



Synthesis And Characterization Of Novel Derivatives Of Benzeimidazole

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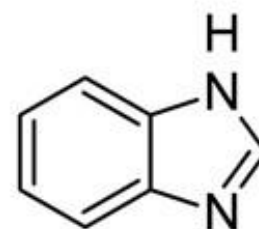
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ABSTRACT : An efficient and straightforward synthetic route for the preparation of substituted benzimidazole derivatives was developed, utilizing a one-pot multicomponent reaction. This approach offers advantages such as mild reaction conditions, high yields, and simplified purification. The structures of the synthesized compounds were confirmed by ¹H NMR, ¹³C NMR, IR, and mass spectrometry. The methodology's versatility was demonstrated by the synthesis of a library of benzimidazole derivatives with diverse substitution patterns.

Key Words : Benzimidazole, o-phenylenediamine, Formic acid, Piperazine, Morpholine, Spectroscopic characterization.

INTRODUCTION :

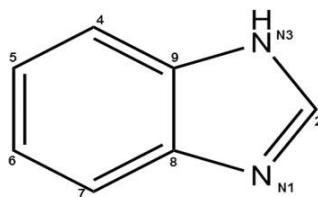
The molecular framework of Benzimidazole features a fused benzene and imidazole ring system, characteristic of heterocyclic aromatic compounds.¹ Notably, Benzimidazole exhibit relatively low toxicity while demonstrating potent activity against various pathogens.² Furthermore, derivatives of Benzimidazole have been found to display a broad spectrum of biological activities, including antimicrobial, antiparasitic, antiviral, anticancer, and antihypertensive properties.³



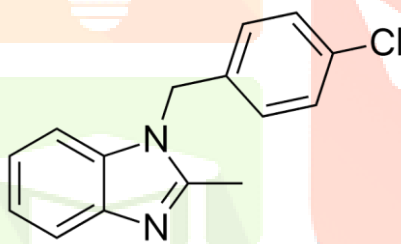
The development of Benzimidazole and its derivatives marks a significant milestone in the treatment of parasitic infections in humans and animals. The unique chemical properties of Benzimidazole, including its ability to undergo electrochemical reactions, have led to the creation of stable compounds with diverse applications. Benzimidazole-based compounds have demonstrated efficacy in treating various diseases affecting humans and animals, including livestock and companion animals. Their versatility and effectiveness have made them a valuable addition to the pharmaceutical arsenal.⁴

The structural optimization of Benzimidazole derivatives has yielded several potent therapeutic agents, including albendazole, omeprazole, and mebendazole, which are currently in use. Building on our ongoing research into Benzimidazole derivatives, we try to design and synthesize novel compounds within this class and evaluate their antimicrobial properties.⁵

Heterocyclic compounds play a vital role in various aspects of life sciences. These molecules perform diverse significant functions in nature, medicine, and technology. Among them, nitrogen-containing heterocycles, particularly the azole family, have garnered significant interest in synthesis due to their widespread occurrence in pharmacologically active natural products and multifunctional materials. For example piperazine, pyrrolidine, morpholine, etc. Attachment of these Heterocyclic compounds with Benzimidazole moiety gives another highly potent derivatives of Benzimidazole that gives antimicrobial activity.⁶



Benzimidazoles exhibit distinct physical and chemical properties. The introduction of substituents at the 1-position typically lowers the melting point. These compounds are generally soluble in polar solvents, but less soluble in nonpolar organic solvents. However, adding nonpolar substituents to the Benzimidazole ring enhances solubility in nonpolar solvents.⁷ For example Chlormidazole antifungal agent.⁸

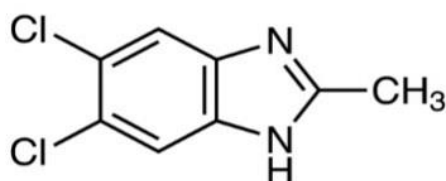


Chlormidazole

Research has shown that modifying the substituent at position 2 of 5(6)-substituted benzimidazoles significantly impacts their anthelmintic properties. To better understand this relationship, various structural changes have been made at this site. As a result, a range of 2-alkyl and 2-arylbenzimidazoles have been synthesized through condensation reactions involving o-phenylenediamines and different carboxylic acids, aldehydes, amides, esters, and nitriles in acidic conditions. Generally, introducing an alkyl or aryl group at position 2 results in compounds with relatively weak anthelmintic activity.⁹

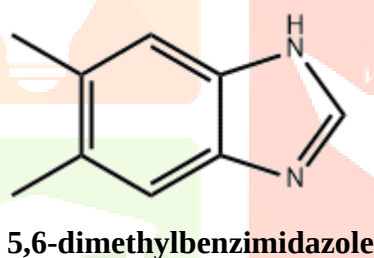
Conversely, incorporating polar groups increases solubility in polar solvents. Benzimidazoles demonstrate thermal stability, remaining unchanged above 300°C. They exhibit weak basicity, being less basic than imidazoles, and are soluble in dilute acids. Additionally, benzimidazoles display acidic properties, making them soluble in aqueous alkali and capable of forming N-metallic compounds. The acidic behavior is attributed to resonance stabilization of the ion. More acidic benzimidazoles may dissolve in weaker basic solutions, such as potassium carbonate.⁷

5,6-Dichloro-2-methylbenzimidazole is a derivative of benzimidazole, and it has been reported to exhibit antimicrobial and antifungal activities. The presence of the dichloro substituents and the methyl group at the 2-position may contribute to its biological activity.¹⁰

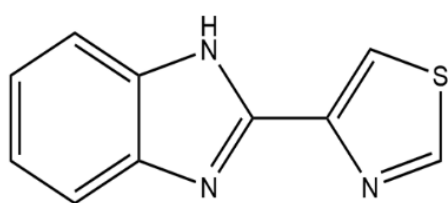


5,6-Dichloro-2-methylbenzimidazole

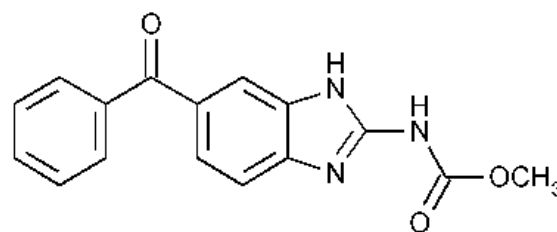
Benzimidazole derivatives exhibit a broad spectrum of biological activities, making them valuable in various pharmaceutical applications. Notably, vitamin B12 features a 5,6-dimethylbenzimidazole moiety coordinated to the Co(II) ion. Several drugs, including the antiparasitic agents such as thiabendazole, albendazole, mebendazole, flubendazole, fenbendazole, oxfendazole and triclabendazole contain benzimidazole derivatives. These compounds have shown promising therapeutic properties.¹¹



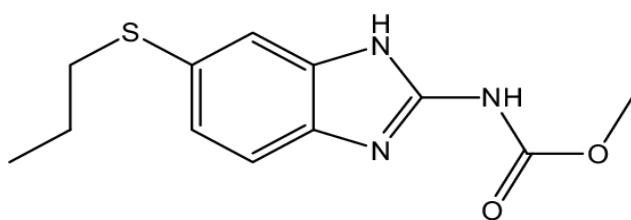
5,6-dimethylbenzimidazole



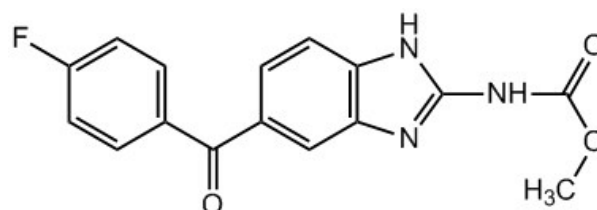
Thiabendazole



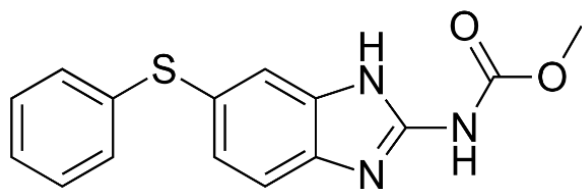
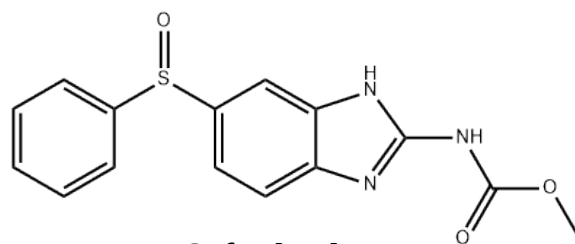
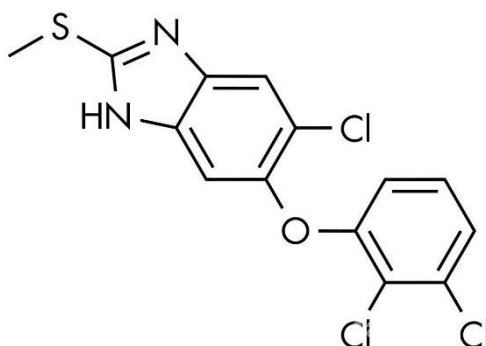
Mebendazole



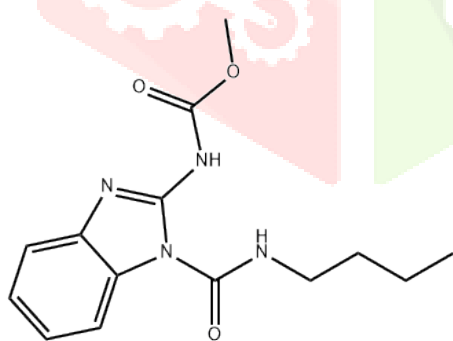
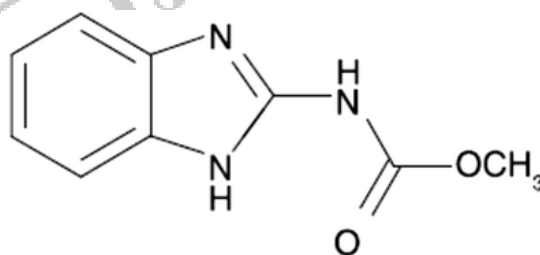
Albendazole



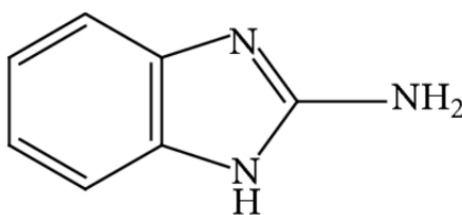
Flubendazole

**Fenbendazole****Oxfendazole****Triclabendazole**

Benzimidazoles' ability for facile electrophilic, nucleophilic, and cyclocondensation reactions enables the synthesis of diverse substituted benzimidazoles and benzimidazoheterocycles. Many of these compounds have proven effective against roundworm, tapeworm, and fluke infections in humans and domestic animals. Furthermore, some benzimidazoles are utilized in pest control.¹² For example Benomyl and Carbendazim act as fungicides.¹³

**Benomyl****Carbendazim**

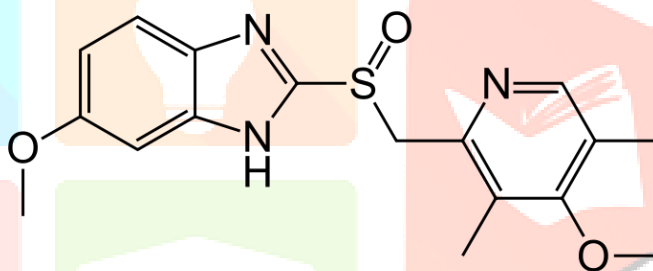
Research by Holloway et al. Has identified 2-aminobenzimidazoles as antibacterial agents that inhibit Trypanothione reductase, a key bacterial enzyme. While 1-substituted benzimidazole compounds have shown limited antimicrobial activity. Substituents at both the 1 and 2 positions have yielded potent antimicrobial agents. Specifically, introducing semicarbazide, thiosemicarbazide, or carbamate groups at the 1-position, along with a methyl group at the 2-position, has resulted in the development of compounds, which exhibit strong bactericidal properties.¹⁴



2-aminobenzimidazoles

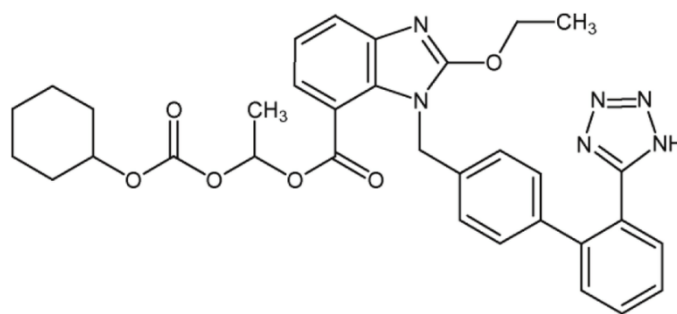
Benzimidazole derivatives have garnered significant attention due to their structural resemblance to naturally occurring nucleotides. This similarity enables them to interact effectively with biopolymers, making them potential candidates for various biological applications.¹⁵

Benzimidazole derivatives exhibit anti-ulcer properties by inhibiting H⁺/K⁺-ATPase. The clinical effectiveness of these drugs in managing peptic ulcers and related gastrointestinal disorders has spurred the development of new, more potent compounds with improved therapeutic profiles. For example Omeprazole.¹⁶

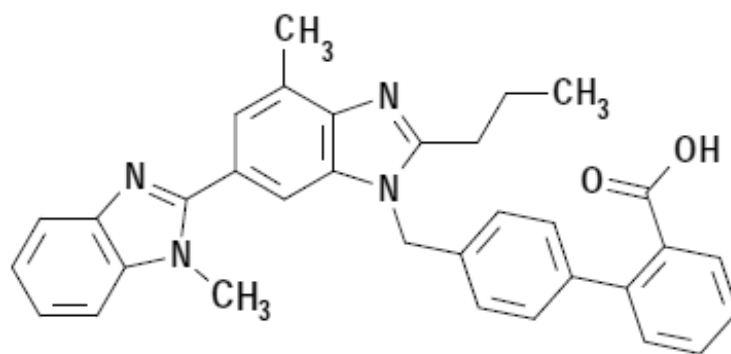


Omeprazole

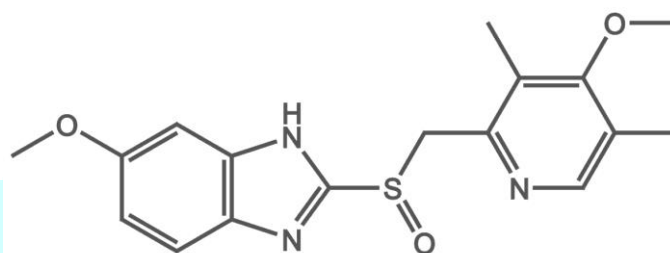
Several benzimidazole derivatives possess significant pharmacological properties and are commercially available, including : Atacand , Micardis , Nexium , Vermox .¹⁷



Atacand (Candesartan)



Micardis (Telmisartan)



Nexium (Esomeprazole)

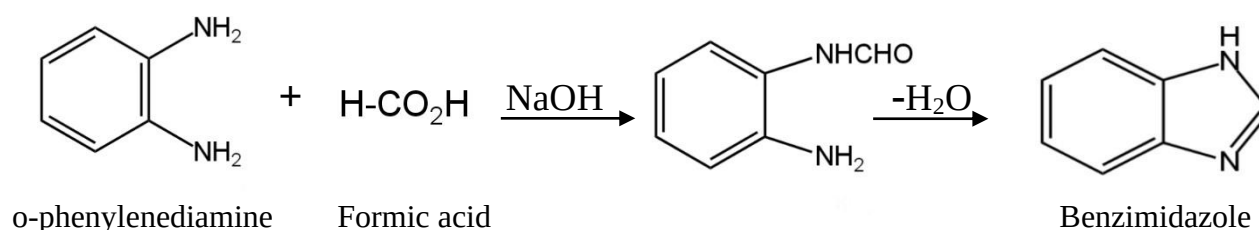
METHOD AND MATERIAL :

Procedure for Synthesis of Benzimidazole :

Dissolve 27g of o-phenylenediamine in a 250mL round-bottom flask. Add 17.5g of formic acid to the solution. Heat the mixture at 100°C for 2 hours using a water bath. Allow the mixture to cool, then slowly add a 10% sodium hydroxide solution while constantly rotating the flask, until the mixture reaches a slightly alkaline pH. Filter the resulting crude benzimidazole using a vacuum pump, and wash it with ice-cold water. Repeat the washing step with an additional 25mL of cold water to ensure complete purification.

Recrystallization : To purify the synthesized product, dissolve it in 400 mL of boiling water. Add 2 g of activated carbon to remove impurities and heat the mixture for 15 minutes. Filter the solution rapidly through a preheated Buchner funnel under vacuum. Allow the filtrate to cool to approximately 10°C, then collect the crystallized benzimidazole by filtration. Wash the product with 25 mL of cold water and dry it at 100°C. This recrystallization process yields 25 g of pure benzimidazole, characterized by a melting point of 171-172°C.

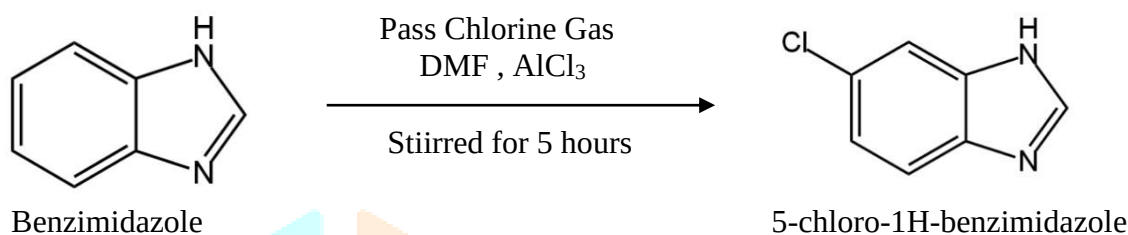
Reaction :



Preparation of 5-chloro-1H-benzimidazole :

In a conical flask take 2 gm of Benzimidazole, Dissolved in 10 ml of N,N-Dimethylformamide (DMF). Add 1 gm of Aluminium chloride as catalyst to it and mix well. Generating Chlorine gas by treating Potassium permagnate and Concentrated HCl take 5 gm Potassium permagnate and add 10 ml concentrated Hydrochloric acid to induce Chlorine gas. Passing the chlorine gas into the reaction mixture of Benzimidazole. Now, Stirring the reaction mixture for 5 hours. Prepare 10% solution of Hydrochloric acid. After 5 hours stirring, add 10% Hydrochloric acid solution to the mixture until pH is acidic to neutral. A white, fluffy precipitate formed, Collect the precipitates and dry it completely.

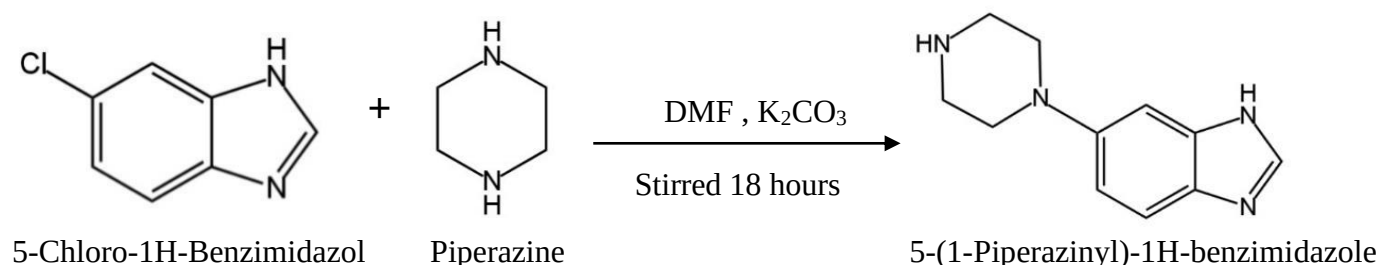
Reaction :



Preparation of 5-(1-Piperazinyl)-1H-benzimidazole :

In a beaker, add 1gm of 5-chlorobenzimidazole and 10 mL of N,N-Dimethylformamide (DMF). Add 1 gm of Potassium carbonate. Stir and heat the mixture at 50°C - 60°C temperature until the 5-chlorobenzimidazole is fully dissolved. In a separate beaker, dissolve 2gm of piperazine in 10 mL of DMF. Add both the solutions in a single conical flask and the mixture is stirred for 18 hours using a magnetic stirrer. Then, pour the mixture into ice cold water to precipitation. Collect the resulting precipitate and dry it thoroughly. Recrystallize the synthesized product with mixture of ethanol and water.

Reaction :



Procedure for TLC of 5-(1-Piperazinyl)-1H-benzimidazole :

Step 1 : Preparation of TLC Plate

Take a TLC plate and spread silica gel past eventually on the TLC plate. Dry the plate in hot air oven for 20 minutes at 100°C.

Step 2 : Prepare the sample

Dissolve the 5-(4-Piperazinyl)-1H-benzimidazole sample in methanol to obtain a concentration of about 1-2 mg/mL.

Step 3 : Apply the sample

Using a capillary tube, apply a small spot (about 1-2 μL) of the sample solution onto the TLC plate, about 1 cm from the bottom edge.

Step 4 : Preparation of Mobile phase

Prepare the mobile phase using Ethyl acetate (9 mL) and Methanol (1 mL) .

Ethyl acetate : Methanol (9:1)

Step 5 : Develop the plate

Place the TLC plate in the TLC chamber, ensuring the sample spot is at the bottom. Pour the mobile phase into the chamber, making sure the plate is not submerged. Cover the chamber and let it develop until the solvent front reaches about 1 cm from the top edge.

Step 6 : Visualize the plate

Remove the plate from the chamber and let it air dry. Visualize the plate using Iodine vapour to detect the presence of 5-(4-Piperazinyl)-1H-benzimidazole.

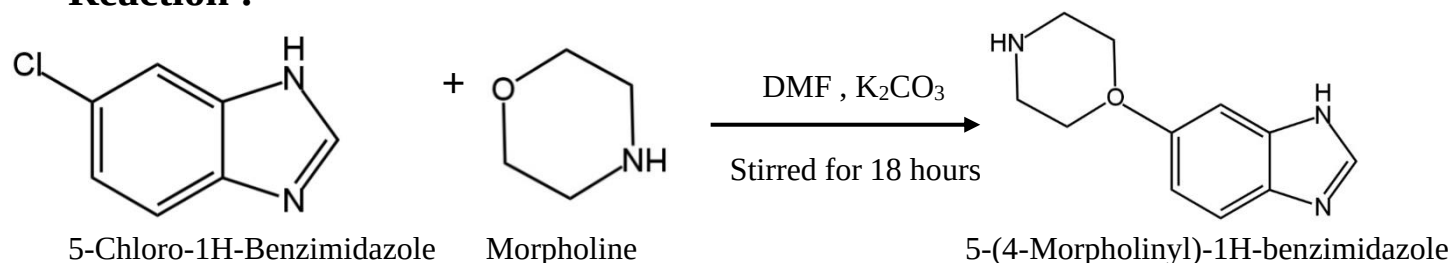
Step 7 : Record the Rf value

Measure the distance traveled by the sample from the origin to the center of the spot. Calculate the Rf value using the formula:

$$R_f = \frac{\text{(distance traveled by compound)}}{\text{(distance traveled by solvent front)}}$$

Preparation of 5-(4-Morpholinyl)-1H-benzimidazole :

In a beaker, add 1gm of 5-chlorobenzimidazole and 10 mL of N,N-Dimethylformamide (DMF). Add 1 gm of Potassium carbonate. Stir and heat the mixture at 50°C-60°C temperature until the 5-chlorobenzimidazole is fully dissolved. In a separate beaker, add 2 ml of morpholine in 10 mL of DMF. add both the solutions in a single conical flask and the mixture is stir for 18 hours using a magnetic stirrer. Then, poured the mixture in to ice cold water to get precipitation. Collect the resulting precipitate and dry it thoroughly. Recrystallize the synthesized product with mizture of methanol and water.

Reaction :**Procedure for TLC of 5-(4-Morpholinyl)-1H-benzimidazole :****Step 1 : Preparation of TLC Plate**

Take a TLC plate and spread silica gel past eventually on the TLC plate. Dry the plate in hot air oven for 20 minutes at 100°C.

Step 2 : Prepare the sample

Dissolve 5-(4-Morpholinyl)-1H-benzimidazole sample in methanol to obtain a concentration of about 1-2 mg/mL.

Step 3 : Apply the sample

Using a capillary tube, apply a small spot (about 1-2 μL) of the sample solution onto the TLC plate, about 1 cm from the bottom edge.

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Step 7 : Record the R_f value

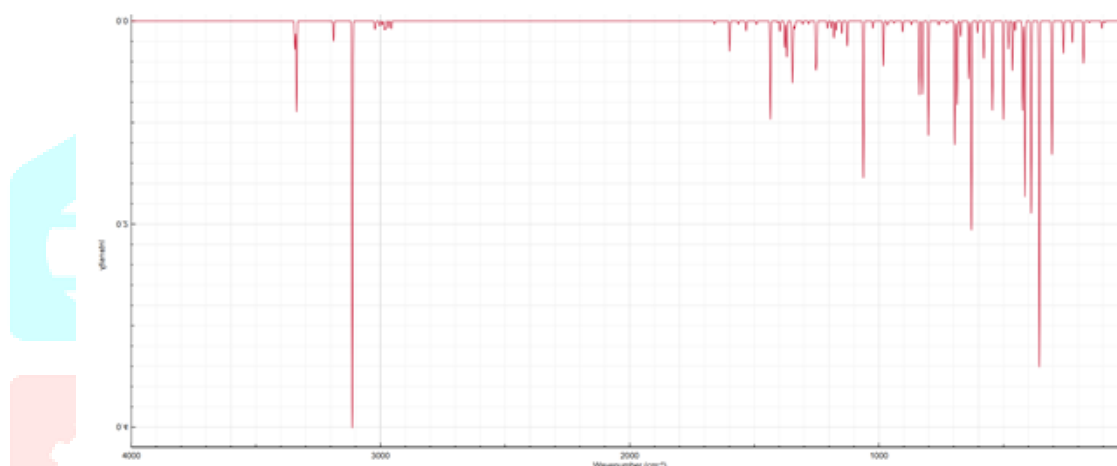
Measure the distance traveled by the sample from the origin to the center of the spot. Calculate the R_f value using the formula:

$$R_f = \frac{(\text{distance traveled by compound})}{(\text{distance traveled by solvent front})}$$

SPECTRAL CHARACTERIZATION OF DERIVATIVES :

IR characterization of Piperazine derivative :

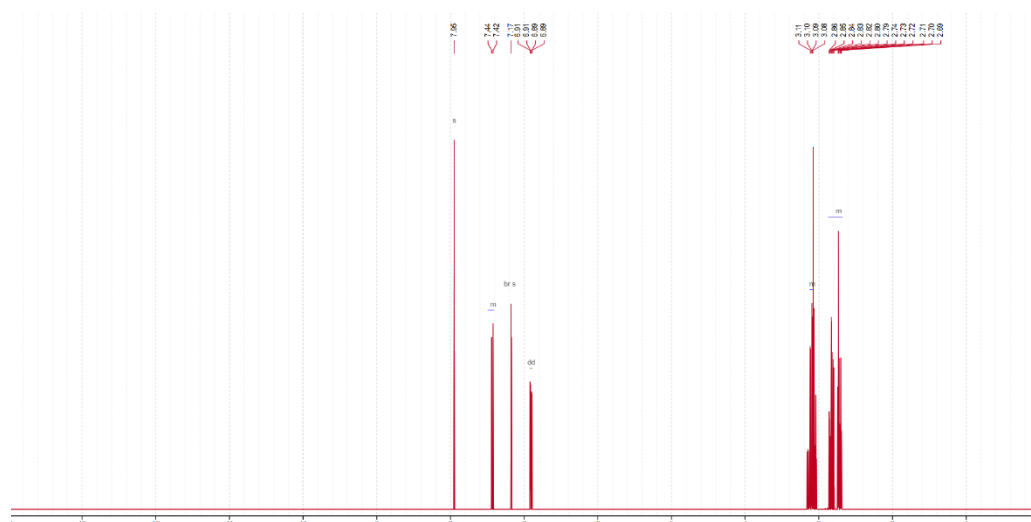
N-H stretching vibration between Nitrogen atom and Carbon atom connected by single bond . This peak appear at in the range $3400-3200\text{ cm}^{-1}$. C-H stretching vibration between Carbon atom and Hydrogen atom connected by single bond. This peak appear at in the range $3100-3000\text{ cm}^{-1}$. C=N stretching vibration between carbon atom and Nitrogen atom connected by double bond. This peak appear at in the range between $1650-1550\text{ cm}^{-1}$. C=C stretching vibration between two Carbon atoms connected by double bonds. This peak appear at in the range $1550-1450\text{ cm}^{-1}$. C-N stretching vibration between Carbon atom and Nitrogen atom for benzimidazole connected by single bond. This peak appear at in the range $1320-1280\text{ cm}^{-1}$. C-N stretching vibration between Carbon atom and Nitrogen atom (complex band) connected by single bond. This peak appear at in the range $1140-1100\text{ cm}^{-1}$.



IR spectra of Piperazine derivative

NMR characterization of Piperazine derivative :

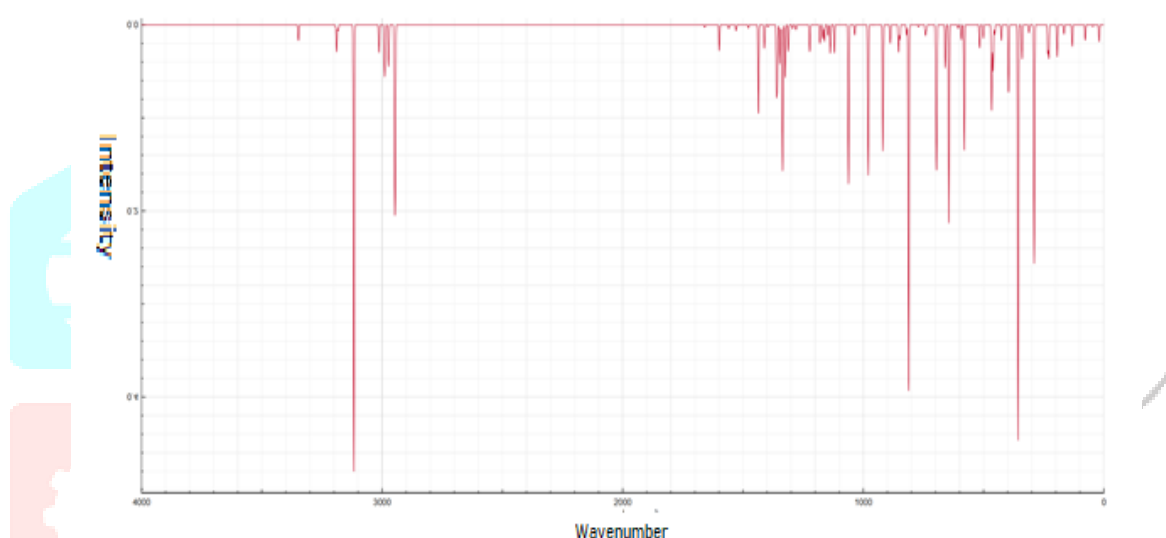
^1H NMR: δ 2.77 (4H, ddd, $J = 13.3, 6.7, 2.5\text{ Hz}$), 3.09 (4H, ddd, $J = 13.5, 6.7, 2.5\text{ Hz}$), 6.91 (1H, dd, $J = 8.1, 1.2\text{ Hz}$), 7.17 (1H, dt, $J = 1.2, 0.5\text{ Hz}$), 7.43 (1H, ddd, $J = 8.1, 0.6, 0.4\text{ Hz}$), 7.95 (1H, t, $J = 0.5\text{ Hz}$).



NMR Spectra of piperazine derivative

IR characterization of Morpholine derivative :

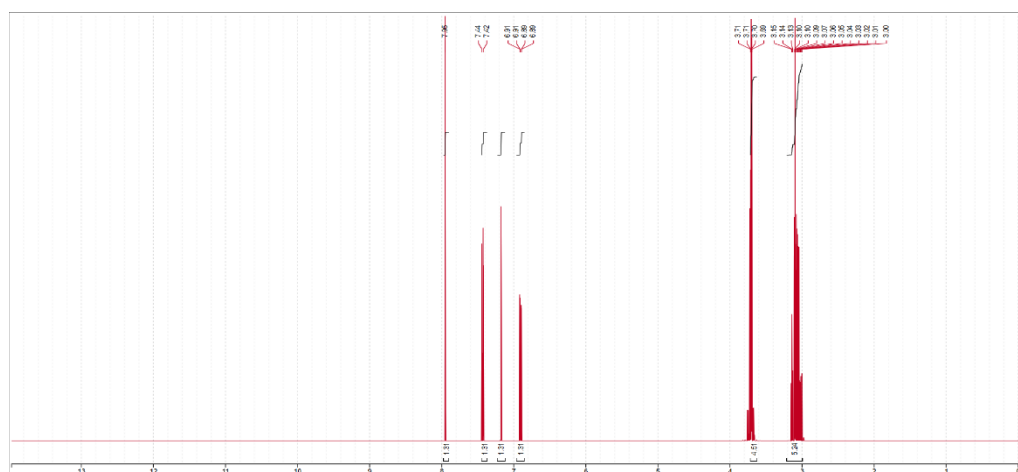
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IR spectra of Morpholine derivative

NMR characterization of Morpholine derivative :

^1H NMR: δ 3.08 (4H, ddd, $J = 16.8, 6.7, 2.5$ Hz), 3.71 (4H, ddd, $J = 13.4, 6.7, 2.5$ Hz), 6.90 (1H, dd, $J = 8.0, 1.2$ Hz), 7.17 (1H, dt, $J = 1.2, 0.5$ Hz), 7.43 (1H, ddd, $J = 8.0, 0.6, 0.4$ Hz), 7.95 (1H, t, $J = 0.5$ Hz).



NMR spectra Morpholine derivative

RESULT AND DISCUSSION :

Physical Characterization of derivatives :-

Sr. no	R	Molecular Formula (g/mol)	Molecular weight (g/mol)	Log P value	% Yield	Rf value
1	Piperazine	C ₁₁ H ₁₄ N ₄	202.25	1.4	47	0.55
2	Morpholine	C ₁₃ H ₁₅ N ₃ O	231.28	1.8	46	0.52

Spectral characterization of derivatives :-

Sr. No.	R	IR spectra (cm ⁻¹)	NMR spectra
1	Piperazine	N-H Streching (3400-3200 cm ⁻¹) C-H Streching (3100-3000 cm ⁻¹) C=N Streching (1650-1550 cm ⁻¹) C=C Streching (1550-1450 cm ⁻¹) C-N Streching (1320-1280 cm ⁻¹) C-N Streching (1140-1100 cm ⁻¹)	12.5-13.5 ppm 7.5-8.5 ppm 3.2-3.8 ppm 2.6-3.2 ppm
2	Morpholine	N-H Streching (3400-3200 cm ⁻¹) C-H Streching (3100-3000 cm ⁻¹) C=N Streching (1650-1550 cm ⁻¹) C=C Streching (1550-1450 cm ⁻¹) C-N Streching (1320-1280 cm ⁻¹) C-O Streching (1050-1000 cm ⁻¹)	12.5-13.5 ppm 7.5-8.5 ppm 3.5-4.5 ppm 2.5-3.5 ppm

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