Multidisciplinary

Use of histidine derivatives in pharmaceuticals as novel cyclic compounds

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Received 9 Feb 2025; Accepted 26 March 2025; Published 6 Apr 2026
DOI: https://doi.org/10.64601/9hexft12

Abstract
The study involved the preparation of several new histidine derivatives through multiple pathways. In the first pathway, histidine was treated with absolute ethanol and parachlorobenzylaldehyde in the presence of concentrated sulfuric acid to obtain derivative (1). In the second pathway, histidine was treated with parahydroxyacetone phenone and absolute ethanol in the presence of concentrated sulfuric acid to obtain derivative (2). Both chemical reactions were monitored using thin-layer chromatography (TLC). The physical properties of the prepared compounds were also investigated using elemental analysis (C.H.N. analysis) and spectroscopic methods (FT-IR, ^{1}H NMR, ^{13}HSQC, HMBC).

Keywords: Histidine derivatives, C.H.N. analysis, FT-IR

Introduction

Heterocyclic compounds and their types are compounds that contain one or more heteroatoms in their cyclic structure, such as oxygen, nitrogen, and sulfur, in addition to carbon atoms [1]. Other heteroatoms may also be present, such as silicon, silicon, and others. Heterocyclic compounds are widespread in nature and are a fundamental source of life. Most sugars and their derivatives are heterocyclic compounds. Furthermore, a number of vitamins and enzymes that play a vital role in the metabolism of all living cells contain heterocyclic compounds, for example, Vitamin C, which contains a furan ring in its structure, and Vitamin D [2].

Histamine is a chemical messenger produced by the human body's immune system as an allergic or inflammatory response. It is found in almost all body tissues, but in higher concentrations in the lungs, skin, and digestive tract. Histamine is released when cells are damaged by bacterial or viral infections, such as in cases of the common cold [3], or after an insect bite. Allergies to certain foods, fabrics, cosmetics, or cleaning products, as well as exposure to pollen, can also trigger histamine release in the body. When histamine is released, it binds to one of its four receptors on the surface of cells in the body [4]. This leads to contraction of the smooth muscles in the airways, dilation of blood vessels, and stimulation of nerve endings, resulting in allergy symptoms such as skin redness, itching, coughing, shortness of breath, increased nasal mucus production, sneezing, facial swelling, and increased stomach acid secretion. These widespread and bothersome symptoms led to the development of antihistamines, which counteract this substance [5].

Histidine antagonists work by blocking the action of histidine receptors, which are divided into four types. However, types one and two are the receptors most commonly targeted by antihistamines, [6] as types three and four are not as prevalent in the body's cells, and their roles are not yet fully understood. The mechanism of action of this drug is competitive; it competes for histidine receptors with the body's own histidine, thus inhibiting its action [7]. While another type of drug inhibits the production of histidine, antihistamines work by competing with the body's own histidine at histidine receptors. Histidine antagonists are available in various forms, including tablets, capsules, creams, lotions, gels, and nasal sprays.

First-generation antihistamines commonly cause dizziness, difficulty concentrating, dry mouth, and drowsiness. They can also cause photophobia (sensitivity to light) or blurred vision, and constipation [8]. Side effects of second-generation antihistamines include headache and dry mouth and nose. First-generation antihistamines can interact with other medications, such as antidepressants and alcohol, potentially causing serious harm. They should not be taken with Alzheimer's medications, as they can reduce their effectiveness. Side effects of second-generation antihistamines include headache, diarrhea, and muscle pain. Dosage depends on the individual's symptoms [9].

Properties of organic materials

In 1854, A. Kekulé demonstrated that the main differences in structure, properties, and reactivity in carbon compounds stem from the unique properties of the carbon atom, which allows for the formation of a vast number of compounds. This is due to the ability of carbon atoms to bond with each other to form chains containing thousands of atoms or rings of varying sizes, something not possible for atoms of other elements [10]. These chains can twist or branch and bond with other atoms, primarily hydrogen, as well as halogens, oxygen, nitrogen, sulfur, phosphorus, and many others. Examples include chlorophyll and hemoglobin. The different arrangement of atoms gives rise to different compounds, each with its own specific chemical and physical properties. Therefore, it is not surprising that the

number of known carbon compounds exceeds ten million, and that this number increases by about half a million compounds annually [11].

The fundamental concept of chemical structure is Wöhler's theory, which was further developed by van 't Hoff and Löbel in 1874. They focused on developing the concept of the spatial distribution of atoms in organic molecules, i.e., the study of spatial structure [12]. According to van 't Hoff's theory, the four valences of the carbon atom in methane are oriented towards the four vertices of a tetrahedron, with the carbon atom at its center and the hydrogen atoms at its vertices.

In its free state, carbon has the following electronic configuration: s1s2 2s2 2p2. Carbon's valence is determined by the electrons in its second shell. When carbon reacts with other atoms, an electron moves from the s2s orbital to the empty z2pz orbital [13]. Carbon shares its four electrons with other atoms to form four covalent bonds of a specific length. In methane, these four orbitals are of the sp3 type, consisting of one sorbital and three p orbitals, with angles between them measuring 109 degrees. In compounds containing double bonds, there are three sp2 hybrid orbitals resulting from the hybridization of one sorbital and two p orbitals, with angles between them measuring 120 degrees [14]. In compounds containing triple bonds, there are two sp hybrid orbitals resulting from the hybridization of one sorbital and one p orbital, with an angle of 180 degrees between them.

Material and Method

Equipment used

The following equipment was used for spectroscopic and physical measurements of the prohibited compounds:

- **Measuring melting points:** The melting points of the prohibited compounds were measured using a Sturt SMP 30 melting point apparatus.
- **Focus-Infrared (FT-IR) measurements:** The measurements were recorded using a Simad 24 FT-IR-8400 spectrophotometer (400-4000 cm^{1}) and KBr discs. The measurements were performed in the Chemistry Department, College of Science.
- **Crystallization:** Crystallization is one of the methods used to purify solid organic compounds and depends on the degree of solubility of different compounds in a given solvent. The solvent is selected based on the crystallization process. It is noted that each compound has its own specific solvent for recrystallization, and the appropriate solvent for the crystallization process is one that dissolves the substance by heating and boiling and allows crystal formation after cooling.

Procedure

The medication was obtained from the pharmacy.

The medication was ground in an electric grinder. Its physical properties were measured before and after crystallization, such as melting point and IR measurement. 28-59 ml of histidine were placed in a beaker, and 30 ml of acetone and 30 ml of chloroform were added. The mixture was hot when the solids were added, so it was placed on a heater. A funnel with a filter paper was placed on top of a conical flask. The mixture was filtered, and the filtrate was collected and placed in ice or a refrigerator to cool. When a precipitate or crystals formed in the conical flask, the flask was shaken and then filtered again under cold conditions [15].

The flask wall is scraped below the liquid surface level using a glass stirrer because it deposits crystals in the pure substance that act as nuclei to attract the remaining crystals. A third filter is performed using a Buchner funnel. Upon completion of the filtration, the filter paper is removed, and the precipitate is collected. This is the pure substance. The pure substance is weighed and weighed (0.19 g) [16]. Its melting point and IR measurement are then recorded. Two experiments are conducted using the pure substance. In the first experiment, histamine reacts with parachlorobenzaldehyde. In the second experiment, histamine reacts with parahydroxyacetone phenone via reflex sublimation (continued).

Measuring the melting points of organic compounds in chemistry laboratories

The melting point of a solid is the temperature at which the solid changes to a liquid state. To measure the melting point, a device known as a melting point meter is used. Organic compounds have low melting points compared to inorganic compounds, which have high melting points. When measuring the melting point, a fine capillary tube, open at one end and closed at the other, is used. The substance whose melting point is to be measured is placed in the capillary tube, and then the melting point of histidine was calculated before and after crystallization [17].

Initial melting point before crystallization = 209°C

Final melting point before crystallization = 217°C

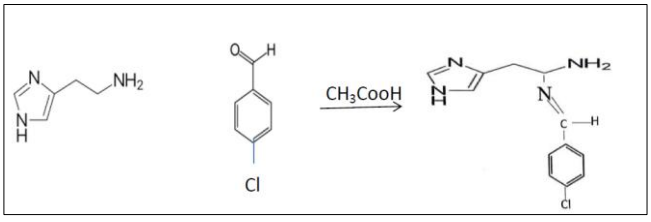
Initial melting point after crystallization = 185°C

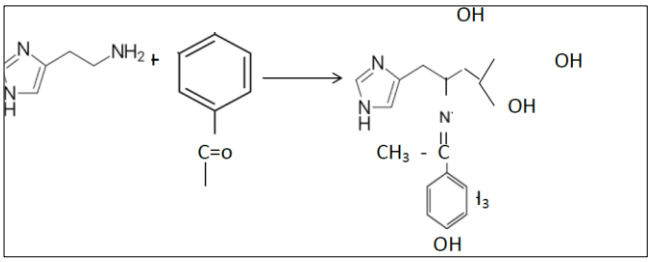
Final melting point after crystallization = 222°C

Melting point of histidine derivative with parachlorobenzyldehyde = 225°C

Melting point of histidine derivative with parahydroxyacetone phenone = 223°C

Methods of preparing the compounds preparation of the histidine derivative with parachlorobenzylaldehyde (0.05 g) of histidine and (0.0045 g) of benzoyl peroxide were dissolved in (20 ml) of alcohol (ethanol, methanol) with the addition of (1 ml) of acetic acid. The mixture was placed in a (50 ml) round-bottom flask and incubated for 6 hours. The reaction was then monitored using thin-layer chromatography (TLC) with a mobile phase of (ethyl acetate and hexane).





Preparation of the histidine derivative with parahydroxyacetone phenol

Take (0.05 g) of histidine and (0.043 g) of parahydroxyacetone phenol and dissolve them in (20 ml) of ethanol with (1 ml) of acetic acid. Place the mixture in a 50 ml triple-necked round-bottom flask equipped with a condenser and stopper. Incubate for 6 hours and monitor the reaction using thin-layer chromatography (TCL) with a mobile phase of ethyl acetate and hexane.

Pseudomonas aeruginosa is a widespread Gram-negative bacterium that can cause diseases in animals, including humans. When it infects a living organism, it destroys its tissues and affects immunocompromised individuals. Symptoms of its diseases include generalized inflammation and sepsis if it spreads to vital organs such as the lungs, urinary tract, or kidneys. It can be fatal because it feeds on moist surfaces.

Proteus

A genus of Gram-negative protobacteria. Proteus bacilli are widely distributed in nature and are found in decaying animal matter (sewage, composted soil, mammalian intestines, and human and animal feces). They are opportunistic pathogens commonly responsible for urinary tract infections and sepsis, and are also frequently found in hospitals.

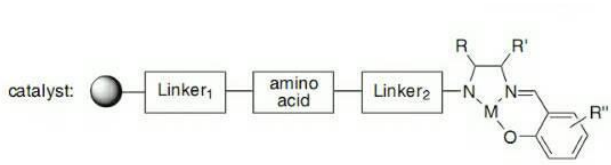
Purified histidine:

- At a concentration of -100%, it showed inhibition of Proteus bacteria by 1.5 cm.
- At a concentration of -75%, it showed inhibition of 1.5 cm.
- At a concentration of -50%, it showed inhibition of 1.5 cm.
- At a concentration of -25%, no inhibition was observed.

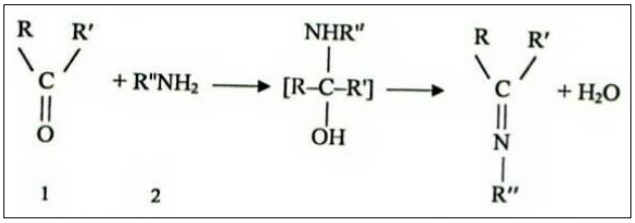
Result and Discussion

Due to the importance of the drug Histadine, we attempted some conversions and modifications. This involved converting the active ingredient by transforming the amine group (NH) into Schiffbase (18). This was achieved through its reaction with parachlorobenzylaldehyde and parahydroxyacetone phenone. Given the unavailability of the raw material (pure form) of Histadine, we were required to use the commercially available drug, which contains several additives to improve certain properties such as solubility, sweetness,(19) and others. We purified this material to obtain the pure form and then recrystallized it using different solvents. The melting point before filtration was measured at 220°C, while the melting point after filtration was 225°C. The infrared (IR) spectrum of Histadine was also measured, and the results were... Infrared (IR) Spectrum of the first derivative... and Infrared (IR) Spectrum of the second derivative... (20) where changes in some physical properties were observed, such as color and the nature of the material. The color of the material turned yellowish, and the nature of the material changed from tablets to powder. It was observed that the pure material, after reacting with parachlorobenzylaldehyde, transformed into Schiff base according to the following reaction (22). It was also observed that the pure material, after reacting with parahydroxyacetone phenone, transformed into Schiff base according to the following reaction. After preparing the two derivatives, their melting points and infrared (IR) radiation were measured. The melting point of the first derivative was 225°C, while the melting point of the second derivative was 223°C. The result of the infrared (IR) measurement for the first derivative and the result of the infrared (IR) measurement for the second derivative (23)

Chef's rules



Schiff bases are organic compounds containing an isomethine group (azomethine-CH=N). They were first prepared by the German scientist Hugo Schiff in 1864 by the condensation of aliphatic or aromatic aldehydes or ketones with primary amines (alpha or aromatic). Hence their name. These bases have been given several names, including (anil) and (ketimines) when derived from ketones, or (aldimine) when derived from aldehydes. This condensation occurs between the carbonyl group and the primary amines. A monoalkyl amine (R-NH2) or a monoaryl amine (Ar-NH2) is added to the carbonyl group of the aldehyde or ketone, forming an intermediate compound, carbinolamine. This is followed by the loss of a water molecule to form an N-substituted imine, which represents the Schiff base as the final product.



Condensation of carbonyl and amine compounds

Condensation of carbonyl and amine compounds: benefits of Schiff bases

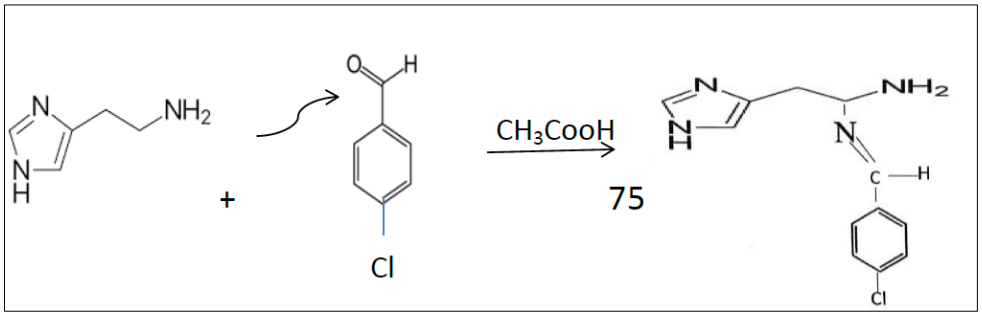
- Catalysts: Some Schiff bases and their complexes have been used as catalysts, such as the Ruthenium-Schiff base complex (Ru-Schiff base), which is a good catalyst for the synthesis of tri-substituted allyl diazoacetates.
- Also among the catalysts are the tridentate Schiff base, which is important in organic biochemical reactions and

links amino acids to Schiff bases, forming important active sites in photochemical reactions.

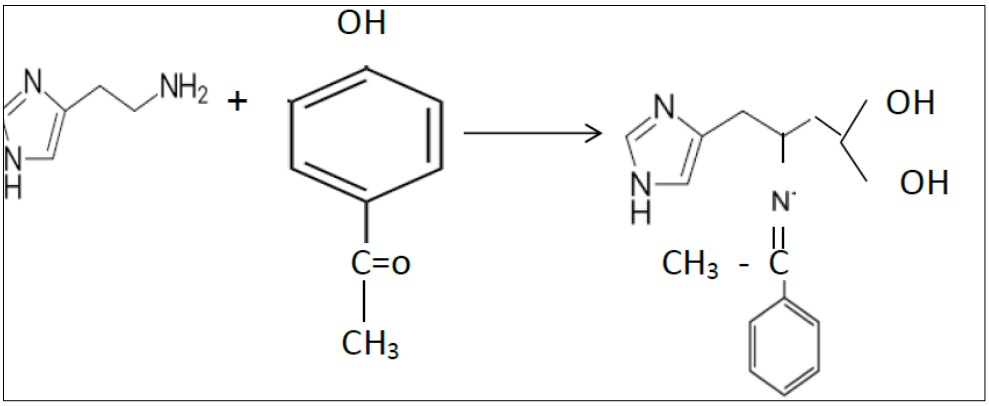
- Electrochemical Reactions: In organometallic chemistry, Schiff bases and their complexes are important and versatile because (i) they are easy to prepare and (ii) they exert various spatial configurations or electronic effects on the products of the complexes. Furthermore, the products can be modified and used as catalysts, especially when these bases are used in the Ruthenium-Based Olefin Metathesis Catalysts.
- In Biotechnology and Medicine, selective encapsulation of nickel (II) cationic Schiff bases with DNA has been identified in biotechnology research.
- In the pharmaceutical industry, it is one of the most important drugs with anticancer, fungicidal, and bactericidal activity.

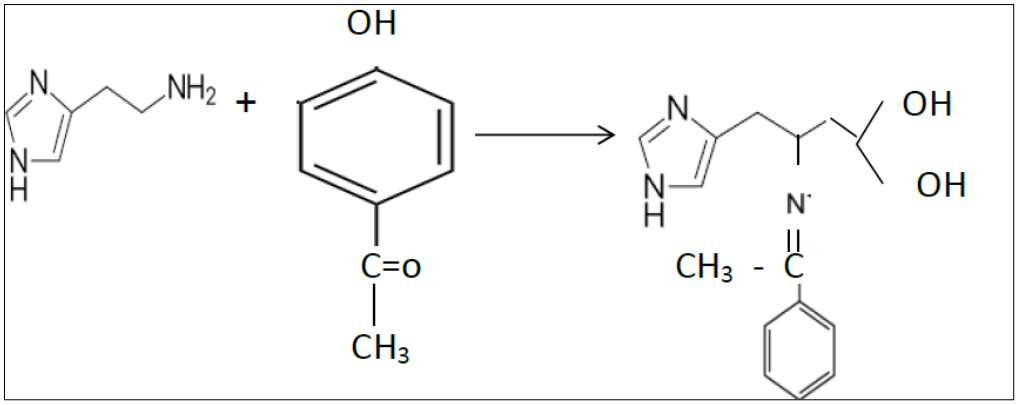
Preparation of new reconstitution methods

First: Reconstitution rules for the preparation of histidine with parachlorobenzyldehyde



Second: Rules for preparing the histidine solution with para-hydroxyacetone phenome





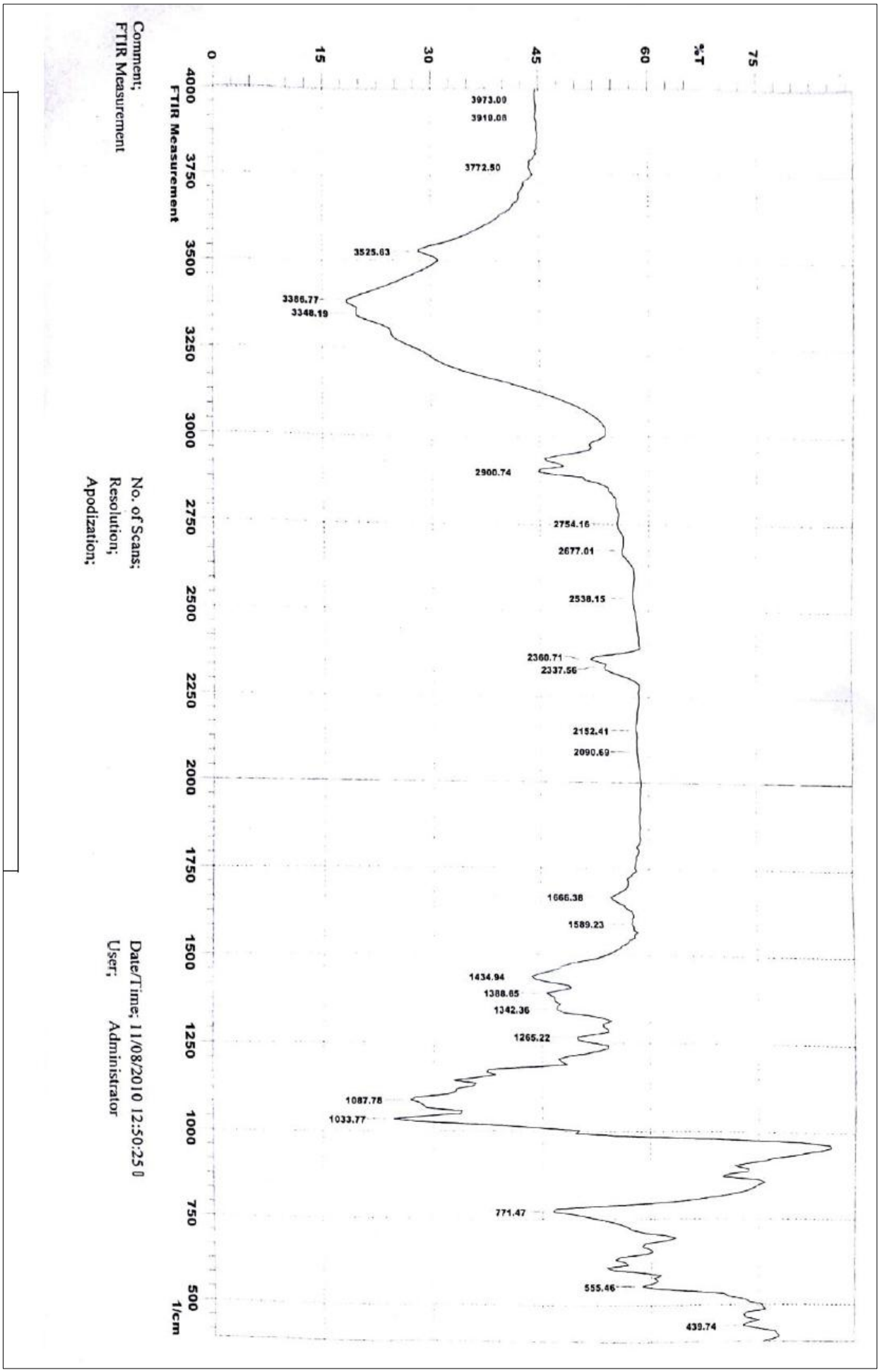

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Fig 1

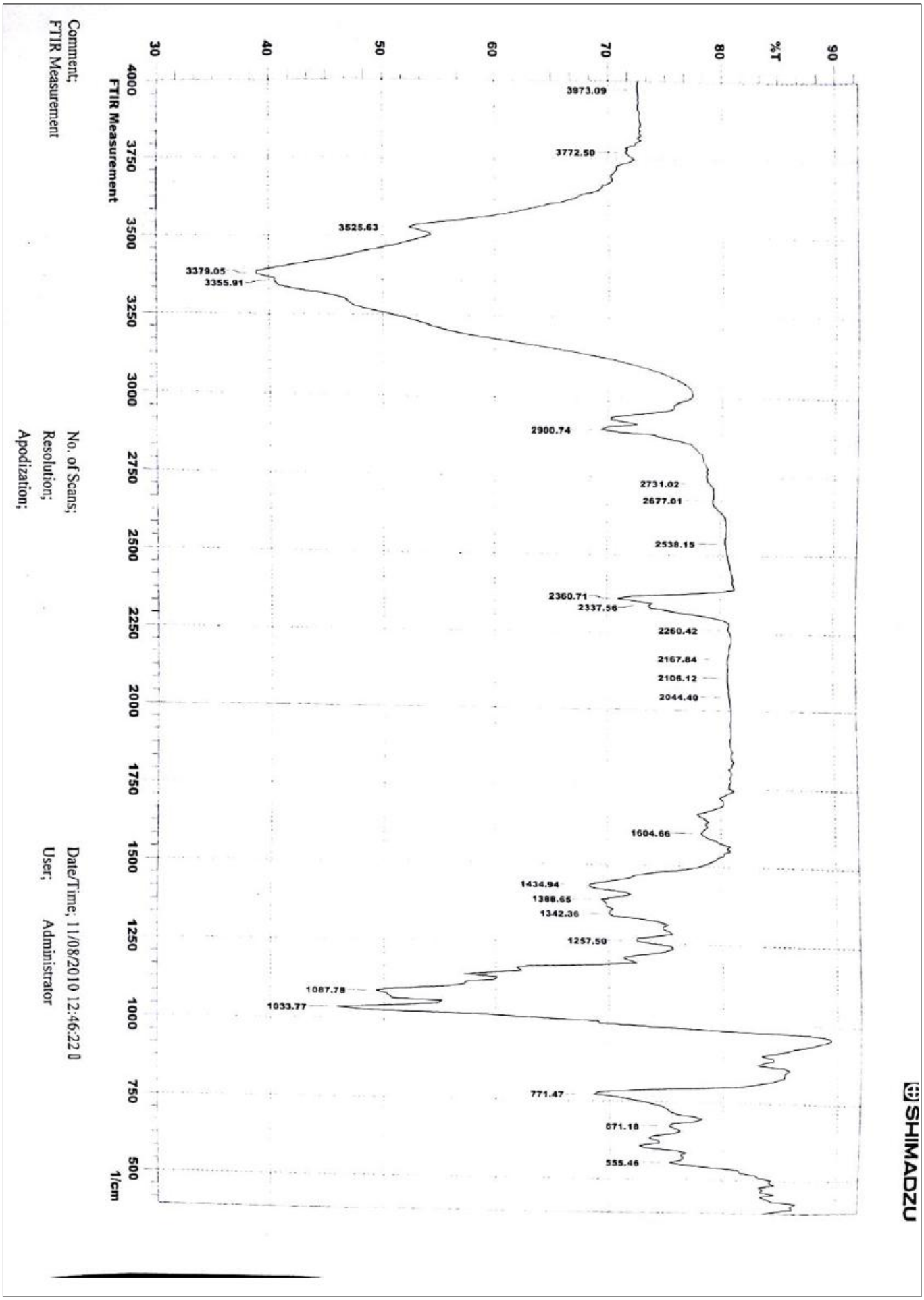
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Fig 2

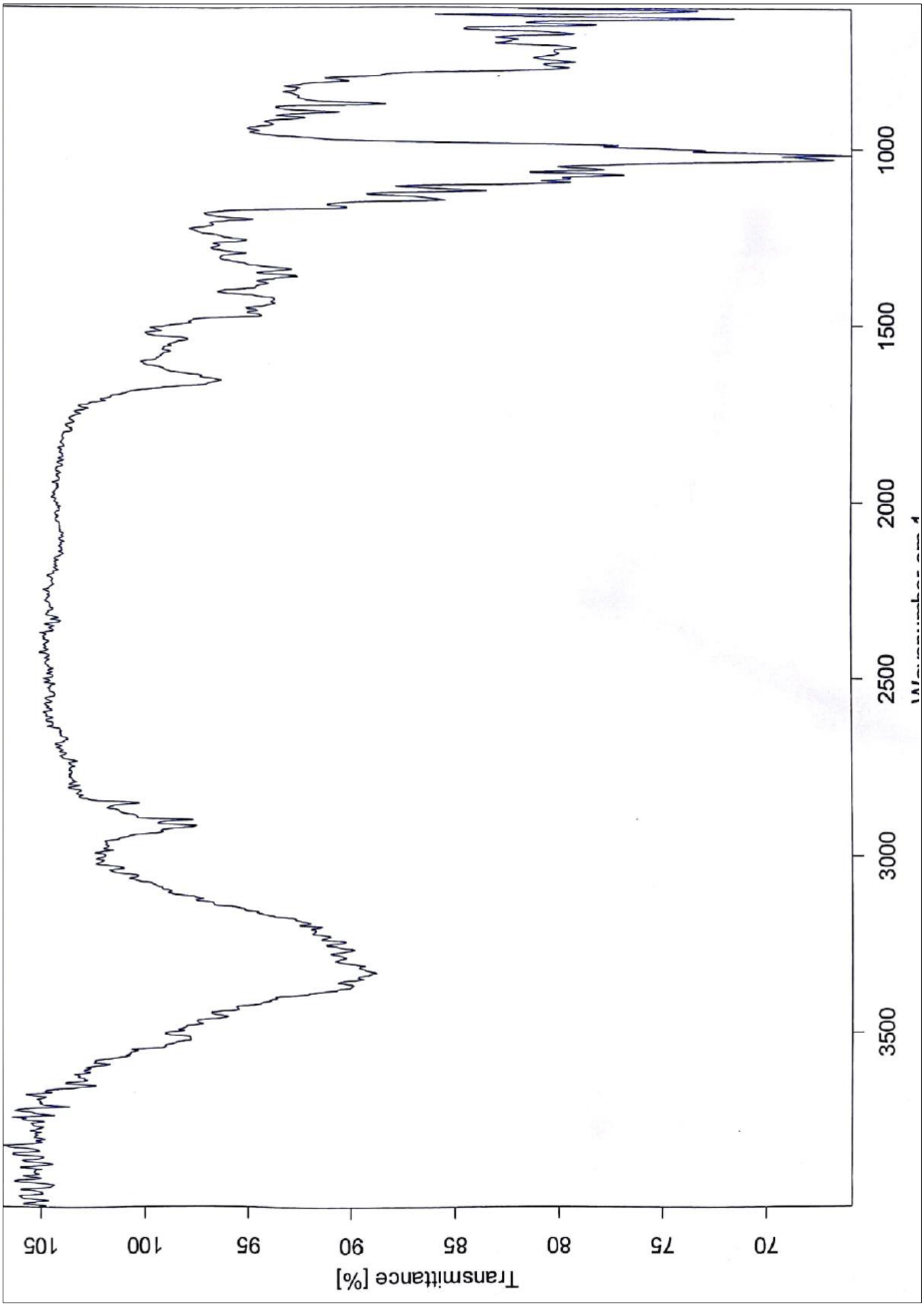
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Fig 3

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