2.516 ppm correspond to the proton methyl group of the pyridine ring [32]. The singlet signals observed in the chemical shift range of 8.839-8.889 ppm are attributed to proton H-4 [33], and singlet signals at range (7.165-7.399 ppm) are related to proton H-10. All spectra showed doublet signals at the range (7.412-7.557 ppm) and (8.054-8.114 ppm) pertaining to the protons H-1 and H-6, respectively[34]. Compound (4b) showed a singlet signal at 3.768 ppm associated with the proton of the OCH_3 group [35].

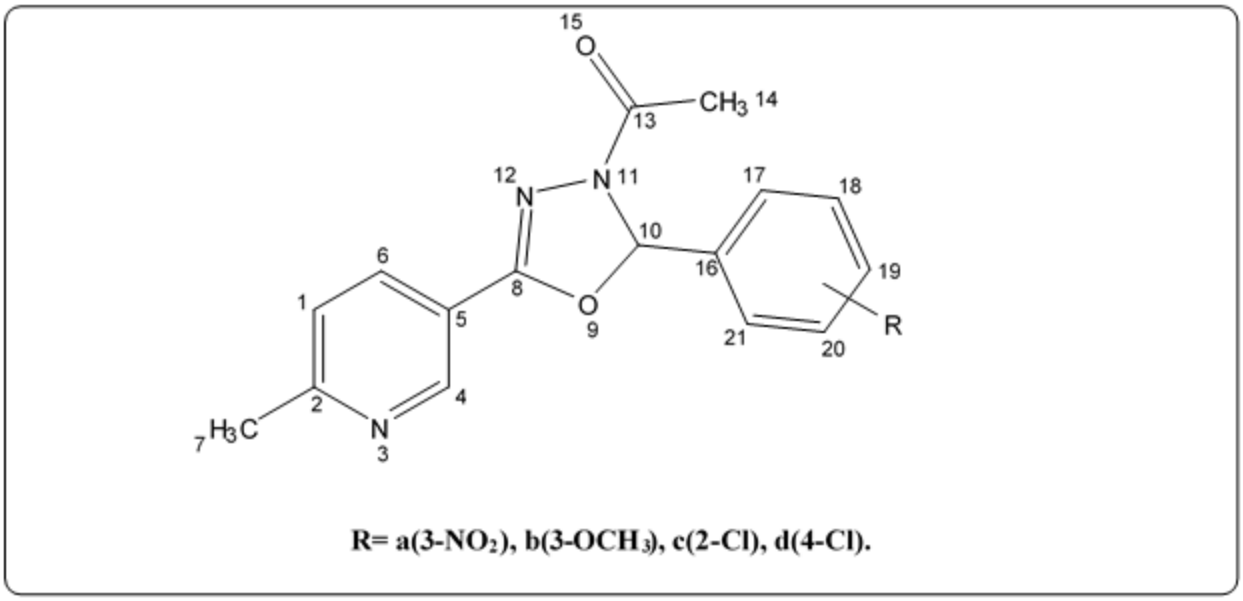


Figure 6: Structure of the oxadiazoline compounds for explanation of NMR

Table (3): Data of ^{1}H-NMR spectra of oxadiazoline compounds

Compd.	CH_3-pyridine (7) (s)	H (1) (d)	H (4) (s)	H (6) (d)	H (10) (s)	$COCH_3$ (14) (s)	O-CH_3 (s)	Aromatic C-H
4a	2.516	7.457	8.889	8.114	7.399	2.297	-	7.770-8.372
4b	2.514	7.412	8.862	8.068	7.165	2.283	3.768	7.034-7.368
4c	2.509	7.557	8.839	8.054	7.349	2.293	-	7.418-7.493
4d	2.508	7.440	8.860	8.085	7.215	2.268	-	7.523

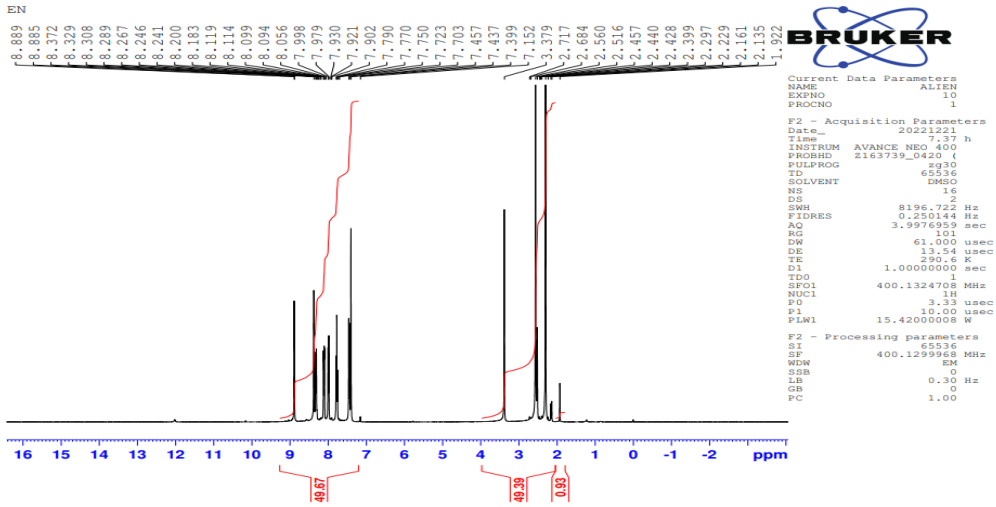


Figure 7: ^{1}H-NMR spectrum of 4a

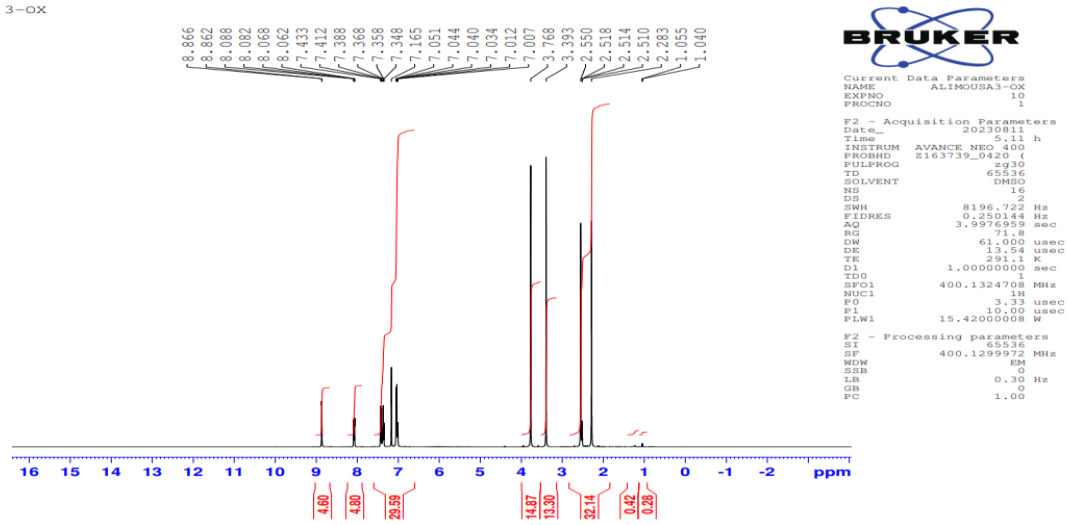


Figure 8: ^{1}H-NMR spectrum of 4b

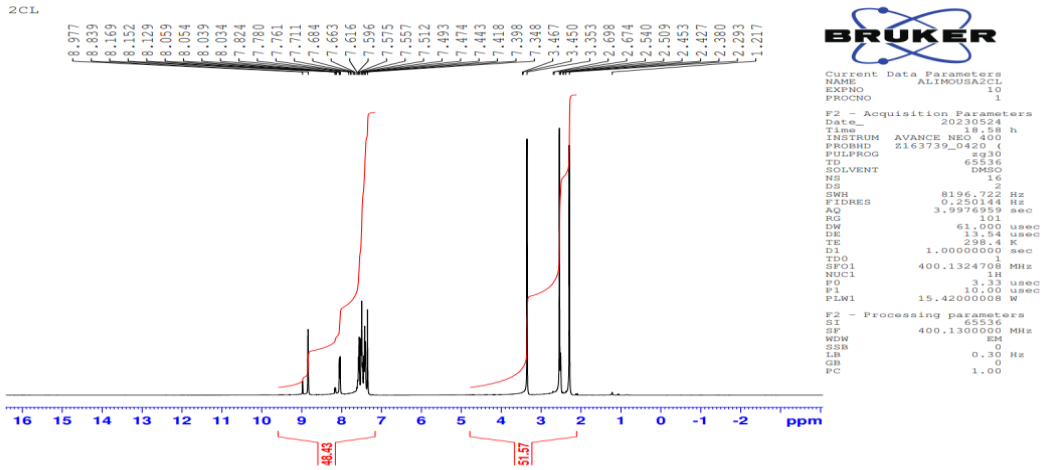


Figure 9: ^{1}H-NMR spectrum of 4c

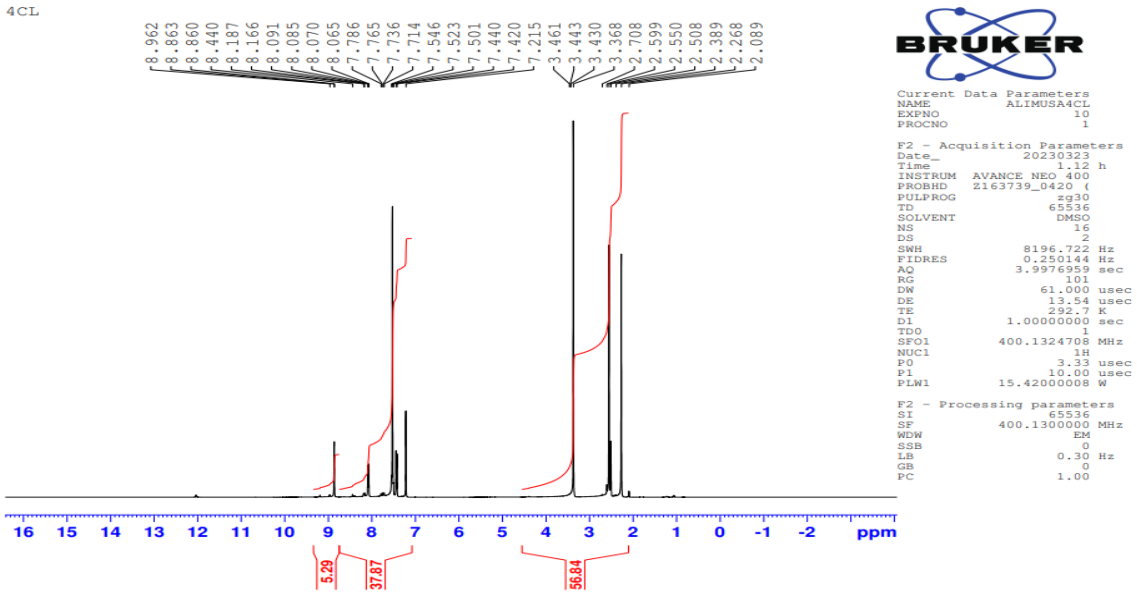


Figure 10: ^{1}H-NMR spectrum of 4d

4.3. ^{13}C-NMR spectra of oxadiazoline compounds (4a- 4d):

The oxadiazoline compounds generated were characterized using 13C-NMR spectroscopy with deuterated DMSO as the solvent. The ^{13}C-NMR spectra of the synthesized compounds are presented in **Figures (11) to (14)** and **Table (4)**. All spectra exhibited a peak at 39.9 ppm attributable to the DMSO solvent[36].

In all 13C-NMR spectra, signals corresponding to carbons 14 and 13 have consistently appeared within the range of (21.51-21.69 ppm) and (167.31-167.74 ppm) respectively [37][38]. The spectral signals within the range of 24.66-24.69 ppm correspond to the methyl group (C-7) that is bonded to the pyridine ring [39]. The signal in the range (147.12-148.40 ppm) is related to the C-4[40], and the peak between 90.86 and 92.30 ppm corresponds to the C-10 atom of the oxadiazoline ring.[41]. Moreover, all observed signals within the range of 153.40-153.74 ppm are associated with the C atom located at position 8, while signals ranging from 162.12-162.29 ppm correspond to the carbon atom (C-2) within the pyridine ring.[42].

Table 4: Data of ^{13}C-NMR spectra of oxadiazoline compounds.

Comp.	Carbon of pyridine ring		Methyl C-7	Oxadiazoline ring		Acetyl group		OCH_3 C-23	Aromatic C From (C-16 to C-21)
	C-2	C-4		C-8	C-10	C-13	C-14		
4a	162.29	148.40	24.69	153.74	91.14	167.74	21.51	-	122.23-147.28
4b	162.12	147.17	24.67	153.64	92.30	167.31	21.69	55.67	112.88-159.90
4c	162.13	147.12	24.66	153.40	90.86	167.38	21.62	-	128.66-133.23
4d	162.19	147.20	24.69	153.65	91.69	167.38	21.68	-	129.14-135.84

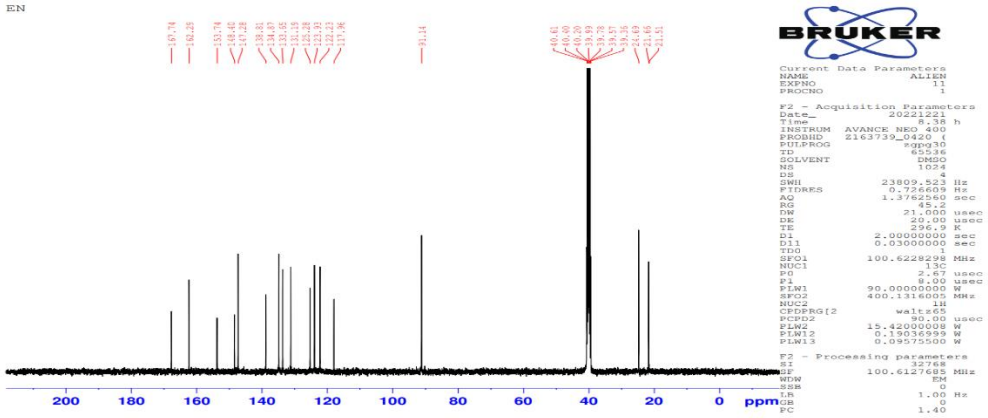


Figure 11: ^{13}C-NMR spectrum of 4a

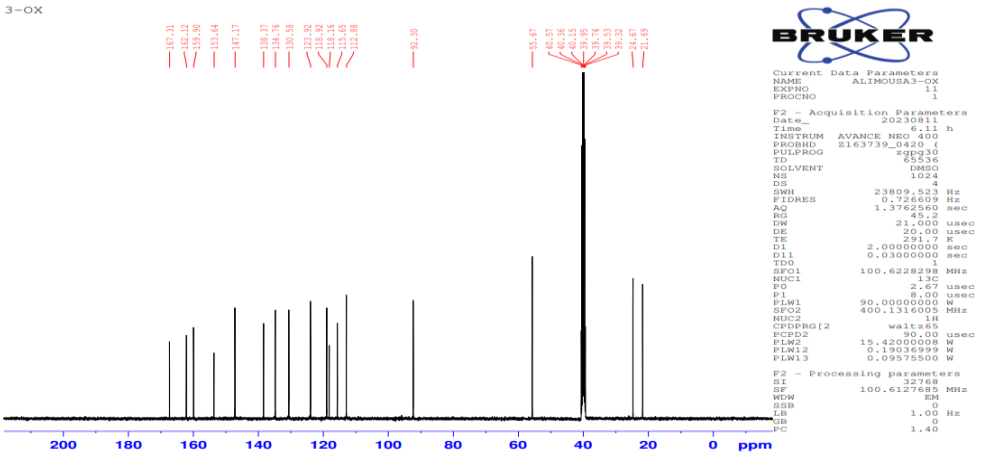


Figure 12: ^{13}C-NMR spectrum of 4b

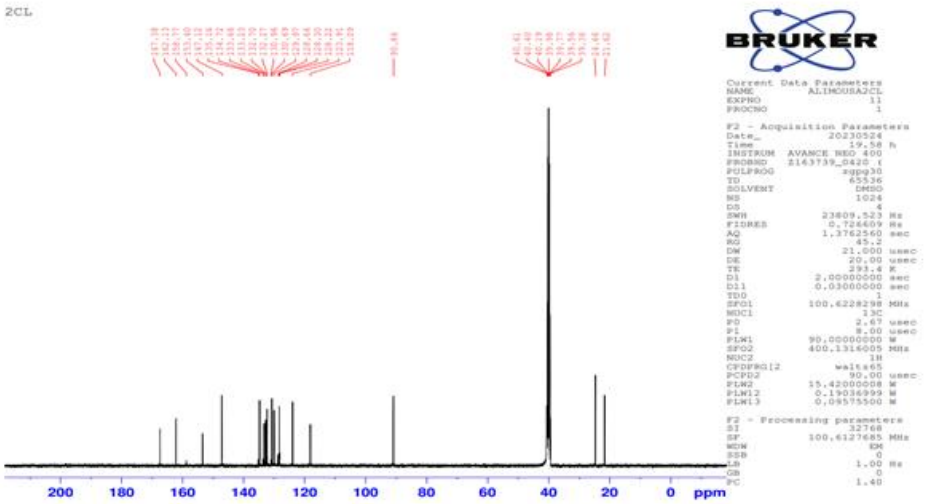


Figure 13: ^{13}C-NMR spectrum of 4c

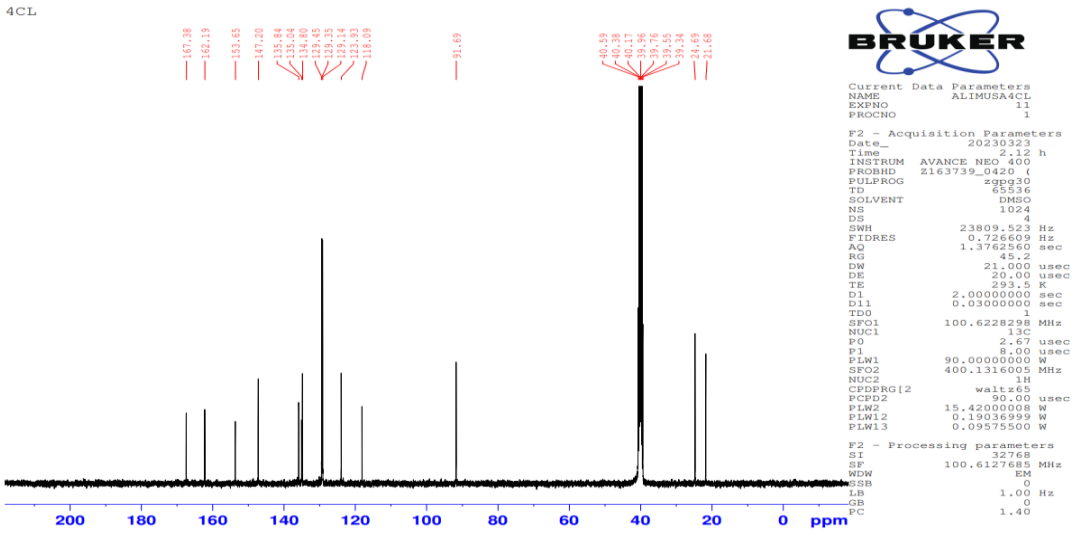


Figure 14: ^{13}C-NMR spectrum of 4d

5. Conclusion:

The research entails creating new 1,3,4-oxadiazoline compounds through the cyclization reaction of hydrazone (3a-3d) with acetic anhydride. The thorough examination of FT-IR, 1H NMR, and 13C NMR data offers undeniable proof of the successful synthesis of the targeted compound.

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