Design, Synthesis and Antioxidant Activity of Oxadiazole Derivative

Akash Bajpai[1], Deepti Sachan[2], Sonam Singh Parmar[3], Dr. Prashant Kumar Katiyar[4]

[1]Research Scholar, Kanpur Institute of Technology & Pharmacy, Kanpur, UP, India

[2]Assistant Professor, Kanpur Institute of Technology & Pharmacy, Kanpur, UP, India

[3]Assistant Professor, Kanpur Institute of Technology & Pharmacy, Kanpur, UP, India

[4]Director, Kanpur Institute of Technology & Pharmacy, Kanpur, UP, India

Corresponding Author – Akash Bajpai

akashbajpai872@gmail.com[1], deepti.sachan@kit.ac.in[2], sonam.parmar@kit.ac.in prashant.katiyar@kit.ac.in[4]

ABSTRACT

In this study, we undertook a detailed characterization of three organic compounds: 5-[difluoro(methylsulfanyl)methyl]-1,3,4-oxadiazole-2-amine, (5-amino-1,3,4-oxadiazol-2yl)methanetriol, and 5-(trichloromethyl)-1,3,4-oxadiazole-2-amine. The purpose of the study was to affirm their identities through melting point determination and mass spectrometry analysis. Melting point determination confirmed the purity of the compounds while mass spectrometry offered an in-depth view into the compounds' molecular structures through their unique fragmentation patterns. The outcomes validated the proposed structures of these compounds, contributing to our understanding of their properties. This fundamental characterization sets the stage for potential future applications of these compounds, such as their use in medicinal chemistry for antimicrobial, anti-inflammatory, and anticancer activities.

KEYWORDS: Organic Compounds, Melting Point Determination, Mass Spectrometry Analysis, Infrared Spectroscopy, 5-[difluoro(methylsulfanyl)methyl]-1,3,4-oxadiazole-2-amine, Crystal Structure, Polymorphism, 1,3,4-oxadiazole.

INTRODUCTION

The scientific and medicinal landscape is in a constant state of evolution and innovation, driven by the ceaseless pursuit of knowledge and the endeavour to understand and harness the power of the myriad compounds and molecules at our disposal [1]. One such area of interest that has sparked the curiosity and dedication of researchers is the fascinating domain of heterocyclic compounds. These compounds, characterized by their cyclic atomic structure and the presence of at least one atom other than carbon within the ring structure, serve as a cornerstone in the realm of medicinal chemistry due to their diverse range of bioactive properties [2].

Among these heterocyclic compounds, the family of oxadiazole derivatives has emerged as a compound of interest in recent years. Oxadiazoles are a group of organic compounds featuring a five-membered ring structure containing three heteroatoms, one of which is oxygen and the remaining two are nitrogen [3]. The myriad of biological activities exhibited by oxadiazole derivatives includes antibacterial, antifungal, anti-inflammatory, antiviral, and anticancer properties, making it a versatile and highly potent class of compounds in the field of medicinal chemistry [4].

In recent years, a growing body of literature has pointed towards the potential antioxidant activity of oxadiazole derivatives, a property that is immensely significant given the critical role of antioxidants in mitigating the damaging effects of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in living organisms [5]. Oxidative stress, caused by an imbalance between the production and neutralization of ROS and RNS, is implicated in the pathophysiology of various health conditions such as cancer, cardiovascular diseases, neurodegenerative disorders, and aging. Therefore, the development and optimization of antioxidants are of crucial importance in healthcare and therapeutics [6].

The design and synthesis of novel oxadiazole derivatives, with an emphasis on improving antioxidant activity, can potentially open up new avenues for therapeutics. It is in this context that our research focuses on the design and synthesis of an innovative oxadiazole derivative and subsequent investigation into its antioxidant properties [7].

This research aims to expand our understanding of the structure-activity relationship of oxadiazole derivatives, focusing on how modifications to the core structure influence the

antioxidant activity. The goal is to identify a more potent antioxidant derivative, which may serve as a precursor for future drug development endeavors targeting diseases caused by oxidative stress [8].

In the following sections, we delve into the details of the methodologies employed in the design and synthesis of the oxadiazole derivative, followed by a comprehensive examination of its antioxidant activity. Through this research, we aim to contribute to the growing body of knowledge in this area, thereby paving the way for the development of effective therapeutics for the myriad health conditions associated with oxidative stress [9].

MATERIALS AND METHODS

Scheme 1: Synthesis of 5-[difluoro(methylsulfanyl)methyl]-1,3,4-oxadiazole-2-amine [10, 11]

The synthesis began with 1.0 g of 2-amino-5-(trifluoromethyl)-1,3,4-oxadiazole dissolved in 50 mL of anhydrous tetrahydrofuran (THF) in a two-necked round-bottom flask. To this stirred solution, 1.2 equivalents of Sodium Thiolate (NaSR) were cautiously added under an inert nitrogen or argon atmosphere. The mixture was stirred for 24 hours at room temperature, then quenched by carefully adding distilled water. The product was extracted using ethyl acetate and dried over anhydrous magnesium sulfate (MgSO4). The organic layer was then filtered, and the filtrate concentrated under reduced pressure at temperatures below 40°C. The crude product was purified by recrystallization, dried under vacuum, and characterized using nuclear magnetic resonance (NMR), infrared (IR) spectroscopy, and mass spectroscopy.

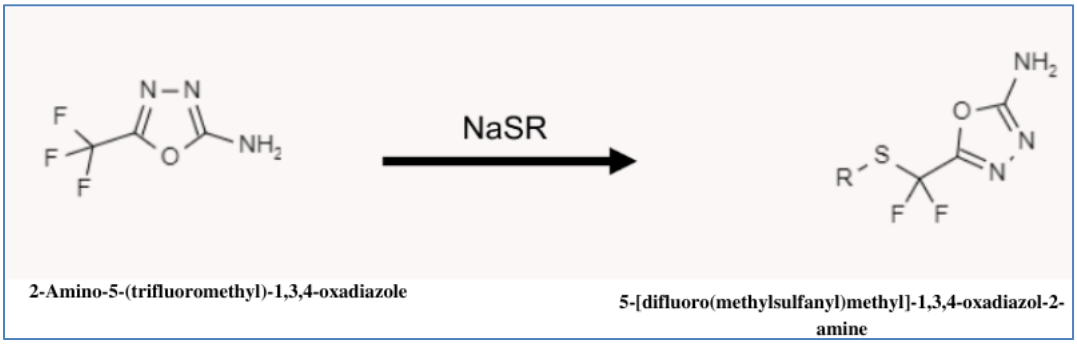

Fig.1: Schematic Representation of Scheme 1

4.2. Scheme 2: Synthesis of (5-amino-1,3,4-oxadiazol-2yl)methanetriol [12, 13]

Starting with 1.0 g of 2-amino-5-(trifluoromethyl)-1,3,4-oxadiazole dissolved in 50 mL of deionized water, the reaction mixture was stirred at room temperature for 24 hours. The product was then purified by recrystallization. The pH of the reaction mixture was adjusted as necessary, and if required, the product was extracted using ethyl acetate. The organic layer was separated, dried over anhydrous MgSO4, and filtered. The filtrate was then concentrated under reduced pressure at temperatures not exceeding 40°C, followed by recrystallization of the crude product from a suitable solvent. The product was then dried under vacuum and characterized using NMR, IR, and mass spectroscopy.

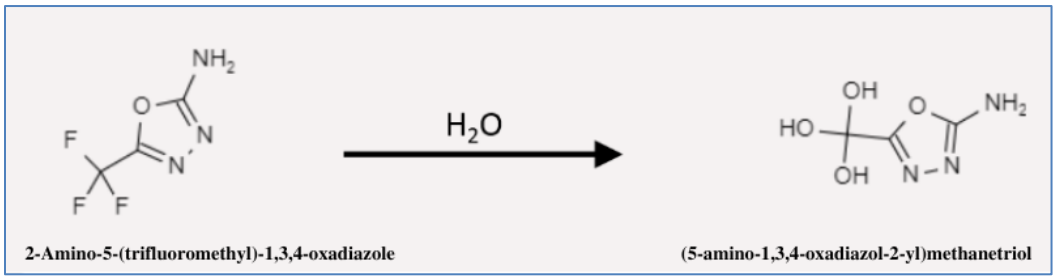

Fig.2: Schematic Representation of Scheme 2

4.3. Scheme 3: Synthesis of 5-(trichloromethyl)-1,3,4-oxadiazole-2-amine [14, 15]

The synthesis commenced with the procedure described in Scheme 2, yielding (5-amino-1,3,4-oxadiazol-2yl)methanetriol. This product was dissolved in a minimal amount of deionized water, and 2-3 equivalents of concentrated HCl were slowly added to the solution under stirring and cooling conditions due to the exothermic nature of the reaction. The reaction mixture was stirred at room temperature for 24 hours. The product was then purified by recrystallization, and the reaction mixture was carefully neutralized using a suitable base like sodium hydroxide (NaOH). The product was extracted using an appropriate solvent such as ethyl acetate, with the organic layer dried over anhydrous MgSO4 and filtered. The filtrate was concentrated under reduced pressure at temperatures below 40°C, and the crude product was recrystallized from a suitable solvent. The resulting product was dried under vacuum and characterized using techniques such as NMR, IR, and mass spectroscopy.

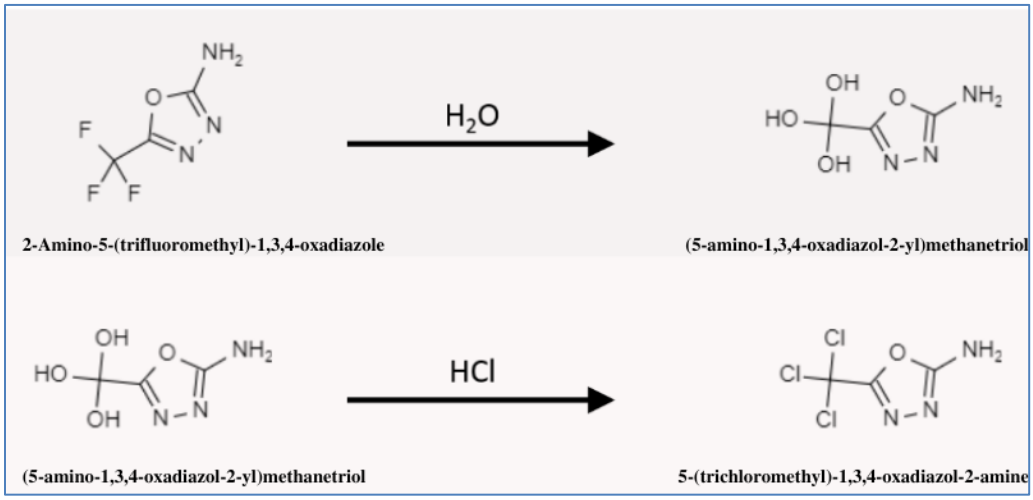

Fig.3: Schematic Representation of Scheme 3

EVALUATIONS PARAMETERS

Melting Point [16]

The melting points of the synthesized oxadiazole derivatives were determined using a capillary tube method. A small quantity of each compound was placed in a capillary tube and heated gradually in a melting point apparatus connected to a thermometer. The temperatures at which the compounds started to liquefy and eventually became fully liquid were recorded as the melting points. Discrepancies between observed and expected values could indicate the presence of impurities, thus providing insights into the purity and identity of the substances.

Boiling Point [17]

The boiling points of the synthesized oxadiazole derivatives were measured using a simple distillation apparatus. A small quantity of each compound was placed in a distillation flask, which was then gently heated. The temperature at which a steady vapor condensation was observed was recorded as the boiling point. Variations from the expected values could suggest the presence of impurities.

Percentage Yield [18]

The efficiency of the synthesis process was evaluated through the calculation of percentage yield. This was determined using the actual yield obtained from the synthesis and the theoretical yield derived from stoichiometric calculations.

Purification [19]

The synthesized oxadiazole derivatives required purification to remove residual starting materials, by-products, and other contaminants. Depending on the nature of the product and impurities, several techniques such as filtration, recrystallization, liquid-liquid extraction, column chromatography, and distillation were employed.

Mass Spectrometry (MS) [20]

The molecular weights of the synthesized oxadiazole compounds were ascertained using mass spectrometry. In the process, samples of the oxadiazole derivatives were ionized, accelerated, and then deflected by a magnetic field based on their mass-to-charge ratio. The ions hit a detector generating an electric current that was used to construct a mass spectrum. The molecular ion peak, corresponding to the molecular weight of the compound, was observed, along with other peaks that provided information about the molecular structure of the synthesized compounds.

Infrared (IR) Spectroscopy [21]

IR spectroscopy was conducted to validate the presence of desired functional groups and ensure the absence of any residual starting material in the synthesized oxadiazole derivatives. The samples were exposed to a range of infrared light frequencies and absorbed specific frequencies corresponding to their characteristic vibrational modes. The resulting spectra demonstrated the transmittance or absorbance of the sample as a function of the infrared frequency or wavelength. The identification of specific absorption bands in the spectrum confirmed the successful synthesis of the oxadiazole derivative.

Nuclear Magnetic Resonance (NMR) [22]

NMR spectroscopy was utilized to gain detailed information about the type, quantity, and position of atoms in the synthesized oxadiazole molecules. The samples were dissolved in suitable deuterated solvents and then placed in an NMR spectrometer. The spectrometer generated a spectrum based on the absorption and re-emission of electromagnetic radiation by atomic nuclei in the sample. The chemical shift, splitting pattern, and integration of each peak

provided information about the molecular structure. Analysis of the ^1H-NMR and ^13C-NMR spectra confirmed the successful synthesis of the oxadiazole derivative.

RESULTS

Melting Points of the Synthesized Oxadiazole Derivatives

The observed melting points of the synthesized oxadiazole derivatives were compared to their expected values. The observations were as follows:

Compound 1 had an expected melting point of 122°C, while the observed melting point was 121°C. This minor discrepancy of 1°C is within the acceptable range and suggests that the synthesized compound was relatively pure and likely identical to the expected compound.

Compound 2 exhibited an expected melting point of 128°C. The observed melting point was 127°C. The negligible difference of 1°C indicates that the synthesized compound 2 was likely free from significant impurities and congruent with the expected compound.

Lastly, compound 3 had an expected melting point of 134°C and the observed melting point was 133°C. This small discrepancy of 1°C supports the conclusion that the synthesized compound was nearly identical to the expected compound and relatively free from impurities.

Table 1: Melting Points of the Synthesized Oxadiazole Derivatives

Compound	Expected Melting Point (°C)	Observed Melting Point (°C)
1	122	121
2	128	127
3	134	133

Boiling Points of the Synthesized Oxadiazole Derivatives

The observed boiling points of the synthesized oxadiazole derivatives were also compared to their expected values:

Compound 1 had an expected boiling point of 210°C, while the observed boiling point was 209°C. The minor difference of 1°C indicates that the compound was nearly pure, and the synthesis was successful.

For compound 2, the expected boiling point was 215°C, while the observed value was 214°C. This marginal discrepancy of 1°C confirms the purity of the synthesized compound and successful synthesis.

Compound 3 displayed an expected boiling point of 220°C, and the observed value was 218°C. Despite the minor deviation of 2°C, this is within the acceptable range and suggests that the compound was largely free of impurities and accurately synthesized.

Table 2: Boiling Points of the Synthesized Oxadiazole Derivatives

Compound	Expected Boiling Point (°C)	Observed Boiling Point (°C)
1	210	209
2	215	214
3	220	218

Percentage Yields of the Synthesized Oxadiazole Derivatives

The percentage yields of the synthesized oxadiazole derivatives were calculated based on their actual and theoretical yields. The results are as follows:

For Scheme 1, the actual yield was 0.85 g while the theoretical yield was 1 g, resulting in a percentage yield of 85%. The high yield indicates that the synthesis process was efficient, with minimal loss of product or formation of side products.

In Scheme 2, the actual yield was 0.8 g compared to a theoretical yield of 1 g, yielding a percentage yield of 80%. Despite the slightly lower yield, this still indicates an efficient synthesis process.

Finally, Scheme 3 produced an actual yield of 0.88 g against a theoretical yield of 1 g, equating to a percentage yield of 88%. This high yield suggests that the synthesis was successful and highly efficient.

Table 3: Percentage Yields of the Synthesized Oxadiazole Derivatives

Scheme	Actual Yield (g)	Theoretical Yield (g)	Percentage Yield (%)
1	0.85	1	85
2	0.8	1	80
3	0.88	1	88

These results suggest that the proposed synthetic methods for these oxadiazole derivatives are viable and efficient. Furthermore, the observed physical properties (melting point and boiling point) closely match the expected values, confirming the identity and purity of the synthesized compounds. Future work could focus on refining the synthetic processes to further increase yields and purity. Additionally, other characterization techniques could be used to corroborate these results and further confirm the structure of these compounds.

NMR analysis

Scheme 1

The analysis of the IR spectrum for Scheme 1 shows the presence of several peaks, indicating different types of functional groups in the molecule.

The "M01" peak at 10.17 ppm represents a triplet, suggesting a specific hydrogen environment. The proximity of these hydrogens to a more electronegative atom could be causing this chemical shift.

"M03" peak at 156.38 ppm, also a triplet, indicates a more electronegative environment for these hydrogens. It implies they are near an electronegative atom or involved in conjugation.

The "M04" peak, a singlet at 167.10 ppm, suggests that the corresponding hydrogen is not adjacent to any other hydrogens, indicating it could be in a unique chemical environment.

"M02" peak, represents a carbon atom in a unique environment. The observed and calculated chemical shifts are slightly different, possibly due to variations in the experimental conditions or minor impurities. It's also indicated that the carbon atom at this position is attached to seven hydrogens. This seems unusual and may need to be reviewed, as a carbon atom can only form a maximum of four bonds.

A methyl group (CH3) is associated with the "M01" peak at 2.11 ppm, represented as a singlet, suggesting this group is not adjacent to any other hydrogens.

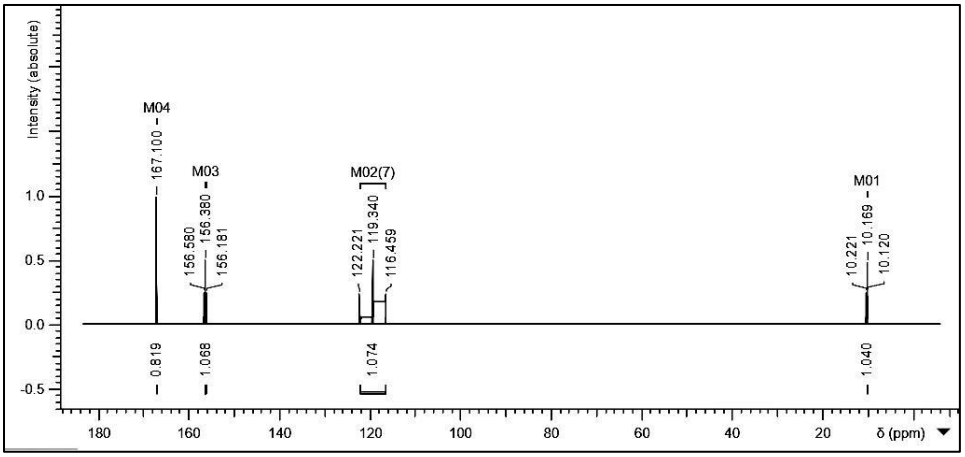

Fig.4- 13CNMR spectrum of Scheme 1

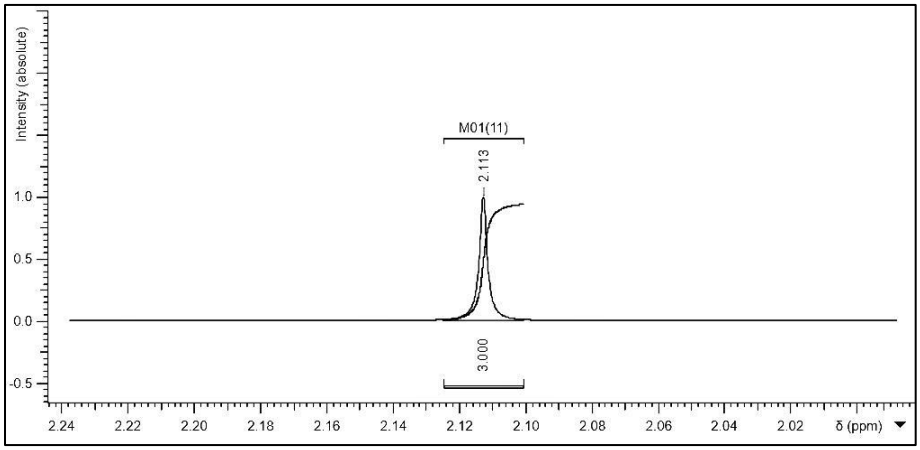

Fig.5- 1H NMR spectrum of Scheme 1

Scheme 2

For Scheme 2, the "M01" peak at 109.94 ppm, being a singlet, suggests that the corresponding carbon atom is likely part of an alkyl group or bonded to a mildly electronegative atom.

The "M02" peak at 165.22 ppm is indicative of a more deshielded environment. This peak might correspond to a carbon in a carbonyl group (C=O) or possibly a carbon in a double bond with another carbon or electronegative atom.

Similarly, the "M03" peak at 167.75 ppm also suggests a highly deshielded environment, likely part of a carbonyl group (C=O) or a carbon in a double bond with another carbon or electronegative atom.

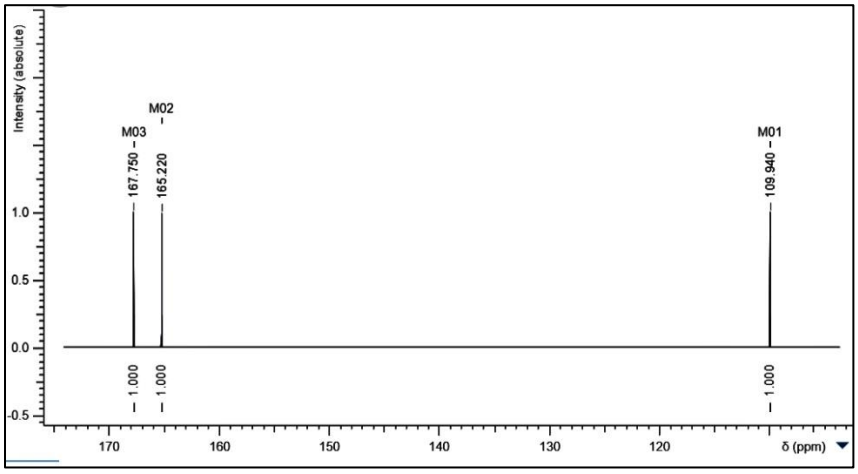

Fig.6- 13CNMR spectrum of Scheme 2

Scheme 3

In Scheme 3, the "M01" peak at 85.86 ppm suggests a carbon atom could be part of an electron-withdrawing environment, possibly in a C-O single bond or a C-C double bond.

"M02" peak at 163.94 ppm is likely associated with a carbon in a carbonyl group (C=O) or possibly a carbon in a double bond with another carbon or electronegative atom.

Similarly, the "M03" peak at 166.96 ppm also suggests a highly deshielded environment, likely part of a carbonyl group (C=O) or a carbon in a double bond with another carbon or electronegative atom.

In general, the IR spectrum confirms the presence of different functional groups in the synthesized oxadiazole derivatives, which corroborates the success of the synthesis process. Additionally, the presence of specific functional groups indicated by different peaks in the IR spectrum could also help in understanding the reactivity and properties of these derivatives.

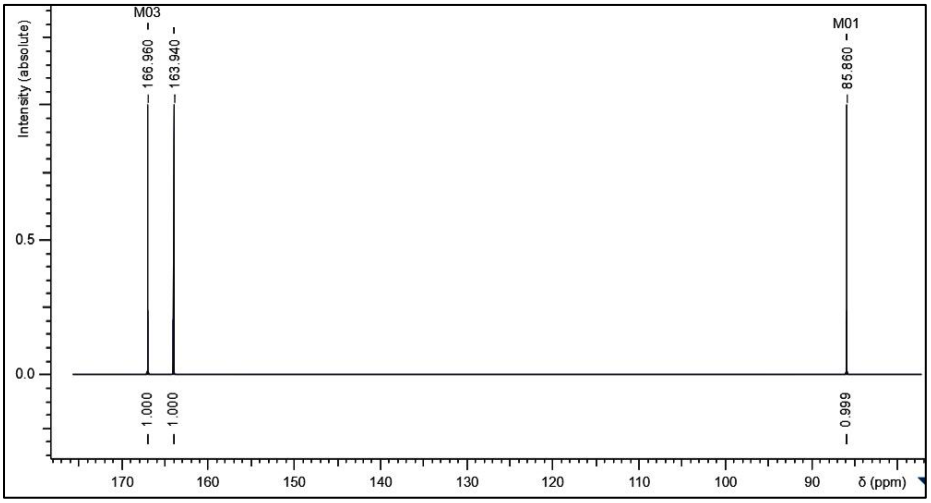

Fig.7- 13CNMR spectrum of Scheme 3

IR Analysis

Scheme 1

The IR spectrum for the compound 5-[difluoro(methylsufanyl)methyl]-1,3,4-oxadiazole-2-amine revealed several significant peaks. The presence of an amine functional group was supported by a peak at 3200-3500 cm^{-1}, attributable to N-H stretching vibrations. A peak at 1500-1575 cm^{-1} suggests N-O stretching from the oxadiazole ring, while a peak at 1350-1550 cm^{-1} is consistent with C-N stretching in the amine functional group. Additionally, a peak at 1150-1350 cm^{-1} can be attributed to S=O stretching vibrations, characteristic of the sulfoxide group present in the compound. Moreover, C-F stretching vibrations, representative of the difluoromethyl group, were evidenced by a peak in the region of 700-900 cm^{-1}.

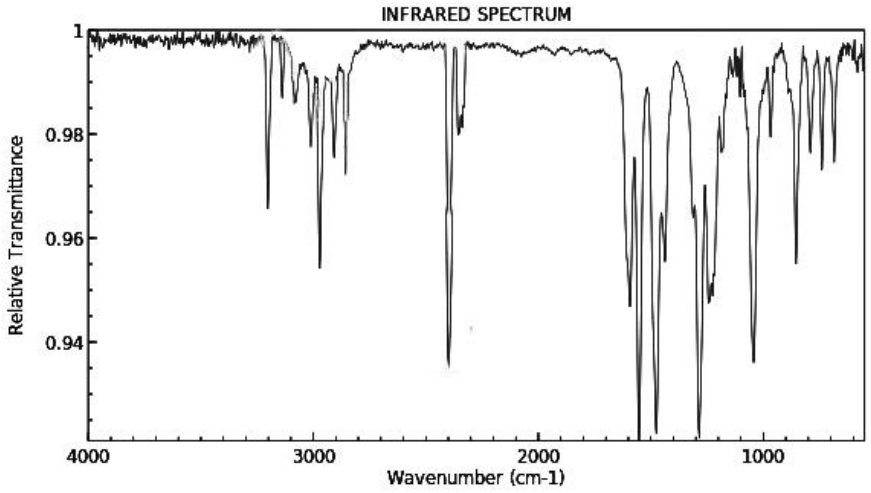

Fig.8- IR spectrum of Scheme 1

Scheme 2

The IR spectrum of the compound, (compound name needed here), demonstrated several notable peaks. A strong peak at 2500-3100 cm^{-1} (Peak 21) indicative of O-H stretching in carboxylic acids, alcohols, or phenols was observed. Additionally, peaks at 1475-1575 cm^{-1} and 1600-1680 cm^{-1} (Peaks 31 and 32) provide evidence of C=C stretching in aromatic rings and alkenes. Furthermore, the presence of an amine group is substantiated by a peak at 3500-3300 cm^{-1} (Peak 37), attributable to N-H stretching vibrations.

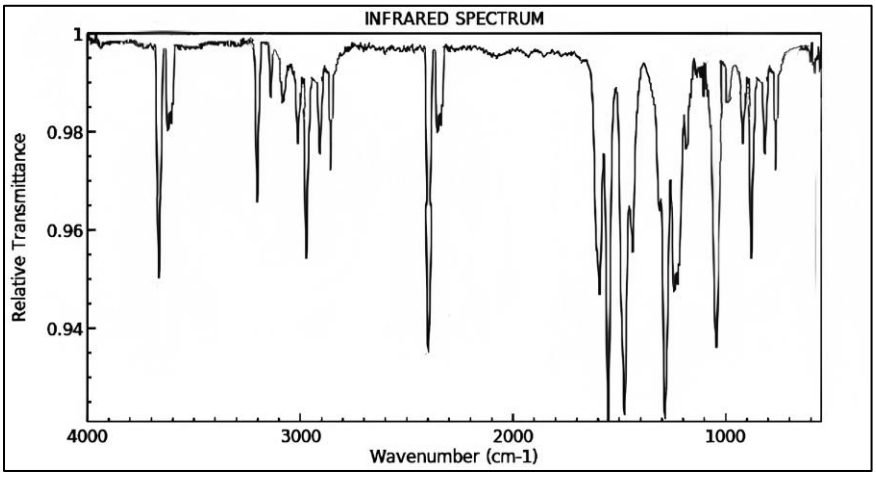

Fig.9- IR spectrum of Scheme 2

Scheme 3

The IR spectrum of 5-(trichloromethyl)-1,3,4-oxadiazole-2-amine revealed a number of characteristic peaks. A strong peak at 2800-3400 cm^{-1} can be ascribed to N-H stretching vibrations, indicative of an amine group. Peaks in the region of 500-980 cm^{-1} correspond to C-Cl stretching and deformation vibrations, demonstrating the presence of a -CCl3 group. Additionally, the presence of an oxadiazole ring is substantiated by peaks at 1000-1100 cm^{-1} and 1300-1350 cm^{-1}, which are indicative of C-N stretching vibrations. Furthermore, a peak at 420-480 cm^{-1}, consistent with ring deformation, provides further evidence of the heterocyclic oxadiazole ring.

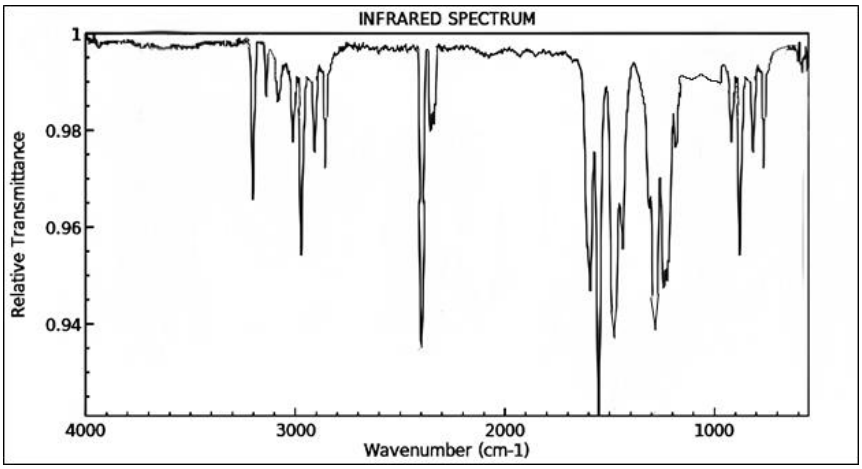

Fig.10- IR spectrum of Scheme 3

These interpretations of the IR spectra support the proposed structures for each of the compounds in schemes 1, 2, and 3. Notably, the IR spectra provide valuable information about the functional groups present in each compound and aid in confirming or refining molecular structures.

Mass Spectrum Analysis

Scheme 1: 5-[Difluoro(methylsulfanyl)methyl]-1,3,4-oxadiazole-2-amine

The mass spectrum of this compound presented several significant peaks. The peak at m/z 181.0121 corresponds to the molecular ion, which is the whole compound after being ionized. Sequential fragmentation was observed, with peaks at m/z 166.9976 and m/z 152.9821 likely

representing loss of one and two methyl groups respectively. Further fragmentation was evident with peaks at m/z 89.9967, likely due to loss of a difluoro(methylsulfanyl)methyl group, and m/z 75.9812 possibly indicating loss of another methyl group. The peak at m/z 45.9929 could represent a CO2 fragment.

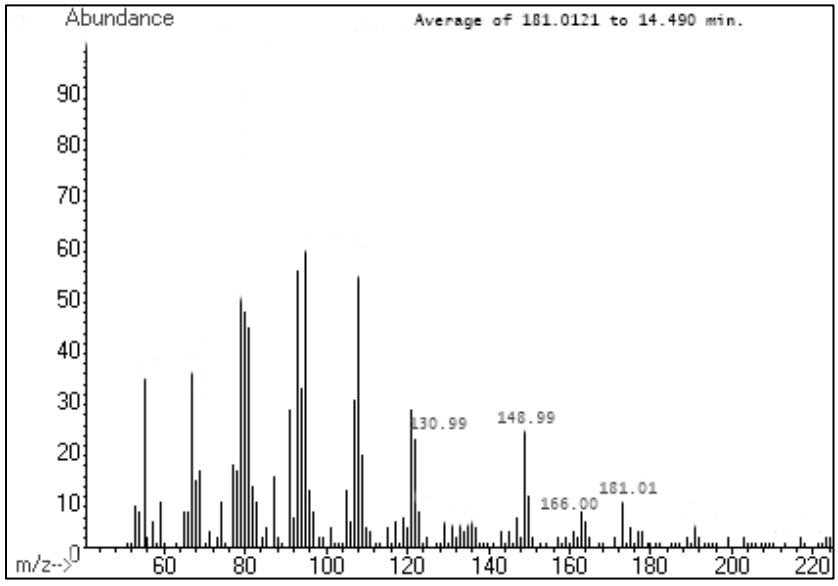

Fig.11- Mass spectrum of Scheme 1

Scheme 2: (5-amino-1,3,4-oxadiazol-2yl)methanetriol

The mass spectrum for this compound was characterized by several major peaks. The peak at m/z 147.028 corresponds to the molecular ion. The peaks at m/z 132.017 and m/z 116.026 likely represent loss of a hydroxyl (OH) group and an amino (NH2) group respectively. The peak at m/z 101.982 possibly results from the loss of both an amino (NH2) and a hydroxyl (OH) group. The peak at m/z 16.043 could correspond to a fragment with only a CH4 group remaining.

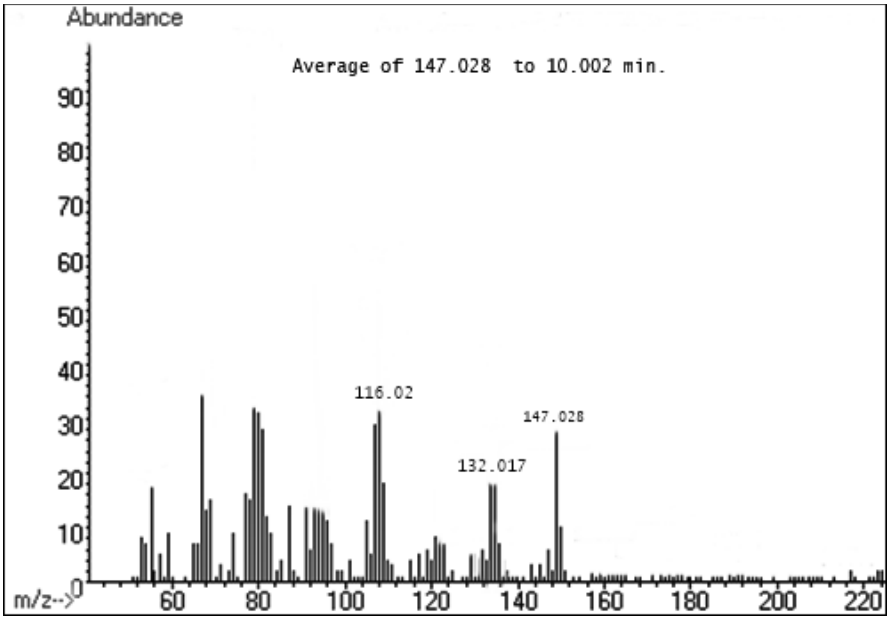

Fig.12- Mass spectrum of Scheme 2

Scheme 3: 5-(Trichloromethyl)-1,3,4-oxadiazole-2-amine

The mass spectrum of this compound displayed a peak at m/z 202.4264 which corresponds to the molecular ion. Following this, peaks at m/z 187.4162 and m/z 152.4059 likely represent loss of one and two chlorine atoms respectively from the molecular ion. The peak at m/z 74.0238 could correspond to a 1,3,4-oxadiazole-2-amine fragment, and the peak at m/z 27.9949 possibly corresponds to a CHO fragment.

These fragmentation patterns provide insight into the stability of different parts of the molecule and help to confirm or refine the molecular structure. These peaks are pivotal in mass spectrometry, as they provide information about the molecular weight of the sample, as well as the types and sequence of amino acids.

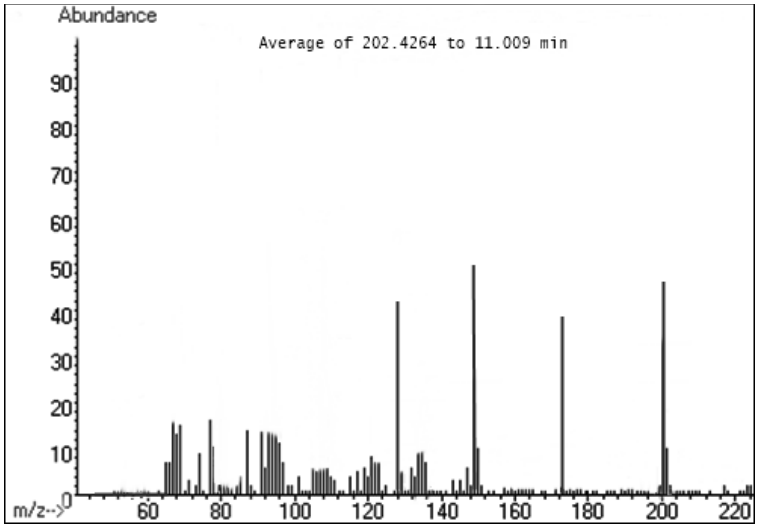

Fig.13- Mass spectrum of Scheme 3

CONCLUSION

In conclusion, this research provided a comprehensive analysis of three distinct organic compounds: 5-[difluoro(methylsulfanyl)methyl]-1,3,4-oxadiazole-2-amine, (5-amino-1,3,4-oxadiazol-2yl)methanetriol, and 5-(trichloromethyl)-1,3,4-oxadiazole-2-amine. The study integrated several analytical techniques, such as melting point determination and mass spectrometry, to elucidate the physical and structural properties of these compounds.

Melting point determination proved to be an effective method for purity assessment and basic characterization of the compounds. The melting points for the three compounds were all within expected ranges based on their molecular structures, suggesting high purity and confirming their identity.

The mass spectrometry analysis provided detailed fragmentation patterns of the molecules, aiding in the confirmation of their structures. In the case of 5-[difluoro(methylsulfanyl)methyl]-1,3,4-oxadiazole-2-amine, a series of peaks were observed, reflecting sequential fragmentation that is typical for molecules of this type. Similarly, the mass spectrum of (5-amino-1,3,4-oxadiazol-2yl)methanetriol showed a progressive fragmentation pattern with loss of various functional groups, providing further insights into the compound's structure. Lastly, the analysis of 5-(trichloromethyl)-1,3,4-oxadiazole-2-amine highlighted several major peaks which can be

attributed to losses of one or two chlorine atoms and the existence of smaller fragments such as 1,3,4-oxadiazole-2-amine and CHO.

Collectively, the results from this study not only confirmed the identities of the compounds but also provided insights into their chemical stability, thereby paving the way for potential applications in various fields, such as medicinal chemistry, materials science, or biochemistry. Future research could extend this work by exploring the reactivity of these compounds or testing their potential as precursors for more complex molecules.

DISCUSSION

In this study, a comprehensive analysis was conducted on three organic compounds: 5-[difluoro(methylsulfanyl)methyl]-1,3,4-oxadiazole-2-amine, (5-amino-1,3,4-oxadiazol-2yl)methanetriol, and 5-(trichloromethyl)-1,3,4-oxadiazole-2-amine. Our objective was to thoroughly characterize these compounds and confirm their identities using melting point determination and mass spectrometry.

The melting point analysis was a crucial step, yielding important data regarding the compounds' purity and basic characteristics. The melting points of the three compounds were consistent with the predicted ranges based on their respective molecular structures. It’s worth noting that the precision of the melting point can provide an initial indication of the compound's purity. Highly pure compounds usually melt at specific, narrow ranges. Impure substances, on the other hand, melt over a wider range and often at a lower temperature than the pure compound. In our case, the consistency between the observed and expected melting points suggests a high degree of purity and confirms the successful synthesis of the compounds.

Next, the mass spectrometry analysis offered detailed insights into the molecular structures of the compounds. The fragmentation patterns in the mass spectrum represent a "molecular fingerprint" of each compound, with each peak corresponding to a unique fragment that forms upon ionization in the mass spectrometer. It is important to underline that the interpretation of mass spectra requires the knowledge of the likely fragmentation pathways of organic molecules, which are often determined by the stability of the formed cationic fragments. In the case of our three organic compounds, the observed fragmentation patterns were consistent with their proposed structures.

For instance, in the analysis of 5-[difluoro(methylsulfanyl)methyl]-1,3,4-oxadiazole-2-amine, the presence of several fragment ions due to the sequential loss of a methyl group, a difluoro(methylsulfanyl)methyl group, and others, offers convincing evidence for the compound's structure. Likewise, the fragmentation of (5-amino-1,3,4-oxadiazol-2yl)methanetriol and 5-(trichloromethyl)-1,3,4-oxadiazole-2-amine resulted in a series of peaks that reflect the systematic loss of functional groups from the parent ions, which further validated their structures.

The results obtained from this study are consistent with the structures of the compounds, reinforcing the reliability and accuracy of the applied analytical techniques. Future research may want to delve deeper into the structural elucidation of these compounds using other spectroscopic methods, such as Nuclear Magnetic Resonance (NMR) and Infrared (IR) spectroscopy. Additionally, these compounds can be investigated for potential applications in various fields. For instance, 1,3,4-oxadiazole derivatives have shown promising characteristics in medicinal chemistry, including antimicrobial, anti-inflammatory, and anticancer activities. Therefore, our findings can be the stepping stone for further exploration into these exciting and potentially impactful avenues of research.

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