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SYNTHESIS, SPECTRAL STUDIES AND PHYSICAL CHARACTERISATION OF SOME NOVEL MORPHOLINE DERIVATIVES

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ABSTRACT

Novel morpholine derivatives are synthesized through multi-step reactions often involving morpholine with alkyl halides, aldehydes, or acid chlorides to form Schiff bases, hydrazides, or cyclic analogues, yielding high-purity compounds confirmed via spectroscopic methods. Spectral studies typically include ^{1}H NMR, ^{13}C NMR, FT-IR and mass spectrometry to assign structures, revealing characteristic morpholine ring protons around 2.4-4.0 ppm, carbonyl stretches at 1650-1700 cm^{-1} and molecular ions matching calculated masses. Physical characterizations involve melting points (often 120-200°C for solids), elemental analysis (CHN), and solubility in polar solvents like DMSO or ethanol, with many showing biological potential like Antibacterial and analgesic activity.

INTRODUCTION

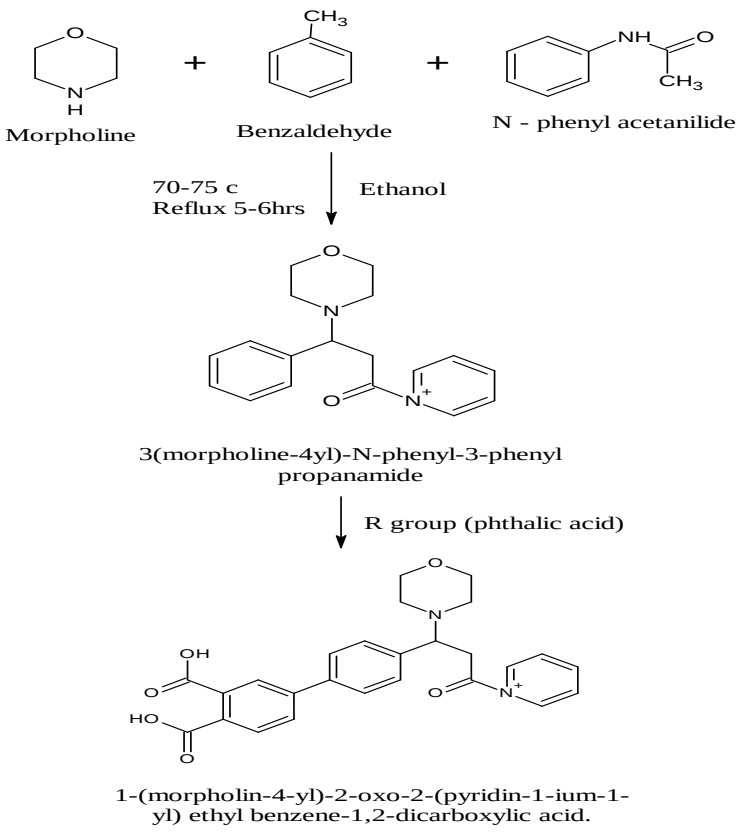
Morpholine was first discovered by German chemist August Wilhelm von Hofmann in 1851, though it was Ludwig Knorr who later named the compound and, initially, mistakenly thought it was related to morphine

Morpholine is a simple heterocyclic organic compound that is important both industrially and in medicinal chemistry. It combines properties of amines and ethers in a single six‑membered ring, which makes it a versatile building block and solvent. It is a clear, colourless, hygroscopic liquid with an ammonia‑ or fish‑like odour and is completely miscible with

Morpholine has the molecular formula [C_4H_9NO] and is systematically known as tetrahydro‑1,4‑oxazine. Its ring contains four methylene groups, one nitrogen, and one oxygen, giving it both amine (basic) and ether (oxygen-containing) functional groups.

Its derivatives are known for exhibiting a broad spectrum of pharmacological activities, including anticancer, anti-inflammatory, antimicrobial, antiviral, antioxidant, analgesic.

SCHEME: Morpholine – Phthalic acid derivative:



MATERIALS METHOD

1. Solubility

- Solubility is a fundamental concept in pharmacy and pharmaceutical chemistry. Solubility is defined as "The maximum amount of solute that can dissolve in a given amount of solvent at a specific temperature and pressure to form a saturated solution".
- The term "Soluble" is sometimes used for materials that can form colloidal suspension of very fine solid particles in a liquid. The quantitative solubility of such substance is generally not well-defined.
- The solubility mainly depends on the composition of solute and solvent (including their pH and the presence of other dissolved substance) as well as on temperature and pressure. The dependency can often be explained in terms of interactions between the particles (atoms, molecules, or ions) of the two substance and of thermodynamic concepts such as enthalpy and entropy.

Principle of Solubility

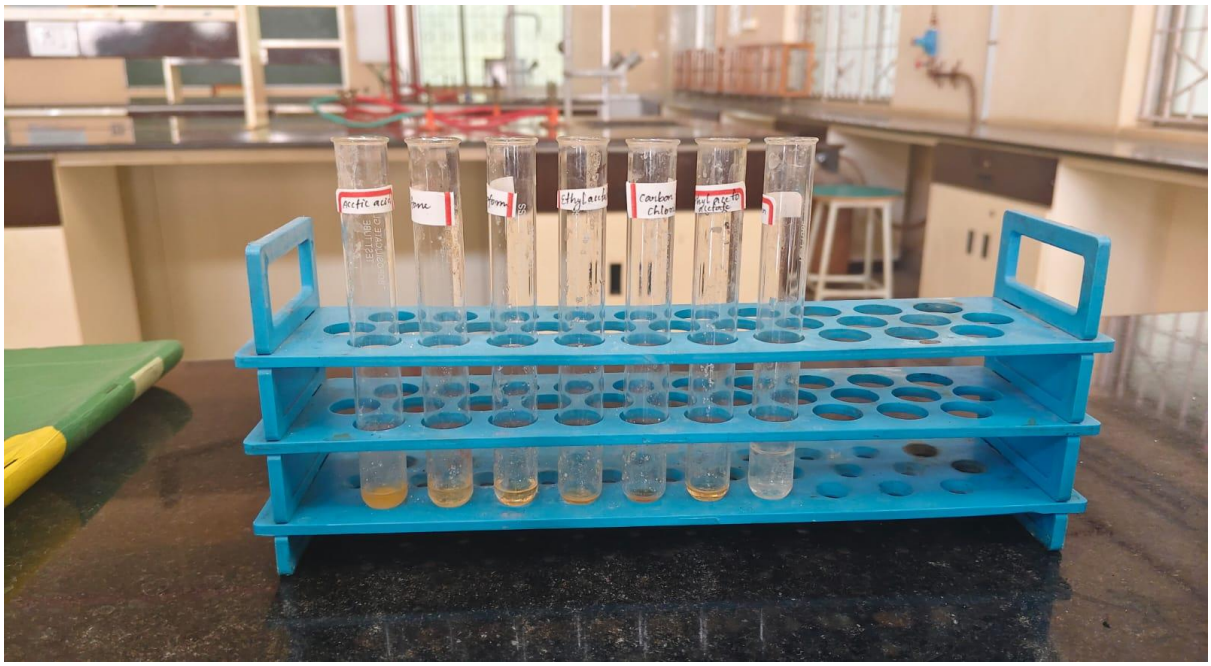
The principle of solubility refers to the factors that determine whether a substance (solute) will dissolve in a solvent to form a solution. The basic rule is often summarized by the phrase: "Like dissolves like."

S No	Derivative	Hot water	Ethanol	Acetone	Acetic acid	Carbon tetra chloride	Ethyl acetate	Ethyl Aceto acetate	Chloroform
1.	Compound - M	- - -	+ + +	+ + +	+ + -	+ + +	+ + -	+ + +	- - -
2.	M-1	- - -	+ + -	- - -	- - -	- - -	+ + +	+ + +	- - -
3.	M-2	- - -	+ + +	+ + +	- - -	+ + +	+ + +	+ + +	+ + +
4.	M-3	- - -	+ + +	+ + +	+ + +	- - -	+ + +	+ + +	+ + +
5.	M-4	- - -	+ + -	+ + +	+ + +	+ + -	+ + +	+ + +	+ + +
6.	M-5	- - -	+ + +	+ + +	+ + +	+ + -	+ + +	+ + +	+ + +
7.	M-6	- - -	- - -	+ + -	+ + +	- - -	+ + +	+ + +	+ + +
8.	M-7	- - -	+ + +	+ + +	+ + +	+ + +	+ + +	+ + -	+ + +
9.	M-8	- - -	+ + +	+ + +	+ + -	+ + +	+ + +	+ + +	+ + +
10	M-9	+ + +	+ + +	+ + +	- - -	+ + +	+ + +	+ + +	+ + -

(+ + +: Freely soluble; **- - -:** Insoluble; **+ + -:** Slightly soluble**)**

01. Morpholine – Benzoic acid Derivatives **(M – 1)**
02. Morpholine – Salicylic acid Derivatives **(M – 2)**
03. Morpholine – Hippuric acid Derivatives **(M – 3)**
04. Morpholine – vanillin Derivative **(M – 4)**

05. Morpholine – Phthalic acid Derivatives **(M – 5)**
06. Morpholine – Camphor Derivative **(M – 6)**
07. Morpholine - Trichloro acetic acid Derivative **(M – 7)**
08. Morpholine – Benzamide Derivative **(M – 8)**
09. Morpholine – Potassium dichromate Derivative **(M – 9)**
10. Morpholine – Boric acid Derivative **(M – 10)**



2. Thin Layer Chromatography (TLC)

Thin layer Chromatography is a quick, sensitive and inexpensive technique which requires less amount of sample for one successful analysis. Thin layer chromatography replaces the paper chromatography. TLC is one of the most commonly used chromatographic technique for Qualitative and Quantitative analysis for separation of organic compounds and also for purification of compounds.

TLC is also known as Open chromatography, Planar chromatography, Strip chromatography, Spread-chromatography, Drop-chromatography and Surface chromatography.

METHODOLOGY

- The TLC involves the distribution of substances from a mixture between two phases which is stationary phases and mobile phases.
- Stationary phase – It consists of thin layer of adsorbent [silica gel, alumina] coated on a plate [glass, aluminium].

- Mobile phase – The liquid which travels the stationary phase along with sample.

1. **Preparation of the TLC Plate**
   - The stationary phase (e.g., silica gel) is spread onto a flat plate (usually a glass or aluminum backing).
   - The plate is often marked with a pencil to indicate where the sample will be spotted.

2. **Spotting the Sample**
   - A small drop of the sample solution is applied to the base of the plate using a capillary tube. This is known as the "spot."

3. **Development**
   - The plate is then placed in a developing chamber with a small amount of the mobile phase (solvent) at the bottom. The solvent moves up the plate via capillary action, carrying the components of the sample with it.

4. **Visualization**
   - After the solvent has travelled a sufficient distance, the plate is removed, and the positions of the separated compounds are visualized.
   - Visualization can be done using UV light, iodine vapour, or chemical reagents, depending on the nature of the compounds.

5. **Analysis**
   - The position of each separated compound on the plate is marked, and the **Retention Factor (Rf)** is calculated for each component:

$$Rf = \frac{Distance\ travelled\ by\ the\ compound}{Distance\ travelled\ by\ the\ solvent\ front}$$

S. No	Derivatives	Rf value
01.	**Compound – M**	0.7
02.	**M – 1**	0.5
03.	**M – 2**	0.9
04.	**M – 3**	0.6
05.	**M – 4**	0.8
06.	**M – 5**	0.4
07.	**M – 6**	0.5
08.	**M – 7**	0.7
09.	**M – 8**	0.9
10.	**M – 9**	0.6
11.	**M – 10**	0.8

3. Melting point

The **melting point** (or, rarely, liquefaction point) of a substance is the temperature at which it changes state from solid to liquid. At the melting point the solid and liquid phase exist in equilibrium. The melting point of a substance depends on pressure and is usually specified at a standard pressure such as 1 atmosphere or 100 kPa.

When considered as the temperature of the reverse change from liquid to solid, it is referred to as the freezing point or crystallization point. Because of the ability of substances to supercool, the freezing point can easily appear to be below its actual value. When the "characteristic freezing point" of a substance is determined, in fact, the actual methodology is almost always "the principle of observing the disappearance rather than the formation of ice, that is, the melting point."

Melting Point Determination

To determine the melting point experimentally:

1. A small sample of the substance is placed in a capillary tube.
2. The tube is heated gradually, and the temperature is recorded.
3. The temperature at which the first drop of liquid forms is noted as the melting point.

Applications of Melting Point

- **Purity Testing:** A substance's melting point can be used to assess its purity. A pure substance has a sharp melting point, whereas an impure substance will melt over a broader range of temperatures.
- **Identification:** The melting point can be used to identify a substance by comparing it to known values.

- **Quality Control:** In industries like pharmaceuticals, the melting point is often a criterion for the quality of raw materials.

SPECTRAL ANALYSIS

The objectives of the spectral analysis to confirm the chemical structure of the synthesized compounds and the various functional groups in the final compounds. The IR spectra of the starting compound and intermediates were taken to confirm the changes at the reactive functional groups and then the final compounds were confirmed by IR spectroscopy.

1. INFRARED SPECTROSCOPY

INTRODUCTION TO IR

Spectroscopy can be defined as the interaction between matter and light. Infrared spectroscopy is a very powerful technique which uses electromagnetic radiation in the IR region for the determination and identification of molecular structure as well as having various quantitative applications within analytical chemistry.

IR spectroscopy is concerned with the study of absorption of IR radiation, which causes vibrational transition in the molecules. Hence, IR spectroscopy is also known as vibrational spectroscopy.

Principles of IR spectroscopy

When a molecule is exposed to IR light, it absorbs radiation at specific frequencies that correspond to the natural vibrational frequencies of its chemical bonds.

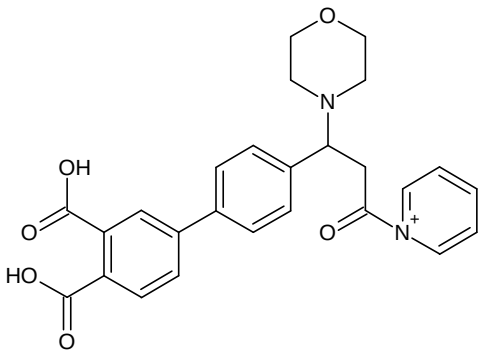
These absorbed frequencies depend on,

- The type of atom in the bond,
- The bond strength, and
- The molecular environment.

Ranges of IR

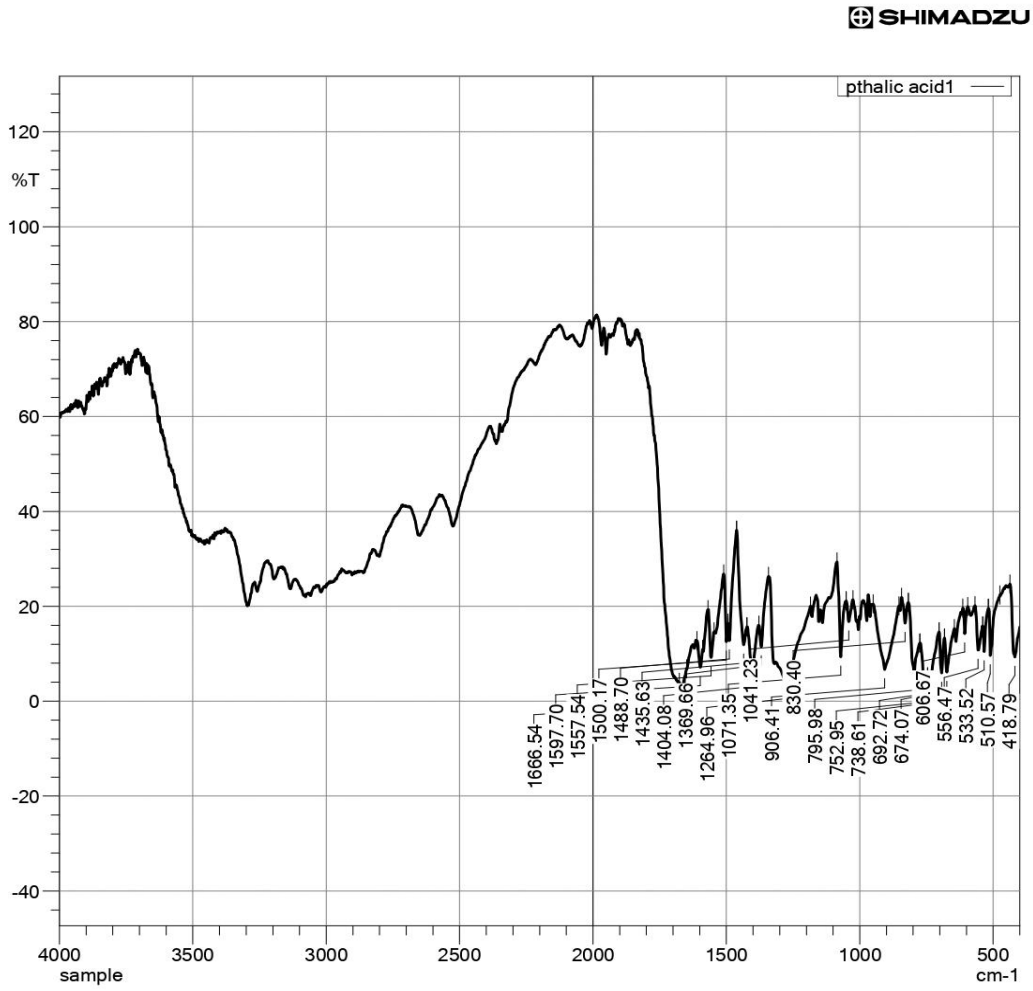
1. Near IR: 0.8 – 2.5
2. Middle IR: 2.5 – 15
3. Fair IR: 15 – 1000.

M-01 (Morpholine – Phthalic acid derivative)



IR Interpretation

C = O	1666.54
C = C	1557.54
C – N	1264.96
IR SPECTRAL DATA (KBr Disc) (in cm)	



D:¥IR Data¥2026¥jan¥pthalic acid1.ispd

sample

	Item	Value
2	Sample name	pthalic acid
3	Sample ID	sample
4	Option	
5	Intensity Mode	%Transmittance
6	Apodization	Happ-Genzel
9	No. of Scans	45

1

2. HIGH PRESSURISED LIQUID CHROMATOGRAPHY (HPLC)

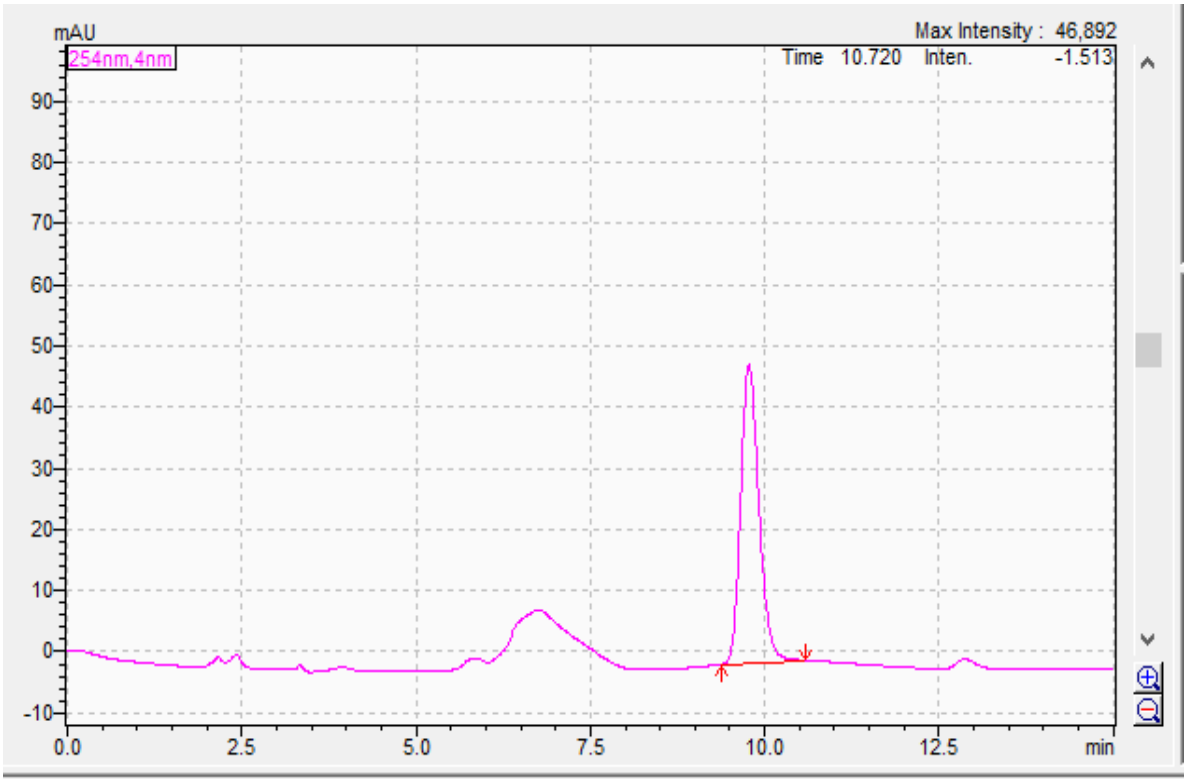
HPLC plays a crucial role in assessing the purity and stability of novel morpholine derivatives post-synthesis, confirming >98% purity levels essential for biological evaluations. Reverse-phase methods on C18 columns with acetonitrile-water gradients effectively separate polar morpholine analogs, often requiring derivatization for UV detection at 254 nm.

HPLC conditions for detecting residual morpholine (MPE) in cobicistat (CCT) involve derivatization with 1-naphthylisothiocyanate in acetonitrile to form a stable thiourea derivative, enhancing UV detectability. Analysis uses a C18 column with an acetonitrile-water mobile phase, achieving linearity from 0.30-1.20 µg/mL, LOD 0.10 µg/mL, and LOQ 0.30 µg/mL, with recoveries of 97.9-100.4%.

Procedure Steps

Morpholine in cobicistat samples reacts with the derivatizing agent, followed by direct injection into the HPLC system for separation and quantification. The method demonstrates high precision (RSD 0.79%) and selectivity, suitable for pharmaceutical quality control.

M-01 (Morpholine – Phthalic acid derivative)



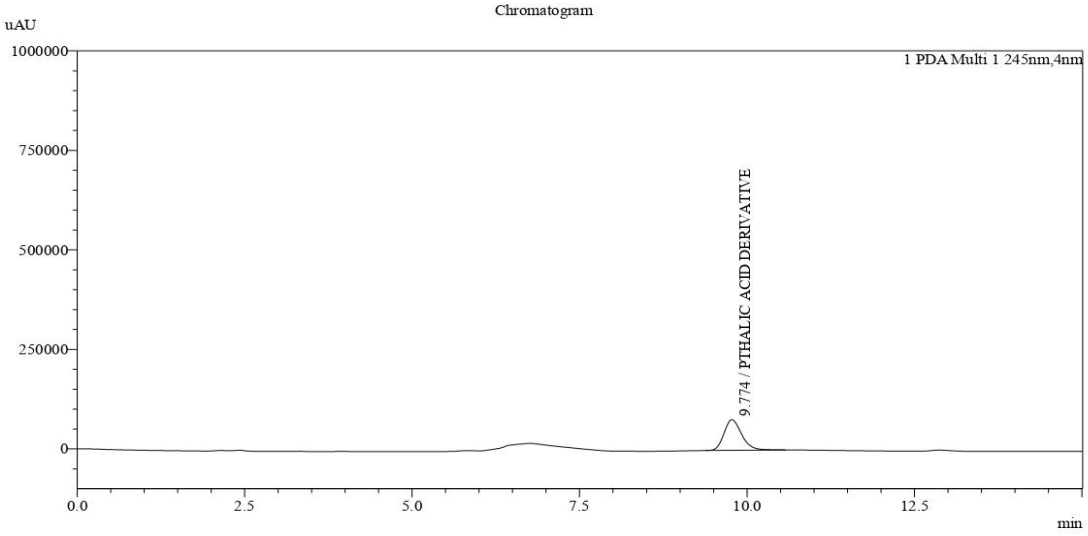
ARUNAI COLLEGE OF PHARMACY

Picture

Sample Information

Acquired by	: System Administrator
Sample Name	: PTHALIC DERIV
Sample ID	: MORPHO
Tray#	: 1
Vial#	: 3
Injection Volume	: 20
Data File	: PTHALIC DERIV001.lcd
Method File	: AS PER DEVELOPMENT 01.lcm
Batch File	: AS PER DEVELOPMENT 01.lcb
Report Format File	: Summary Data Report.lsr
Date Acquired	: 30-01-2026 14:45:29
Date Processed	: 19-02-2026 14:46:07

Chromatogram



Peak Table

PDA Ch1 245nm

Peak#	Ret. Time	Name	Area	Theoretical Plate	Tailing Factor	Capacity Factor(k')
1	9.774	PTHALIC ACID DERIVATIVE	1411492	6857	1.235	--
Total			1411492			

Peak Purity Index	S/N	Resolution(USP2)
Not calculated	105.51	--

Analysed By:

3. NUCLEAR MAGNETIC RESONANCE (NMR)

NMR spectroscopy determines molecular structures by detecting transitions between nuclear spin energy levels in a magnetic field, where nuclei like ^{1}H and ^{13}C absorb radiofrequency energy at specific frequencies influenced by their chemical environment. The principle relies

on nuclei with nonzero spin (e.g., I=1/2 for ^{1}H, ^{13}C) aligning with an external field B_0, then flipping when perturbed by RF pulses, with chemical shifts (δ in ppm) revealing proton environments from 0-12 ppm.

Core Principle

Nuclei precess at the Larmor frequency $\nu = (\gamma/2\pi) B_0$, where γ is the gyromagnetic ratio; relaxation emits a free induction decay (FID) signal Fourier-transformed into a spectrum showing peaks for distinct proton types. For morpholine derivatives, axial/equatorial CH_2 protons appear as multiplets around 2.4-4.0 ppm, while C=N protons resonate at 8-9 ppm. Standard NMR tubes hold ~0.5 mL of 5-20 mg sample dissolved in deuterated solvents like $CDCl_3$ or DMSO-d_6 to lock the field and provide TMS reference (δ=0).

Procedure Steps

- **Sample Prep**: Dissolve 5-10 mg in 0.6 mL $CDCl_3$; filter if needed; seal in 5 mm tube.
- **Instrument Setup**: Insert tube into probe; shim field; set nucleus (e.g., 400 MHz ^{1}H); acquire lock.
- **Acquisition**: Apply 90° RF pulse; collect FID (8-128 scans, 5-10 s recycle delay); process with Fourier transform and phasing.
- **Analysis**: Integrate peaks for ratios, assign via coupling constants (^{3}J=6-8 Hz), DEPT for $CH_3/CH_2/CH$.

NMR applications in pharmaceutical analysis

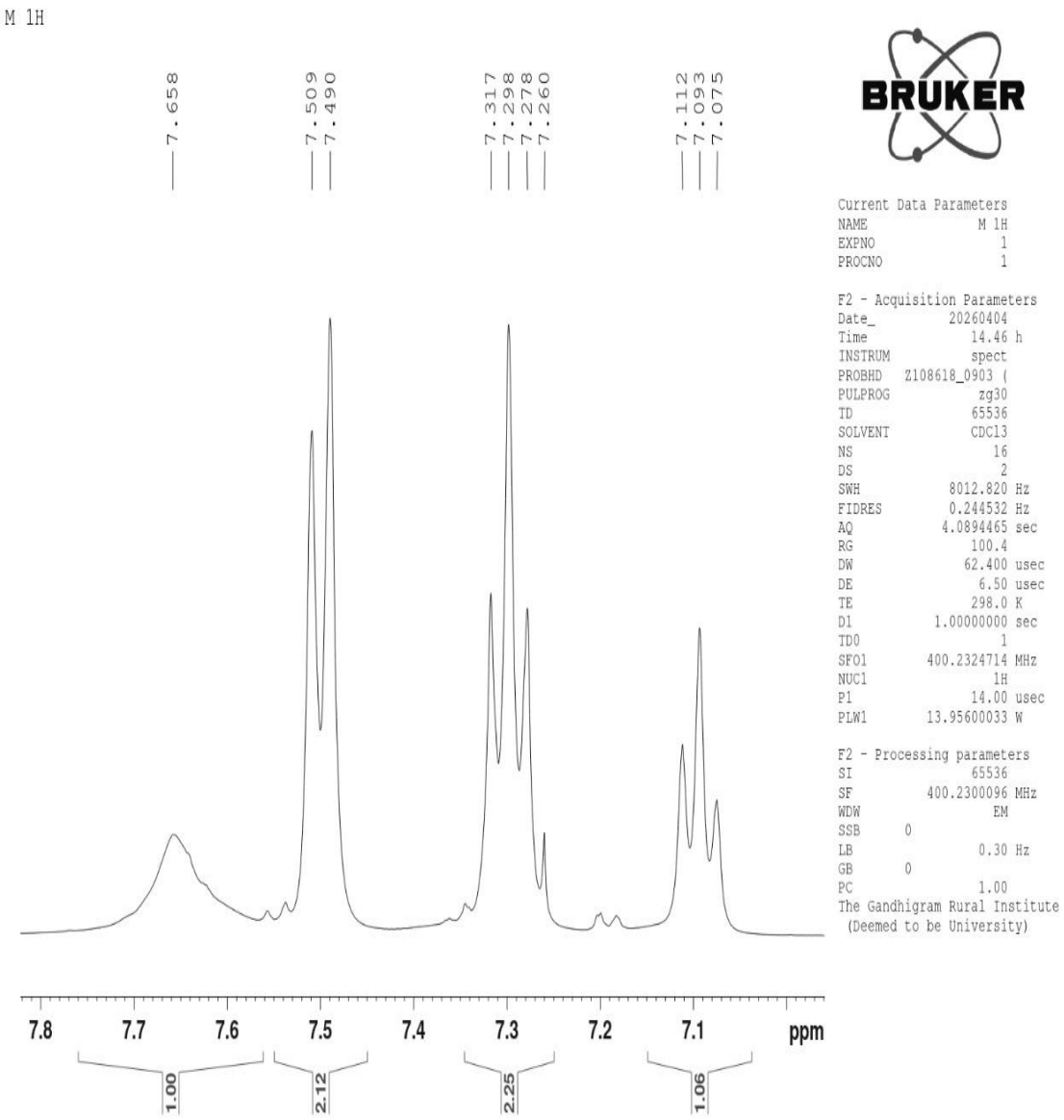
A. Structure Elucidation ^{1}H and ^{13}C NMR assign functional groups, with morpholine CH_2 signals at 2.4-4.0 ppm and C=N at 8-9 ppm, while 2D techniques like COSY, HSQC, and HMBC resolve connectivity and long-range couplings for complex derivatives. This verifies purity and distinguishes isomers, critical before biological testing.

B. Quantitative and Qualitative applications: Quantitative NMR (qNMR) measures drug content, residual solvents (e.g., <0.5% in APIs), and counterion ratios without reference standards, supporting stability studies and formulation development. In polymorph analysis, solid-state NMR differentiates crystalline forms affecting bioavailability. For impurities, it detects trace degradants at 0.1-1% levels, complementing HPLC data.

Types of NMR

- ^{1}H NMR: Detects hydrogen environments; multiplets for CH_2 in morpholine; integration gives proton ratios.
- ^{13}C NMR: Carbon skeleton; quaternary/deuterated solvent peaks absent; DEPT distinguishes CH_3/CH_2/CH/QUAT.
- Other nuclei: ^{15}N, ^{19}F, ^{31}P for specific heterocycles or substituents**.**

01. Morpholine – Benzoic acid derivatives (M – 1)



CONCLUSION

In the present study, a series of novel morpholine derivatives were successfully designed, synthesized, and analysed with the aim of identifying new compounds with promising characterised. The rational design strategy, based on structural modification of the morpholine scaffold, enabled the incorporation of various substituents that significantly influenced spectral studies.

The synthesized compounds were characterized using standard analytical and spectroscopic techniques, confirming the proposed chemical structures and purity. Notably, derivatives bearing electron-withdrawing and heteroaryl substituents demonstrated enhanced activity, suggesting a strong structure–activity relationship (SAR) within this series.

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