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Synthesis, Characterization of various Imidazole-1,3,4-Oxadiazole Derivative

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ABSTRACT

The heterocyclic system (such as imidazole, Oxadiazole) and their derivatives have attracted so much attention due to their valuable properties. Imidazole, Oxadiazole compound have caught so much attention due to their vital used in various fields or disease. Imidazole can be used as anti-fungal, antiprotozoal, antihypertensive, Oxadiazole can be used as antitussive, anti-inflammatory, anesthetic, vasodilator, anthelmintic, antiallergic and antiplatelet. The syntheses of these five derivatives were carried out. In first step Ethyl 2-(1H-imidazol-1-yl) acetate is prepared, this Ethyl 2-(1H-imidazol-1-yl) acetate is used to prepare 2–(1H–imidazol-1–yl) acet–hydrazide. Afterward in this benzaldehyde (i.e. 4-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, 3-nitrobenzaldehyde, 4-aminobenzadehyde, 3-methoxybenzaldehyde) is added, in next step by adding acetic anhydride the desired derivatives were formed. ATR-FTIR studies were carried out in which the groups present in of compound were determined such as such as C-H group, C-O group, C-O-C group, N-C group, C=O group, O-H group. 1H-NMR studies were also performed. The structures of different derivatives were determined by 1H-NMR. According to the nature or number of hydrogen present on the neighboring atom the splitting of peaks occurs.

Keywords- Activity, Fourier Transform Infrared Spectroscopy (FTIR), Imidazole, Nuclear magnetic resonance (NMR), Oxadiazole, Synthesis, Preparation

INTRODUCTION

Imidazole and its derivatives have had a special place in heterocyclic chemistry. Imidazole and its derivatives exhibit a wide range of chemical characteristics. The DNA base structure, histamine, vitamin B12, and other components of human beings all have an imidazole nucleus as their primary structural component. Numerous pharmacological compounds, both natural and man-made, include imidazole. Heinrich Debus made the initial discovery of imidazole in 1858 [1, 2].

A five-membered heterocyclic moiety is imidazole. Imidazole has two double bonds, four hydrogen atoms, two nitrogen atoms, and three carbon atoms. 1, 3-Diazole is another name for imidazole. Amphoteric in nature, or having both acidic and basic qualities, is how we would describe 1, 3-diazole. It is a solid that is white or colorless. In water and other polar solvents, it is very soluble. Imidazole has the general chemical formula $C_3H_4N_2$. The first and third places of the ring, which are not neighboring locations, contain nitrogen atoms.

Two nitrogen atoms make up imidazole, one of which is a hydrogen atom and the other of which is referred to as pyrrole type nitrogen [3]. “Imidazole” word is coined by a German chemist Arthur Rudolf Hantzsch in 1887. Imidazoles are classified as a diazole. Imidazole has non-adjacent nitrogen atoms. It has two nitrogen in positions 1 and 3 and is a planar five-membered heterocyclic with three carbons and two nitrogen because glyoxal and ammonia were used in the initial synthesis, imidazole was formerly known as gluoxaline [4].

It is highly polar compound having dipole moment 3.61D [5]. It is nearly pentagon-shaped planar molecule. It is classified as an aromatic compound because of existence of delocalized electrons sextet and it occurs in two resonating forms at room temperature [6]. IUPAC name of imidazole is 1*H*-imidazole. Molar weight of 68.08g/mol [7].

Various imidazole based derivatives which show different activity are. Ketoconazole shows anti-fungal activity, anti-bio film activity. Miconazole shows anti-fungal activity, anti-virulence activity, anti-bacterial activity [8-12]. Clotrimazole shows anti-fungal activity [13]. Tioconazole shows antimicrobial activity, anti-fungal activity [14-15].

Econazole shows anti-fungal activity-, anti-sporulant activity, and anti-mycotic activity [16-18]. Tinidazole shows anti-protozoan activity, bactericidal activity [19-21]. Eberconazole and lanoconazole shows anti-fungal activity-. Fenticonazole shows antifungal activity, anti-bacterial activity [22, 23]. Bifonazole shows antifungal activity [24]. Sulconazole shows anti-microbial activity, anti-fungal activity [25, 26]. Luliconazole shows anti-fungal activity [27, 28].

A group of artificial compounds known as 1, 3, 4-oxadiazoles has important medicinal applications. The focus of this paper will be on recent discoveries in the pharmacology of 1, 3, 4-oxadiazoles. A major moiety that has been the focus of several recent review publications is the 1, 3, 4-oxadiazole ring system. The numerous biological activities connected with it are summarised on this page. There is no trite name for the 1, 3, 4-oxadiazole ring that has been adopted, such as "azoxime" for 1, 2, 4-oxadiazole or "furazan" for 1, 2, 5-oxadiazole. Five-membered rings called Oxadiazole include one oxygen atom and two nitrogen atoms [29].

There are several biological uses for heterocyclic molecules containing a five-membered Oxadiazole nucleus. Because of their diverse biological activities, the 1, 3, 4-oxadiazole and 3-aroylpropionic acid moieties are essential. Compounds with the 1, 3, 4-oxadiazole nucleus, in particular, are known to have specific anti-oedema and anti-inflammatory properties. Other substituted Oxadiazole moieties have been shown to possess other intriguing properties, such as analgesic, antibacterial, anti-tubercular, anti-convulsant, and anti-hepatitis B-viral activity. Non-steroidal anti-inflammatory drugs, or NSAIDs, are a group of pharmaceutical substances that are often used for their anti-inflammatory, analgesic, and antipyretic effects [30].

One oxygen atom, two nitrogen atoms, two double bonds, and two carbon atoms makeup the five-membered heterocyclic molecule known as Oxadiazole. Furan is the source of Oxadiazole. Two pyridine type nitrogen atoms (-N=) were used in place of two methane groups (-CH=) in furan. There are four different types of Oxadiazole isomers, which were created, based on the location of the nitrogen atom in the ring [31].

MATERIAL AND METHOD

Material

IR spectrophotometer was used to determine the functional group of the compound

NMR spectrophotometer is use to determine the structure of compound (derivative).

Method

Steps for the preparation of derivatives

There are various steps for the preparation of derivatives. The initial compound used for the preparation of derivative is imidazole. In this imidazole is reacted with ethyl chloroacetate, dry acetone and the crystals are formed these crystals are then reacted with hydrazine hydrate and ethanol. This mixture is reacted with 4-hydroxybenzyldehyde [32]. This mixture of A3 is then reacted with acetyl chloride. For last step, aromatic aldehyde is added, various derivatives of this aromatic aldehyde

Preparation of Ethyl 2-(1H-imidazol-1-yl) acetate (A1)

A mixture of imidazole, ethyl chloroacetate, dry acetone and potassium carbonate was reflux for 6 hours with stirring at 80°C. The solution is filtered after the solvent evaporates under pressure, and the separated result is ethanol that has been recrystallized to produce crystals.

Preparation of 2–(1H–imidazol-1–yl) acet–hydrazide: (A2)

A1 and Hydrazine Hydrate in Ethanol were refluxed for three hours, and then the residual solution was concentrated and chilled. Crystals were produced by re-crystallizing the product from ethanol after it had been filtered and purified.

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Preparation of Preparation of N-(aryldine)-2-(1H-imidazol–1-yl) acetamide: (A3)

Ethanol that contains A2 and 4-hydroxybenzyldehyde. Concentrate the solution after 4 hours of refluxing the mixture. Filtration was used to separate the product, and ethanol was used to crystallize it again.

Preparation of 5-(1H-imidazol-1-yl) methyl) 3-Nacetyl-2-(aryl)-1, 3, 4-(2H)-Oxadiazole

A3 and acetyl chloride were combined, and the combination was refluxed for six hours before distillation removed the solvent. The crushed ice was combined with the residue. Filtration separated the outcome.

Synthesis of Imidazole-1, 3, 4 Oxadiazole

Imidazole-1, 3, 4 Oxadiazole derivatives were synthesized (Fig. 1). Steps to synthesize Imidazole1,3,4-oxadiazole derivatives are preparation of A1, preparation of A2, preparation of A3, preparation of 5-(1H-imidazol-1-yl)methyl 3-Nacetyl-2-(aryl)-1,3,4-(2H)-Oxadiazole [33].

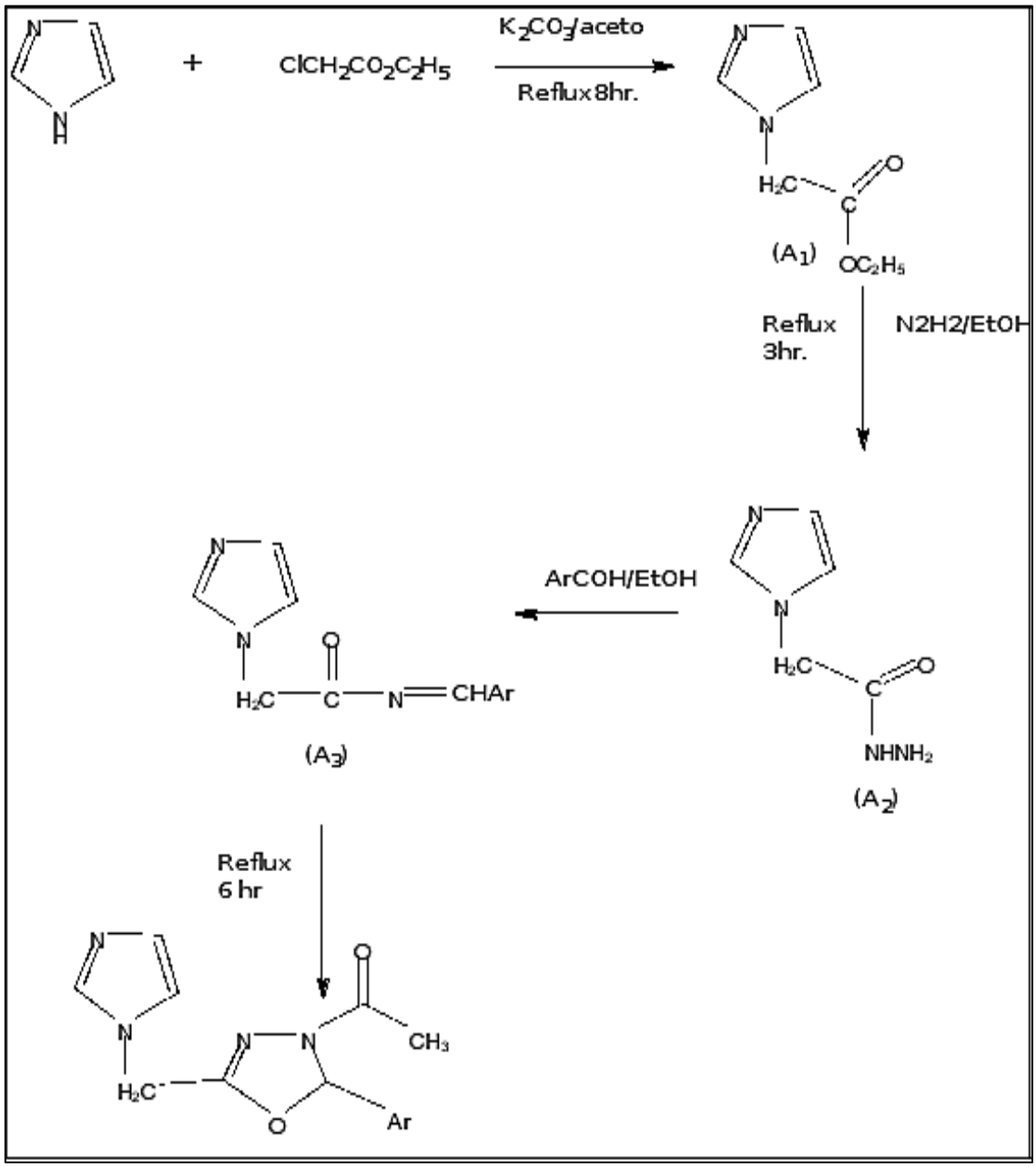

Figure 1: *Synthesis of imidazole 1, 3, 4-oxadiazole derivative.*

Ps1 derivative synthesis

There are various steps for the preparation of derivatives. For last step, 4 hydroxybenzaldehyde is added, various derivatives of this aromatic aldehyde

Preparation of Ethyl 2-(1H-imidazol-1-yl) acetate (A1)

Imidazole, ethyl chloroacetate, dry acetone, and potassium carbonate were combined and heated in a reflux for 6 hours at 80°C while being stirred. The solution is filtered after the solvent evaporates under pressure, and the separated result is ethanol that has been recrystallized to produce crystals.

Preparation of 2–(1H–imidazol-1–yl) acet–hydrazide (A2)

A1 and Hydrazine Hydrate in Ethanol were refluxed for three hours, and then the residual solution was concentrated and cooled. Crystals were produced by re-crystallizing the product from ethanol after it had been filtered and purified.

Preparation of A3

Ethanol that contains A2 and 4-hydroxybenzyldehyde. Concentrate on the solution after 4 hours of refluxing the mixture. Filtration was used to separate the product, and ethanol was used to crystallize it again.

Preparation of Ps1 derivative

A3 and acetyl chloride were combined, and the combination was refluxed for six hours before distillation removed the solvent. The crushed ice was combined with the residue. Filtration separated the outcome (Fig. 2).

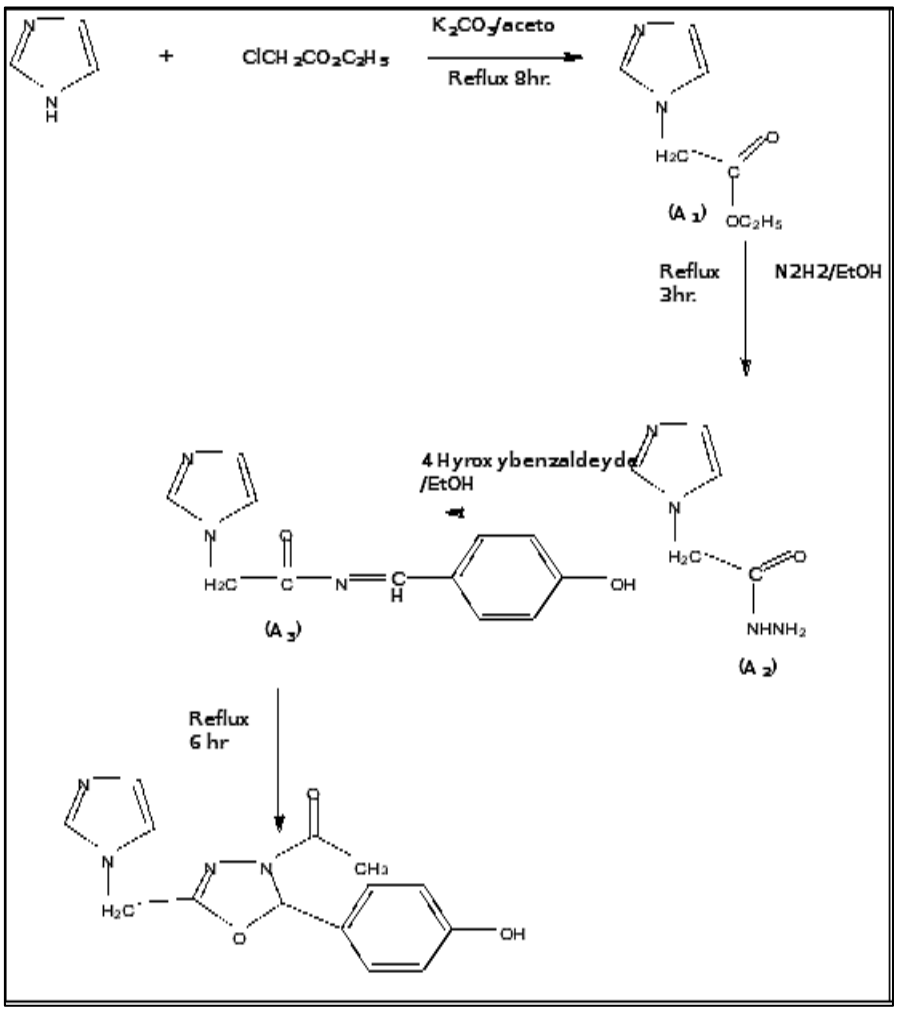

Figure 2: *Synthesis of Ps1 imidazole-1, 3, 4-Oxadiazole.*

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Ps2 derivative synthesis: There are various steps for the preparation of Ps 2 derivatives. The initial compound used for the preparation of Ps2 derivative is imidazole.

In this imidazole is reacted with ethyl chloroacetate, dry acetone and the crystals are formed these crystals are then reacted with hydrazine hydrate and ethanol. This mixture is reacted with 4-hydroxybenzyldehyde. This mixture of A3 is then reacted with acetyl chloride. For last step 3 hydroxybenzaldehyde is added [34].

Preparation of Ethyl 2-(1H-imidazol-1-yl) acetate (A1)

Imidazole, ethyl chloroacetate, dry acetone, and potassium carbonate were combined and heated in a reflux for 6 hours at 80°C while being stirred. The solution is filtered after the solvent evaporates under pressure, and the separated result is ethanol that has been recrystallized to produce crystals.

Preparation of 2–(1H–imidazol-1–yl) acet–hydrazide (A2)

A1 and Hydrazine Hydrate in Ethanol were refluxed for three hours, and then the residual solution was concentrated and chilled. Crystals were created by re-crystallizing the product from ethanol after it had been filtered and purified.

Preparation of A3

Ethanol with a combination of A2 and 3-hydroxybenzyldehyde, Concentrate on the solution after 4 hours of refluxing the mixture. Filtration was used to separate the product, and ethanol was used to crystallize it again.

Preparation of Ps2 derivative

A3 and acetyl chloride were combined, and the combination was refluxed for six hours before distillation removed the solvent. The crushed ice was combined with the residue. Filtration separated the outcome (Fig. 3).

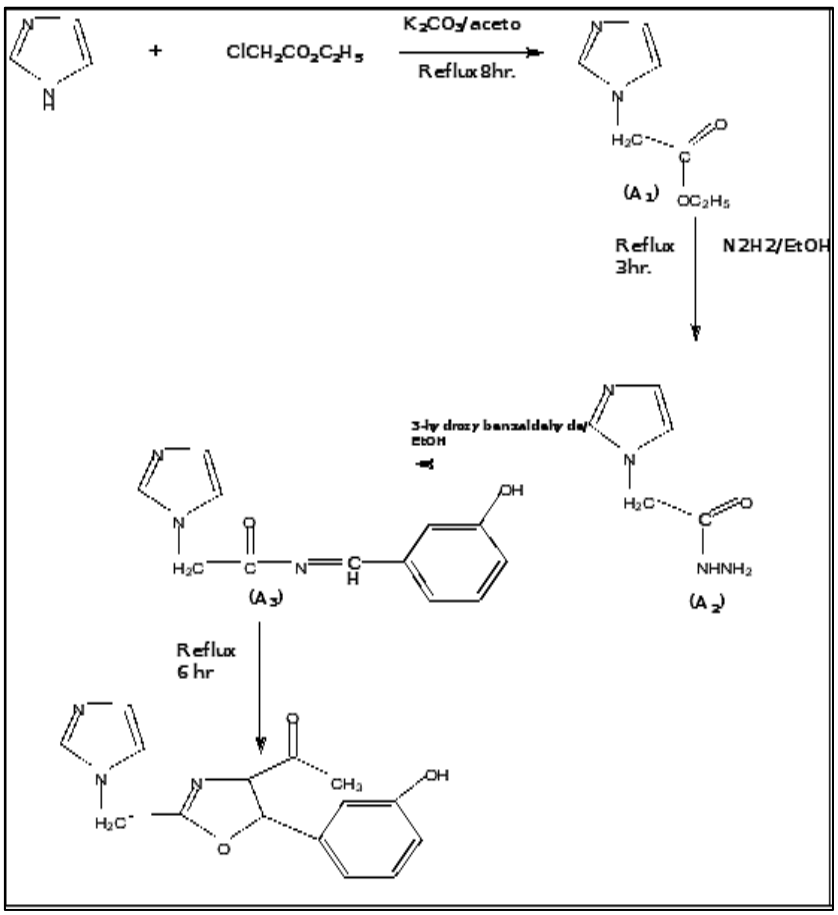

Figure 3: *Synthesis of Ps2 imidazole-1, 3, 4-Oxadiazole derivative.*

Ps3 derivative synthesis

There are various steps for the preparation of Ps 3 derivatives (Fig. 4). For last step 3 nitrobenzaldehyde is added.

Preparation of Ethyl 2-(1H-imidazol-1-yl) acetate (A1)

Imidazole, ethyl chloroacetate, dry acetone, and potassium carbonate were combined and heated in a reflux for 6 hours at 80°C while being stirred. The solution is filtered after the solvent evaporates under pressure, and the ethanol-derived product is then recrystallized to produce crystals.

Preparation of 2–(1H–imidazol-1–yl) acet–hydrazide (A2)

A1 and Hydrazine Hydrate in Ethanol were refluxed for three hours, and then the residual solution was concentrated and chilled. Crystals were produced by re-crystallizing the product from ethanol after it had been filtered and purified.

Preparation of A3

Ethanol that contains a combination of A2 and 4-nitrobenzyldehyde. Concentrate on the solution after 4 hours of refluxing the mixture. Filtration was used to separate the product from the ethanol, and then it was re-crystallized.

Preparation of Ps3 derivative:

A3 and acetyl chloride were combined, and after 6 hours of refluxing, the solvent was distilled away. The crushed ice was combined with the residue. Filtration separated the outcome.

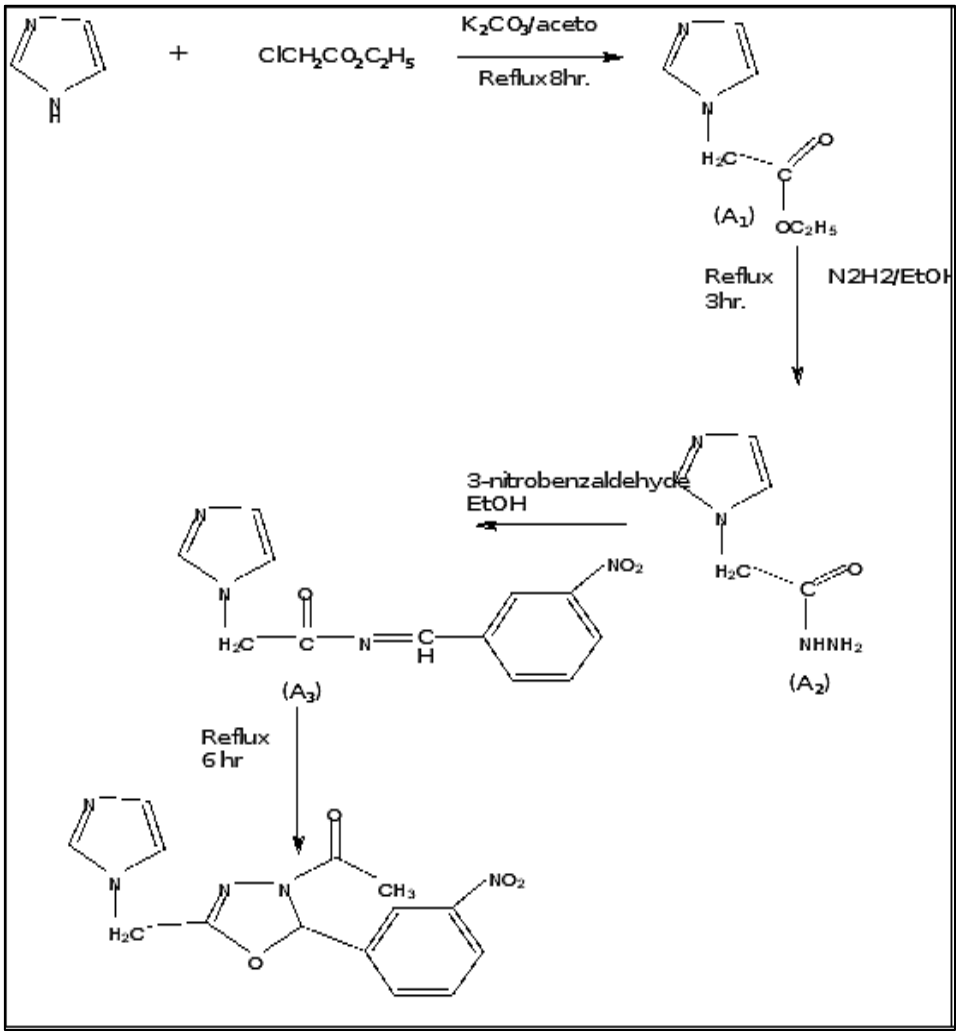

Figure 4: *Synthesis of Ps3 imidazole-1, 3, 4-Oxadiazole derivative.*

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Ps4 derivative synthesis

There are various steps for the preparation of Ps 4 derivatives (Fig. 5). The initial compound used for the preparation of Ps4 derivative is imidazole. In this imidazole is reacted with ethyl chloroacetate, dry acetone and the crystals are formed these crystals are then reacted with hydrazine hydrate and ethanol. This mixture is reacted with 4-hydroxybenzyldehyde. This mixture of A3 is then reacted with acetyl chloride. For last step 4 amino benzaldehyde is added.

Preparation of Ethyl 2-(1H-imidazol-1-yl) acetate (A1)

Imidazole, ethyl chloroacetate, dry acetone, and potassium carbonate were combined and heated in a reflux for 6 hours at 80°C while being stirred. The solution is filtered after the solvent evaporates under pressure, and the separated result is ethanol that has been recrystallized to produce crystals [35-38].

Preparation of 2–(1H–imidazol-1–yl) acet–hydrazide (A2)

A1 and Hydrazine Hydrate in Ethanol were refluxed for three hours, and then the residual solution was concentrated and chilled. Crystals were produced by re-crystallizing the product from ethanol after it had been filtered and purified.

Preparation of A3

Ethanol with a combination of A2 and 4-aminobenzyldehyde (Fig. 4). Concentrate on the solution after 4 hours of refluxing the mixture. Filtration was used to separate the product, and ethanol was used to crystallize it again.

Preparation of Ps4 derivative

A3 and acetyl chloride were combined, and the combination was refluxed for six hours before distillation removed the solvent. The crushed ice was combined with the residue. Filtration separated the outcome.

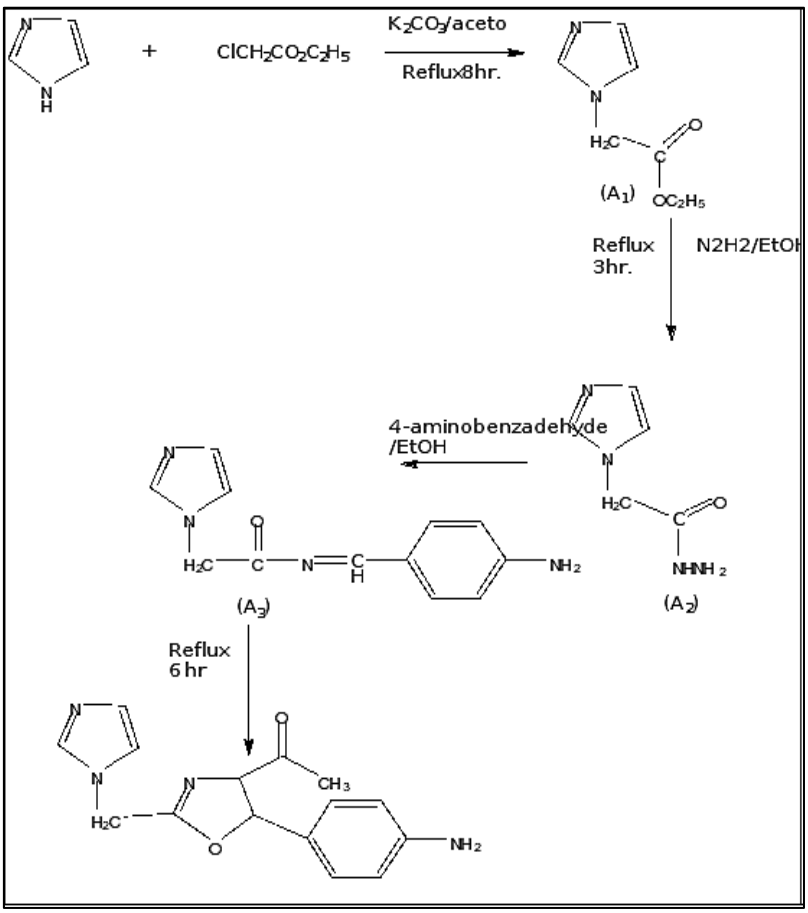

Figure 5: *Synthesis of Ps4 imidazole-1, 3, 4-Oxadiazole.*

ATR-FTIR study

Attenuated total reflectance (ATR), which generates an evanescent wave, uses total internal reflection. The ATR crystal is used to reflect an infrared light beam at least once off of the internal surface of the sample. The reflection creates the evanescent wave that penetrates the sample. For polymer identification, ATR-FTIR analytical characterization was used. ATR-FTIR is used to analyse the samples immediately. The quality of the spectrum is determined by the diamond crystal's close enough proximity to the sample. The employment of a high-pressure clamp is used to create this result. The bands from the polymers in the examined sample were used to interpret the resulting ATR-FTIR spectra. When additives were found in the material, the bands from the characteristic groups of these components were used to identify them. Finally, the resulting spectra were compared to those of polymers and additive reference libraries.

NMR study

Using nuclear magnetic resonance, researchers may examine the physical, chemical, and biological characteristics of substances by taking use of particular nuclei's magnetic properties. The NMR spectrometer must be set to a certain nucleus, in this case the proton. There are other ways to calculate the spectrum, but the continuous wave (CW) technique is the simplest. In order to smooth out any variations in the magnetic field and tube imperfections, a sample solution is put in a uniform 5 mm glass tube and spun between the poles of a powerful magnet. The appropriate amount of radio frequency radiation is sent into the sample using an antenna coil (colored red). A receiver coil surrounds the sample tube, and a computer and specialized electrical apparatus are used to track the emission of radio frequency radiation that has been absorbed. To obtain a NMR spectrum, the magnetic field is changed or swept over a limited range while the sample's RF signal is being examined. Equally effective is changing the rf radiation's frequency while maintaining a constant external field.

In order to smooth out any variations in the magnetic field and tube imperfections, a sample solution is put in a uniform 5 mm glass tube and spun between the poles of a powerful magnet. The appropriate amount of radio frequency radiation is sent into the sample using an antenna coil (colored red). A receiver coil surrounds the sample tube, and a computer and specialized electrical apparatus are used to track the emission of radio frequency radiation that has been absorbed. To obtain a NMR spectrum, the magnetic field is changed or swept over a limited range while the sample's RF signal is being examined. Equally effective is changing the RF radiation's frequency while maintaining a constant external field.

RESULT AND DISCUSSION

FTIR Spectroscopy

In FTIR wavelength was checked from this wavelength the functional groups were determined. Mode of vibration is also checked. Wavelength value, mode of vibration for this characterization was taken from Spectrometric identification of organic compounds.

Derivative Ps-1

C-H group shows stretching vibration at wavelength 2929.30 cm^{-1} for alkane. C-H group shows stretching vibration at wavelength 2873.11 cm^{-1} for methyl group. N-H group shows stretching vibration at wavelength 2320.32 cm^{-1}. C=O group shows stretching vibration at wavelength 1741.28 cm^{-1} .C=C ring shows stretching vibration at wavelength 1503.15 cm^{-1}. O-H shows bending vibration at 1379.37 cm^{-1}. C-O-C group shows asymmetrical stretching vibration at wavelength 1219.40 cm^{-1}. C-O group shows stretching vibration at wavelength 1163.78 cm^{-1}. C-C stretching were shown at wavelength 1031.78 cm^{-1}, 772.35 cm^{-1}, 716.22 cm^{-1} (Fig. 6).

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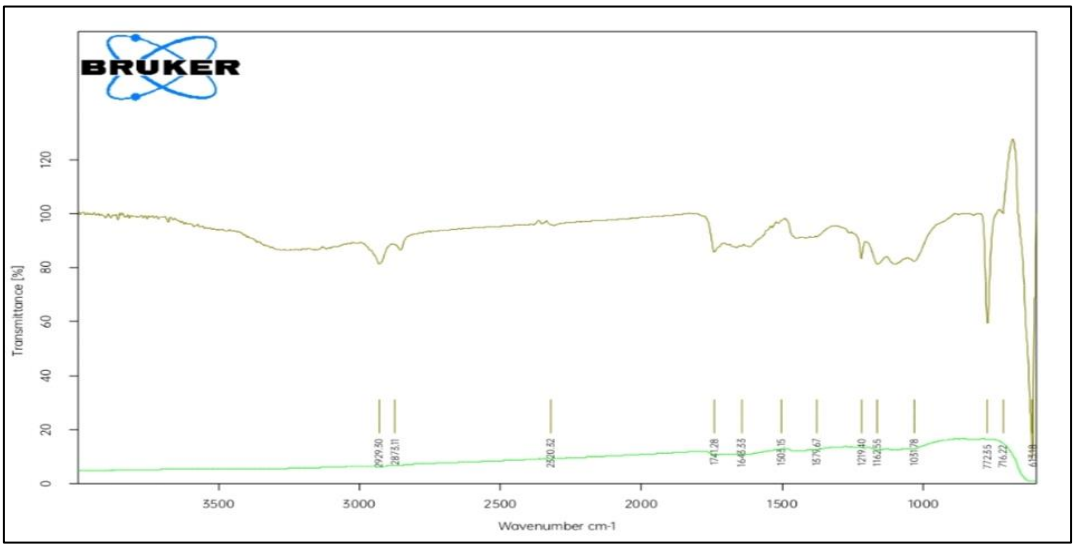

Figure 6: *FTIR Spectroscopy of Derivative Ps-1.*

Derivative Ps-2

C-H group shows stretching vibration at wavelength 2929.30 cm^{-1} for alkane. C-H group shows stretching vibration at wavelength 2873.11 cm^{-1} for methyl group. N-H group shows stretching vibration at wavelength 2320.32 cm^{-1}. C=O group shows stretching vibration at wavelength 1741.28 cm^{-1} .C=C ring shows stretching vibration at wavelength 1503.15 cm^{-1}. O-H shows bending vibration at 1382.37 cm^{-1}. C-O-C group shows asymmetrical stretching vibration at wavelength 1219.40 cm^{-1}. C-O group shows stretching vibration at wavelength 1163.78 cm^{-1}. C-C stretching was shown at wavelength 1031.78 cm^{-1}, 772.35 cm^{-1}, 716.22 cm^{-1} (Fig. 7).

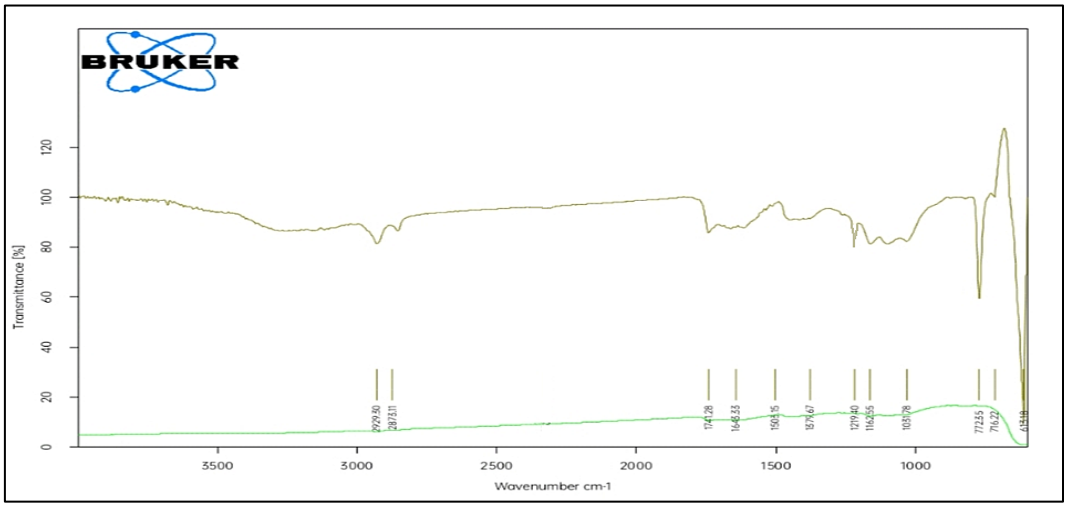

Figure 7: *FTIR Spectroscopy of Derivative Ps-2.*

Derivative Ps-3

C-H group shows stretching vibration at wavelength 2929.30 cm^{-1} for alkane. C-H group shows stretching vibration at wavelength 2873.11 cm^{-1} for methyl group. N-H group shows stretching vibration at wavelength 2320.32 cm^{-1}. C=O group shows stretching vibration at wavelength 1741.28 cm^{-1} .C=C ring shows stretching vibration at wavelength 1503.15 cm^{-1}. O-H shows bending vibration at 1382.37 cm^{-1}. C-O-C group shows asymmetrical stretching vibration at wavelength 1219.40 cm^{-1}. C-O group shows stretching vibration at wavelength 1163.78 cm^{-1}. C-C stretching were shown at wavelength 1031.78 cm^{-1}, 772.35 cm^{-1}, 716.22 cm^{-1}(Fig. 8).

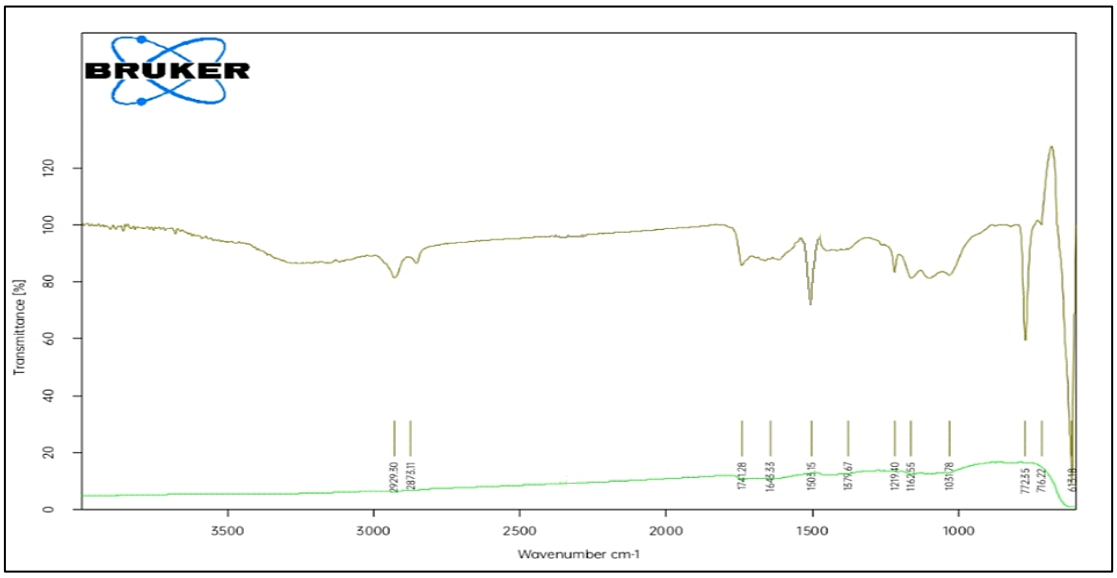

Figure 8: *FTIR Spectroscopy of Derivative Ps-3.*

Derivative Ps-4

C-H group shows stretching vibration at wavelength 2929.30 cm^{-1} for alkane. C-H group shows stretching vibration at wavelength 2873.11 cm^{-1} for methyl group. N-H group shows stretching vibration at wavelength 2320.32 cm^{-1}. C=O group shows stretching vibration at wavelength 1741.28 cm^{-1} .C=C ring shows stretching vibration at wavelength 1503.15 cm^{-1}. O-H shows bending vibration at 1382.37 cm^{-1}. C-O-C group shows asymmetrical stretching vibration at wavelength 1219.40 cm^{-1}. C-O group shows stretching vibration at wavelength 1163.78 cm^{-1}. C-C stretching was shown at wavelength 1031.78 cm^{-1}, 772.35 cm^{-1}, 716.22 cm^{-1}(Fig. 9).

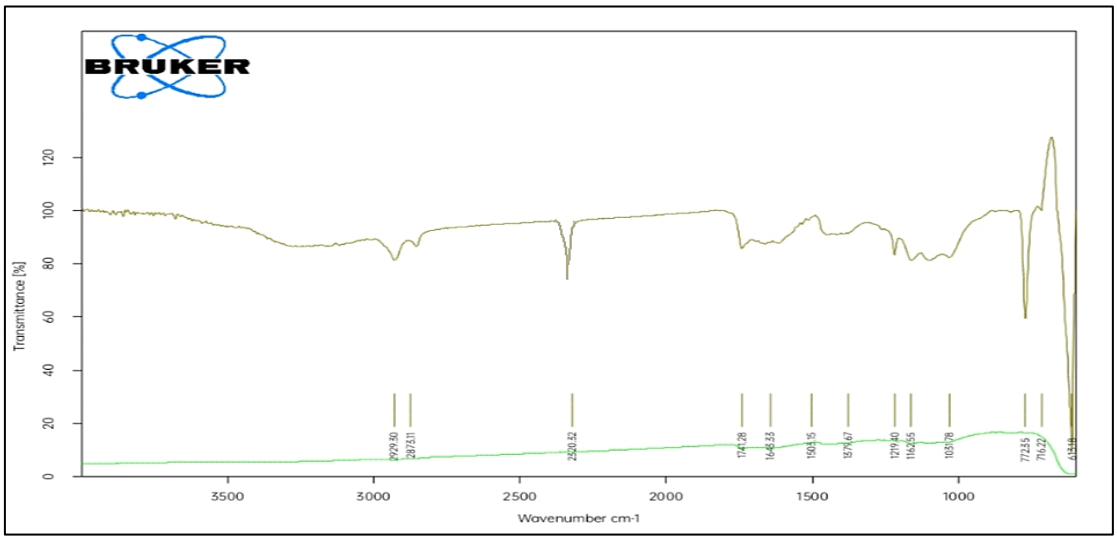

Figure 9: *FTIR Spectroscopy of Derivative Ps-4.*

1*H*-NMR

In 1*H*-NMR the nature of proton is checked. The peak and the splitting in these peaks were checked. The values of these peaks were confirmed by Spectrometric identification of organic compounds. 1*H*-NMR spectra in DMSO-d6 were found on Bruker spectrometers. Chemical shift (d, ppm), multiplicity (s=singlet, d=doublet, dd=doublet of doublets, t= triplet, m= multiplet, q=quartet), and coupling constant (J) in Hz were the 1*H*-NMR data that were acquired (Fig. 10).

Derivative Ps-1

In this spectrum structure Ps1 derivative is a characterized by 1*H*-NMR. 1*H*-NMR (600MHz, DMSO-d6), (s, 4.501 ppm), the phenolic proton peak comes at 4.501 ppm. (s, 1.641 ppm; s, 1.838 ppm). Alkyl peak comes at 1.641 ppm, 1.838 ppm. (d, 2.516 ppm,2.514ppm,1H; s,3.517 ppm). The peak of the carbonyl group appear at 2.5 ppm. 3.5 ppm is the place where the peak of Oxadiazole is appearing. (d, 7.268ppm, 7.255ppm,1H). The peak of imidazole is appearing at 7.2 ppm.

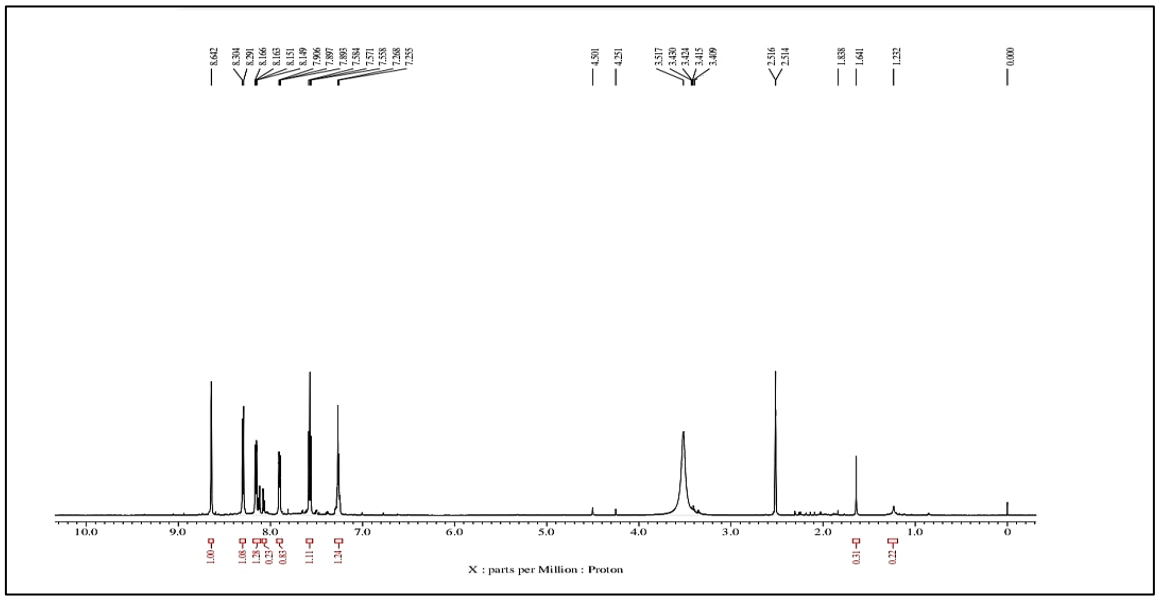

Figure 10: *1H-NMR of derivative Ps-1.*

Derivative Ps-2

In this spectrum, structure Ps2 derivative is a characterized by 1*H*-NMR (Fig. 11). 1*H*-NMR (600MHz, DMSO-d6), (s, 4.251ppm). The phenolic proton peak comes at 4.2 ppm. The phenolic group is present in meta position. (s, 1.641ppm), (s, 1.838ppm). Alkyl peak comes at 1.6 ppm, 1.8 ppm. (d, 2.516 ppm, 2.514ppm,1H), (s,3.517 ppm). The peak of the carbonyl group appear at 2.5 ppm. 3.5 ppm is the place where the peak of Oxadiazole is appearing (d, 7.268ppm, 7.255ppm,1H). The peak of imidazole is appearing at 7.2 ppm.

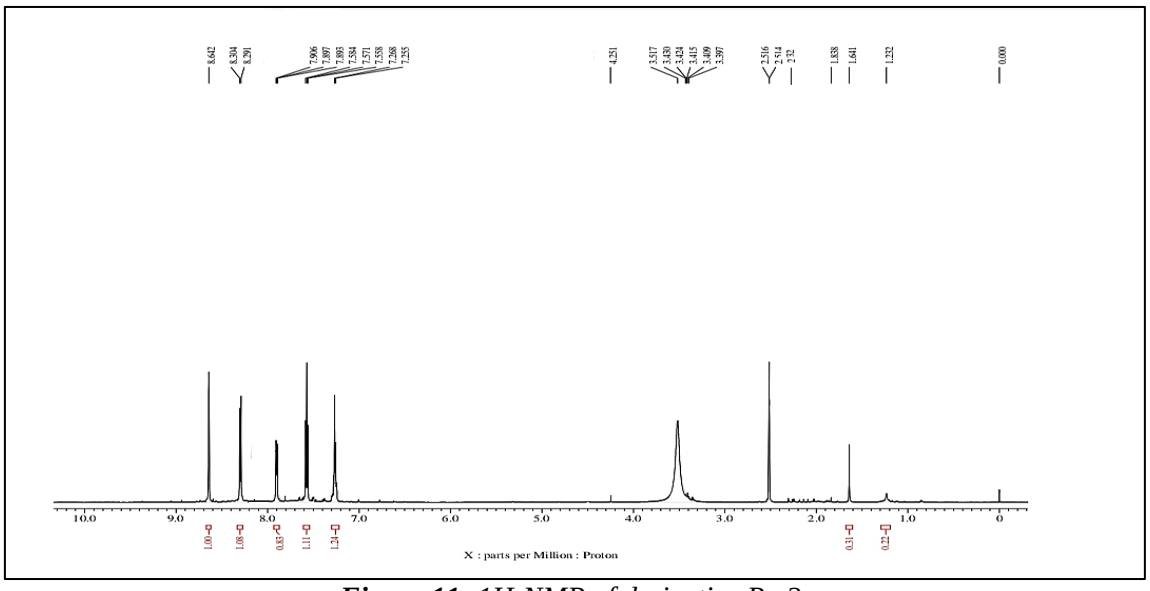

Figure 11: *1H-NMR of derivative Ps-2.*

Derivative Ps-3

In this spectrum, structure Ps3 derivative is a characterized by 1*H*-NMR. 1*H*-NMR (600MHz, DMSO-d6), (s, 0.3ppm). The C-NO_2 peak comes at 0.3 ppm. (s, 1.641ppm; s, 1.838ppm). Alkyl peak comes at 1.6 ppm, 1.8 ppm. (d, 2.516 ppm,2.514ppm,1H), (s,3.517 ppm) (Fig. 12). The peak of the carbonyl group appear at 2.5 ppm. 3.5 ppm is the place where the peak of Oxadiazole is appearing. (d,7.268ppm, 7.255ppm,1H). The peak of imidazole is appearing at 7.2 ppm.

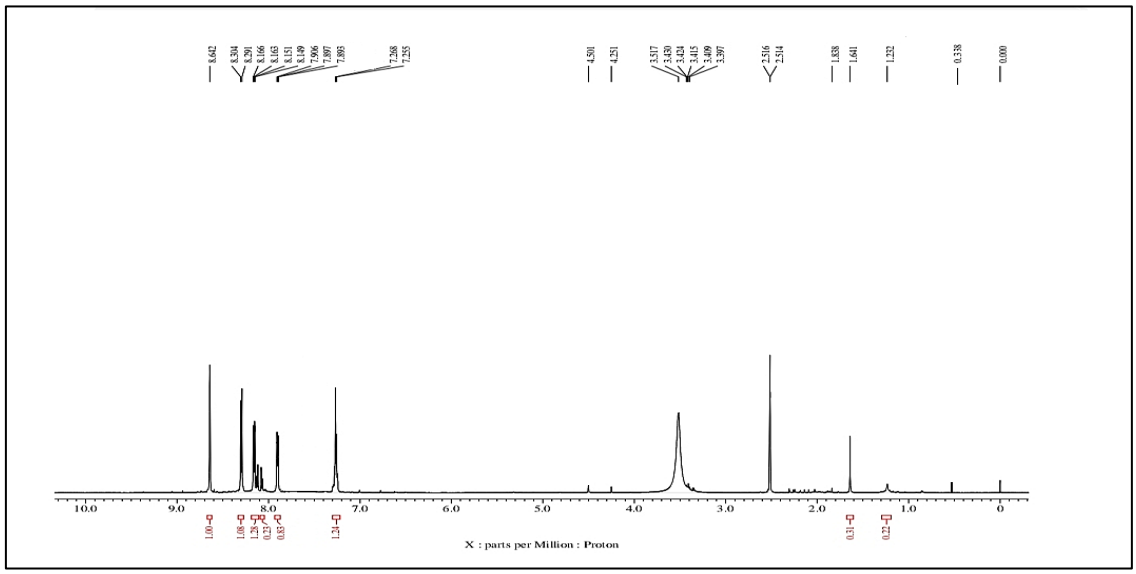

Figure 12: *1H-NMR of derivative Ps-3.*

Derivative Ps-4

In this spectrum, structure Ps4 derivative is a characterized by 1*H*-NMR (Fig. 13). 1*H*-NMR (600MHz, DMSO-d6) (s, 4.2ppm).The R-NH_2 peak comes at 4.2 ppm. (s, 1.641ppm), (s, 1.838ppm). Alkyl peak comes at 1.6 ppm, 1.8 ppm. (d, 2.516 ppm,2.514ppm,1H), (s,3.517 ppm). The peak of the carbonyl group appear at 2.5 ppm. 3.5 ppm is the place where the peak of Oxadiazole is appearing (d,7.277ppm, 7.275ppm,1H). The peak of imidazole is appearing at 7.2 ppm.

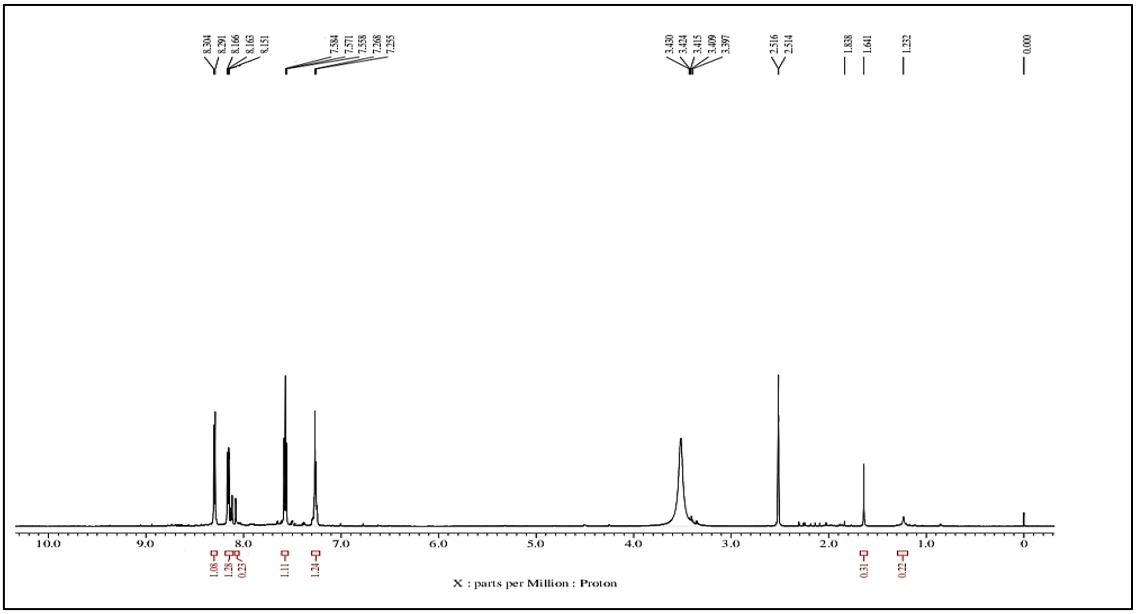

Figure 13: *1H-NMR of derivative Ps-4.*

CONCLUSION

The conclusion of this study is that these four imidazole-1, 3, 4-oxadiazole derivatives were synthesized and their characterization studies were performed. The characterization study such as FTIR and NMR were studied. Four derivatives were synthesized in the lab and characterization studies were done.

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