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Research Article

Synthesis and Evaluation of Pyrimidine Derivatives for Urolithiasis Prevention Activity

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ABSTRACT

Urolithiasis, a prevalent and recurrent urological disorder marked by the development of kidney stones, continues to be a major global health issue. By using synthetic Knoevenagel reaction of barbituric acid with different substituted aromatic aldehydes, I was able to create five novel pyrimidine-based derivatives. I used mass spectroscopy, FTIR, and ^{1}H NMR to verify the synthetic compounds' structural identity. I used an enhanced uniform precipitation technique founded upon the Kramer and Tisdall approach (1921) to assess in vitro antiurolithiatic efficacy. I used eggshell-derived semipermeable membranes to examine each compound's capacity to dissolve calcium oxalate. I found that the ability of derivatives with hydroxyl as well as methoxy substituents to dissolve calcium oxalate was higher than that of derivatives with electron-withdrawing groups. These results showed that derivatives based on pyrimidines would be good options for further antiurolithiatic studies.

INTRODUCTION

As much as 12 percent of people worldwide suffer with urolithiasis, a common and recurring urological condition that causes stones to develop in the urinary tract. Because to hormonal factors, it is much more frequent in men compared to women[1] . Evidence of the condition's recognition dates back thousands of years, as evidenced by early Indian literature and Egyptian mummies. Inherited, environmental, and dietary variables all have an impact on the intricate interaction between crystal regulators and inhibitors that leads to the creation of stones[2]. The 2023 Urolithiasis Standards emphasize the need for better prevention and treatment approaches grounded in current clinical knowledge, as well as the disease's increasing worldwide burden. In pharmaceutical management, a thorough assessment of stone formers is crucial for determining the risk of mineral and bone disorders (MBD) and CKD in addition to preventing recurrence [3]. A sizable

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portion of individuals have a highly recurring type of the disease, even though about 50% of people only have one recurrence. Stone category, recurrent severity, and underlying diseases all influence risk classification[4]. Because of blockage, infection, or related metabolic diseases, urolithiasis may be a contributing factor to the decrease of renal function. Determining these risk variables is essential to directing successful long-term treatment plans[5].

Lithogenesis

The process by which solid deposits or stones form inside the body is known as lithogenesis. The most prevalent kinds of these stones are kidney and gallstones, though they can form in a variety of organs or tissues[6]. There are various steps in the lithogenesis process: Supersaturation: This refers to the first step in which the concentration of a particular component in body fluids (such bile or urine) beyond the limit of solubility[7]. These materials may consist of salts, minerals, and other chemicals. Nucleation: The environment created by supersaturated fluids allows molecules to combine to produce nuclei, which are tiny solid particles. Crystal Growth: Crystal growth can result from other molecules within the fluid attaching to nuclei once they have formed [8]. Aggregation: Crystals have the ability to cluster and aggregate to create bigger solid formations. Retention: Within particular bodily structures, the aggregated crystals may become trapped or remain and stuck in the urinary system[9]. Stone Formation: These conserved formations have the potential to solidify into stones over time through continuous crystal growth and aggregation. Genetics, nutrition, hydration, the pH of body liquids, and underlying medical disorders are some of the elements that might lead to the development of stones. Calcium, which is oxalate, uric acid and cystine are among the chemicals that can cause kidney stones. The main ingredients of gallstones are bilirubin, cholesterol, and other substances present in bile[10,11].

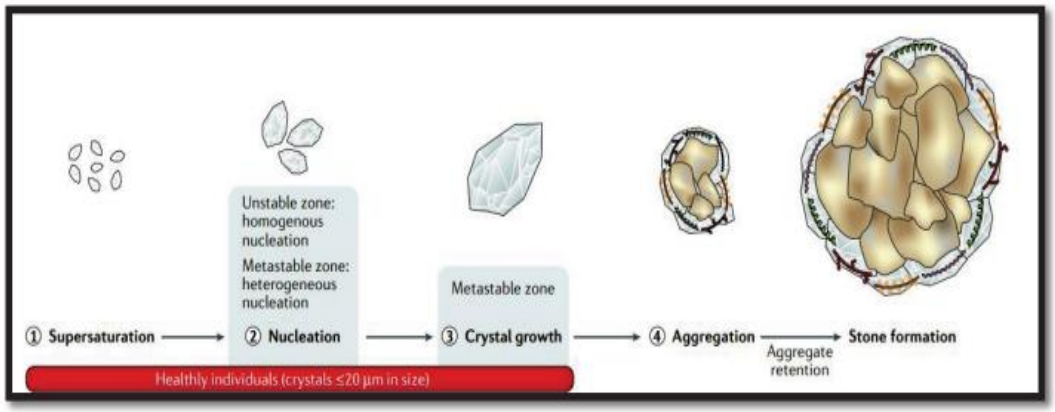


Figure1: Physicochemical process of stone formation

Pyrimidine

Between nitrogen atoms at positions 1 and 3, pyrimidine forms a six-membered aromatic heterocyclic molecule that shares structural similarities with pyridine as well as one of the three diazines. It creates the fundamental structure of the cytosine, thymine, and uracil nucleobases that are necessary for DNA and RNA. In addition to being produced for use in a variety of biological and pharmacological purposes, pyrimidines are found naturally [12]. Pyrimidine chemistry has advanced dramatically since the first laboratory synthesis of barbituric acid in 1879, and it now has a wide range of medicinal uses, covering

antibacterial, anticancer, antiviral, antimalarial, anticonvulsant, and CNS-related medications[13]. Pyrimidine has unique physical and chemical properties, including moderate polarity, aromaticity, and weak basicity. It is more susceptible to nucleophilic than electrophilic substitution and readily forms hydrogen bonds, making it crucial in base pairing. Structurally, its ring allows substitution at positions 2, 4, 5, and 6, aiding drug design and bioactivity modulation[14]. In addition to pharmaceuticals like 5-fluorouracil and barbiturates, pyrimidine derivatives are used in agriculture (as pesticides and herbicides), textile dyeing, and molecular biology research. Their structural flexibility and pharmacokinetic benefits make them valuable scaffolds in modern medicinal and industrial chemistry.The synthesis of the nucleotides needed for DNA and RNA depends on the pyrimidine synthesis pathway. Normal cell development, division, and function depend on the proper balance of pyrimidine synthesis[15]. Disease & cellular imbalance may result from disturbances in this route. Targeting essential enzymes such CPS-II and dihydroorotate dehydrogenase may stop nucleotide synthesis and decrease tumor cell growth, making an understanding of the de novo pyrimidine synthesis pathway therapeutically relevant, especially in the treatment of cancer[16].

Synthesis and Pharmacological Importance of BA (barbituric acid)

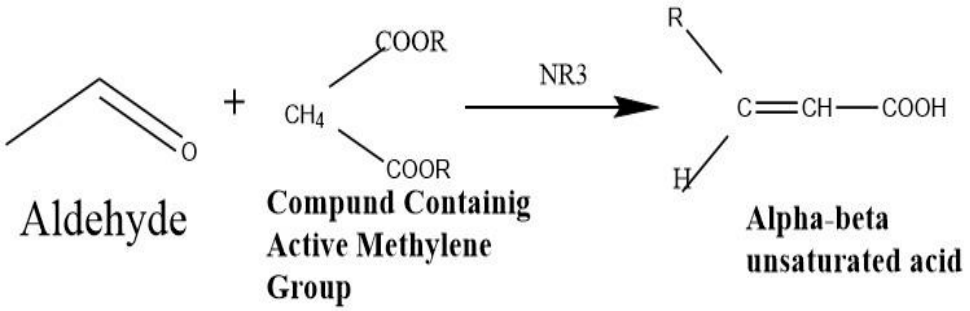
Adolf von Baeyer created barbituric acid, also known chemically as pyrimidine-2,4,6(1H,3H,5H)-trione, as a derivative in 1864 by reacting diethyl malonate with urea. Despite being pharmacologically inactive in and of itself, this molecule acts as a basic scaffold of the synthesis of several barbiturates that have effects on the central nervous system[17]. In Knoevenagel condensation reactions, C-5 is a reactive intermediate due to its inclusion of an active methylene group there, which is surrounded by two carbonyl groups[18]. Because of lactam–lactam tautomerism, barbituric acid ($C_4H_4N_2O_3$) is primarily found in the keto (lactam) form structurally. Having a melting point between 245 and 250°C, this white, crystalline substance dissolves somewhat in cold water but more readily with warm water, ethanol, or acetone. Because of its reactivity and acidic ($pKa_1 = 4.1$, $pKa_2 \approx 8.7$), it is a desirable component in organic synthesis, especially for multicomponent reactions[19]. Derivatives of barbituric acid have demonstrated a broad range of biological activity in pharmacological studies, such as hypnotic, sedative, anticonvulsant, antibacterial, and anticancer effects. For example, a cobalt combination of a ligand based on barbituric acid with potent urease inhibition was described by Barakat et al. (2020). Fahad et al. (2019–2022) produced compounds that had strong antifungal and antibacterial properties. Furthermore, phenobarbital and other barbiturate compounds have long been utilized in therapeutic settings to treat anxiety and seizures. The anticancer potential of barbituric acid was additionally studied. The cytotoxicity of hybrid compounds with barbituric acid or indole moieties has shown promise. Barbituric acid remains an essential molecule in synthetic and medical organic chemistry due to its extensive therapeutic potential and varied chemical reactivity[20,21].

METHODOLOGY

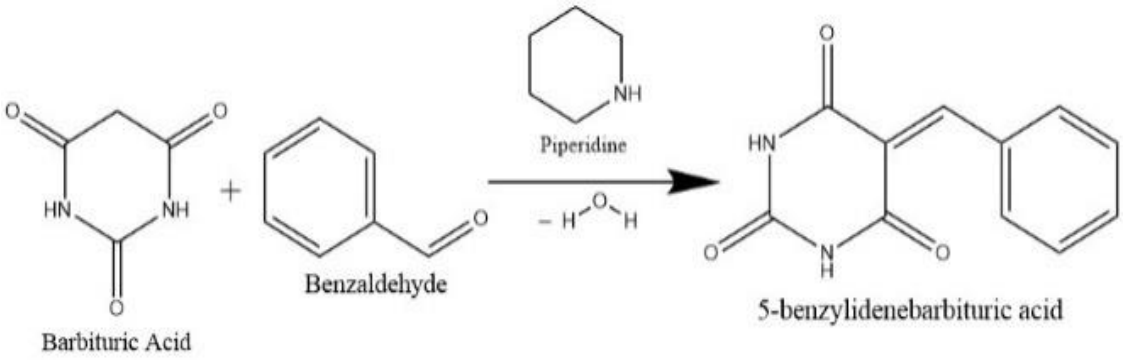
Knoevenagel Reaction-Synthesis

In the presence of a weak base, such as ammonia or amines, aldehydes or ketones condense with active methylene compounds, such as diethyl malonate, in a well-known organic reaction known as the Knoevenagel condensation[22]. This reaction, which is thought to be a variant of aldol condensation, was initially reported by Emil Knoevenagel in 1922 and creates carbon–carbon

double bonds. It works by forming carbanion, attacking the carbonyl carbon with a nucleophile, and removing water[23]. This process is widely used to create benzylidene derivatives and is useful in the chemical and pharmaceutical sectors. Using this technique, pyrimidine-based derivatives with possible antiurolithiatic qualities were created for this investigation[24, 25,].



5-Benzylidene BA synthesis via the KR process: In this reaction, 5-Benzylidene Barbituric acid as well as water are produced when barbituric acid (which functions as a pyrimidine core) combines with benzaldehyde with the help of piperidine. Because barbituric acid contains an active methylene molecule due to the presence of a group of methylene (CH2) flanked by two electron-withdrawing groups, it is employed as a launching material[26].



Procedure: Measure 212 µL (2 mmol) pure benzaldehyde and weigh 256 mg (2 mmol) of the acid barbituric acid precisely. In a dry, clean round-bottom flask, dissolve each in 10 milliliters of 100% ethanol. As a catalyst, add two to three drops of piperidine to the agitated mixture. Attach a Liebig condenser to the flask, then reflux the chemical reaction mixture for one to two hours while stirring constantly at 78 to 80 °C, which is the point of boiling of ethanol. Thin-layer chromatography with ethyl acetate: hexane (3:7) for the developing solvent is used to track the reaction's development. After finishing, let the reaction mixture drop to ambient temperature before chilling it even more in an ice bath to help the result precipitate. After filtering the resultant yellow solid, rinse with cold ethanol and let it dry for the entire night.

Percentage of yield: Percentage yield = (Actual yield)/(Theoretical yield) × 100

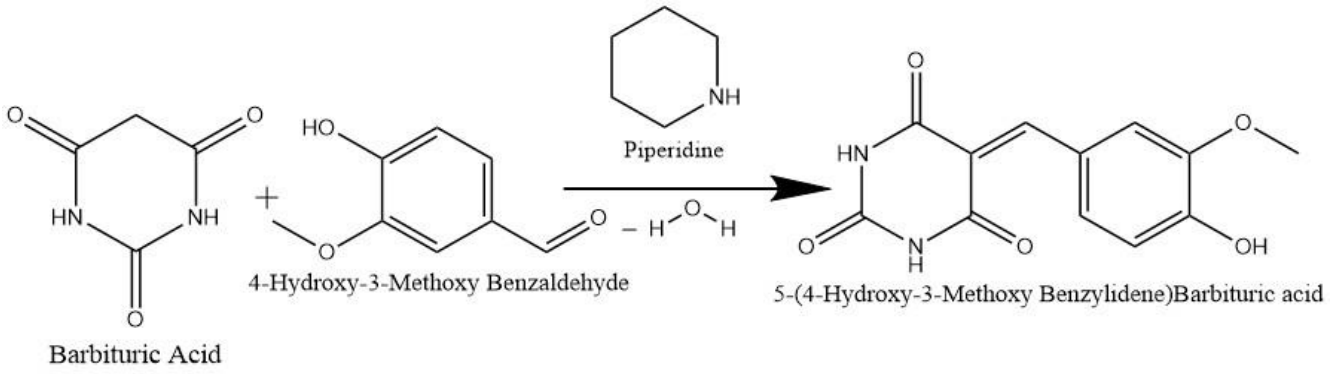
= 390 / 463.9 × 100 = 84.04%

Percentage Yield: 84.04%

5-(4-Hydroxy-3-Methoxybenzylidene)

Barbituric acid synthesis using the Knoevenagel condensation system: In the presence of a catalyst such as piperidine, barbituric

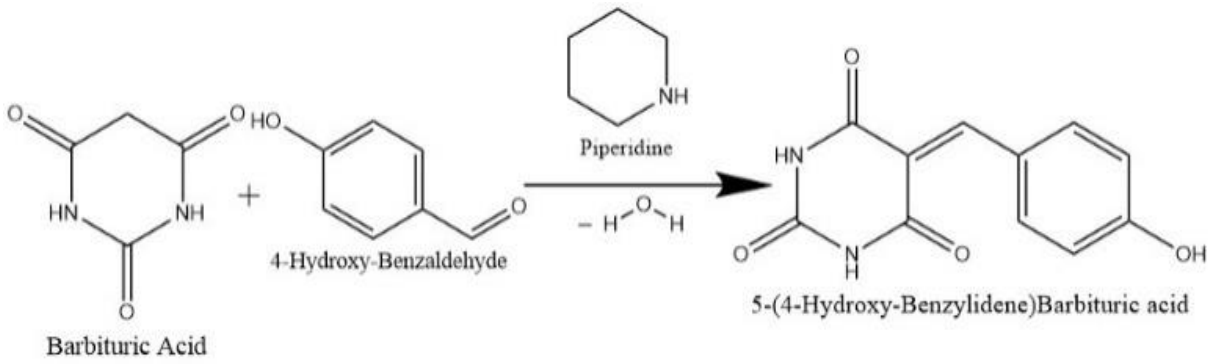
acid, which functions as a pyrimidine core, combines with vanillin (4-hydroxy-3-methoxybenzaldehyde to form a 5-(4-hydroxy-3-methoxylbenzylidene) barbituric acid derivative and water.



Procedure: Weigh 304 mg (2 mmol) of vanillin (4-hydroxy-3-methoxybenzaldehyde) and 256 mg of barbituric acid precisely. In a dry, clean round-bottom flask, dissolve each in 10 milliliters of 100% ethanol. As a catalyst, add two to three drops of piperidine to the agitated mixture. Install a Liebig condenser in the round bottom flask and reflux the chemical reaction mixture for one to two hours while stirring constantly at 78 to 80 °C, which is the point of boiling of ethanol. Utilizing Hexane: ethyl acetate (3:7) as an expanding solution, thin-layer chromatography (TLC) can be used to track the reaction's development. After finishing, let the reaction mixture Allow it to reach room temperature before positioning it in an ice to help the result Precipitate. Use cold ethanol to wash the resultant yellow or orange crystalline solid after filtering it.

Percentage of yield: Percentage yield = (Actual yield)/(Theoretical yield) × 100
= 410/556.48 × 100 Percentage Yield = 73.7%

5-(-Hydroxy-Benzylidene) Barbituric acid synthesis via the Knoevenagel condensation process: In the presence of a catalyst such as piperidine, barbituric acid (which functions as a pyrimidine core) combines with 4-hydroxy-benzaldehyde (4-hydroxy-benzaldehyde) to form a 5-(4-hydroxy-benzylidene) barbituric acid analog and water.



Procedure: Weigh 244 mg (2 mmol) of 4-hydroxybenzaldehyde (4-hydroxy-benzaldehyde) and 256 mg of barbituric acid precisely. In a dry, clean round-bottom flask, dissolve each in 10 milliliters of 100% ethanol. As a catalyst, add two to three drops of piperidine to the agitated mixture.

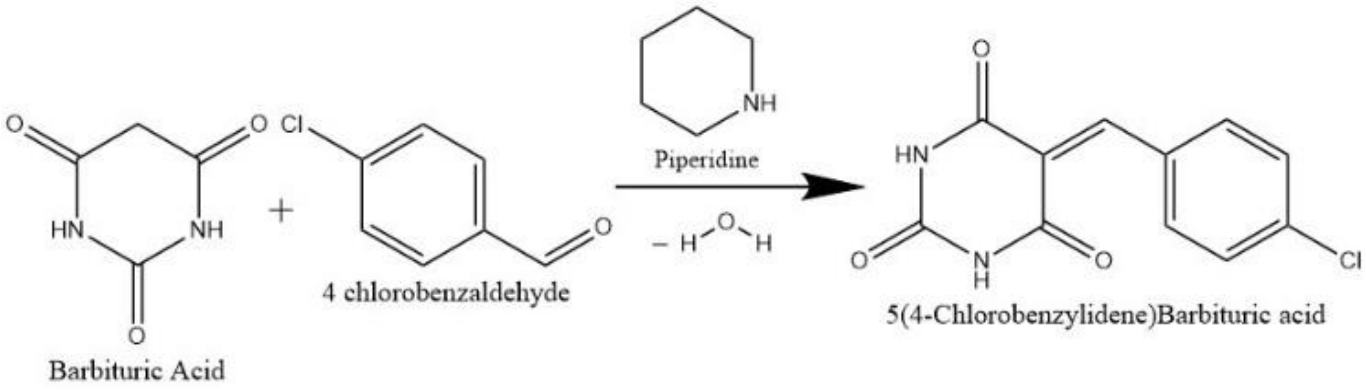
Install a Liebig condenser in the flask then reflux the chemical reaction mixture for one to two hours while stirring constantly at 78 to 80 °C, which is the point of boiling of ethanol. Applying ethyl acetate:hexane (3:7) as the growing solvent system, thin-layer chromatography (TLC) can be used to track the reaction's development. After finishing, let the reaction mixture cool to room temperature before putting it in an ice bath to help the result. Use cold ethanol to wash the resultant yellow or orange crystalline solid after filtering it.

Percentage of yield: Percentage Yield = Actual yield /Theoretical yield × 100

= 360/464.38 × 100

=77.53% Percentage Yield = 77.53%

5-(4-Chloro-Benzylidene-Barbituric acid synthesis via the Knoevenagel condensation process: The 5-(4-Chloro-Benzylidene) Barbituric acid derivative and water are the products of this reaction between Barbituric acid (which functions as a pyrimidine core) and 4-Chlorobenzaldehyde (4-Chloro-Benzaldehyde) with the help of an initiating agent such as piperidine.



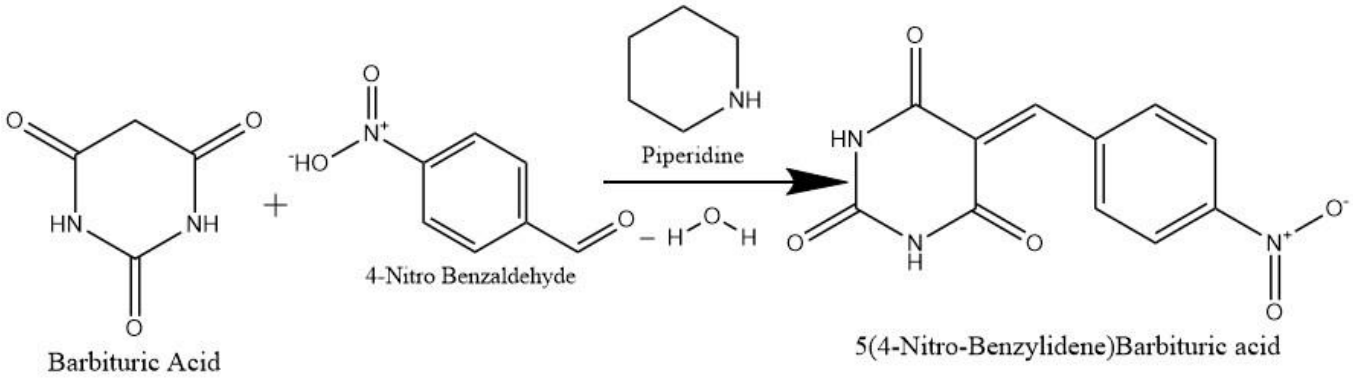
Procedure: 256 mg of barbituric acid with 280 mg (2 mmol) of 4- chlorobenzaldehyde (4-chloro-benzaldehyde) should be weighed precisely. In a dry, clean round-bottom flask, dissolve each in 10 millilitres of 100% ethanol. As a catalyst, add two to three drops of piperidine to the agitated mixture. Install a Liebig condenser in the flask and reflux the chemical reaction mixture for one or two hours while stirring constantly at 78 to 80 °C, which is the point of boiling of ethanol. Use thin-layer chromatography (TLC) to track the reaction's development, employing ethyl acetate: hexane (3:7) as the growth solvent system. After finishing, let the reaction mixture cool down to room temperature before putting it in an ice bath to help the result precipitate. Use cold ethanol to wash the resultant yellow or orange crystalline solid after filtering it.

Percentage of yield: Percentage yield = (Actual yield)/(Theoretical yield) × 100

= 390/499.8 × 100

Percentage Yield =78.03%

5-(4-Nitro Benzylidene) barbituric acid synthesis using the Knoevenagel condensation process: This reaction produces a 5-(4-Nitro-Benzylidene) Barbituric acid analog and water when Barbituric acid, which functions as a pyrimidine core, combines to Nitrobenzaldehyde (4-Nitro-Benzaldehyde) with the help of a catalyst such as piperidine.



Procedure: Weigh 302 mg (2 mmol) of nitrobenzaldehyde (4-nitrobenzaldehyde) and 256 mg of barbituric acid precisely. In a dry, clean round-bottom flask, dissolve each in 10 milliliters of 100% ethanol. As a catalyst, add two to three drops of piperidine to the agitated mixture. Install a Liebig condenser in the flask then reflux the chemical reaction mixture for one to two hours while stirring constantly at 78 to 80 °C, which is the point of boiling of ethanol. After finishing, let the reaction mixture cool down to room temperature before putting it in an ice bath to help the result precipitate. Use cold ethanol to wash the resultant yellow and orange crystalline solid after filtering it.

Percentage of yield: Percentage yield = 74.76%

Compound	Starting Compound	Aldehyde Used	Substituent	Product
P1	Barbituric acid	Benzaldehyde	–CH=CH–C_6H_5	5-Benzylidene barbituric acid
P2	Barbituric acid	Vanillin	–CH=CH–C_6H_3(OH)(OCH_3)	5-(4-Hydroxy-3-methoxy)barbituric acid
P3	Barbituric acid	4-Hydroxy-benzaldehyde	–CH=CH–C_6H_4(OH)	5-(4-Hydroxybenzylidene) barbituric acid
P4	Barbituric acid	4-Chloro-benzaldehyde	–CH=CH–C_6H_4(Cl)	5-(4-Chlorobenzylidene)barbituric acid
P5	Barbituric acid	4-Nitro-benzaldehyde	–CH=CH–$C_6H_4(NO_2)$	5-(4-Nitrobenzylidene)barbituric acid

Characterization of Synthesized Compounds

Determination of the Melting Point by Capillary Tube Method: I made sure that it was dry and ground into a fine powder. I put a tiny bit (1–2 mm) of sample into the open end of a capillary tube that was sealed. To place the sample at the bottom, lightly tap. I put a thermometer and the capillary tube into the point of melting device. I've noticed that the sample may be seen using a magnifying glass or viewing lens. The sample should be heated gradually (1–2°C each minute). I watch for the temperature at which melting starts. When the sample is completely liquid, it reaches the clear point. Pyrimidine derivatives' melting degrees were found to be between 230-250 °C.

Compound	Product Name	Observed Melting Point (°C)
P1	5-Benzylidene Barbituric Acid	239–241
P2	5-(4-Hydroxy-3-Methoxybenzylidene) BA	245–247

P3	5-(4-Hydroxybenzylidene) Barbituric Acid	237–239
P4	5-(4-Chlorobenzylidene) Barbituric Acid	230–232
P5	5-(4-Nitrobenzylidene) Barbituric Acid	248–250

Chromatographic Study: TLC Analysis:

$$\textbf{RF value} = \frac{\textbf{Distance travelled by compound}}{\textbf{Distance travelled by solvent}}$$

Compound Code	Product Name	Rf Value	Mobile Phase
P1	5-Benzylidene Barbituric Acid	0.55	Ethyl acetate : Hexane (3:7)
P2	5-(4-Hydroxy-3-Methoxybenzylidene) Barbituric Acid	0.45	Ethyl acetate : Hexane (3:7)
P3	5-(4-Hydroxybenzylidene) Barbituric Acid	0.40	Ethyl acetate : Hexane (3:7)
P4	5-(4-Chlorobenzylidene) Barbituric Acid	0.50	Ethyl acetate : Hexane (3:7)
P5	5-(4-Nitrobenzylidene) Barbituric Acid	0.49	Ethyl acetate : Hexane (3:7)

FTIR Analysis

The main use of FTIR spectroscopy was the chemical characterization of pyrimidine derivatives in order to evaluate their purity and structural integrity. FTIR spectrophotometer, which operates in the 4000–400 cm^{-1} spectrum band, was used to analyze samples of the produced pyrimidine derivatives at room temperature. 5-benzylidene BA, 5-(4-hydroxy-3-methoxybenzylidene) BA, 5-(4-hydroxybenzylidene) BA, 5-(4-chlorobenzylidene) BA, and 5-(4-nitrobenzylidene) BA were all structurally intact and did not significantly deviate from the expected absorption bands, according to the FTIR spectra in the pyrimidine derivatives. Additionally, FTIR analysis verified the pyrimidine derivative samples' high degree of purity. An FTIR spectrometer operated over the 4,000 to 400 cm-1 spectral range was used to analyse an object of pyrimidine derivatives for chemical characterisation at room temperature. Pyrimidine derivatives' structural integrity is confirmed by the FTIR data, which also shows no discernible departures from the expected absorption bands. The FTIR analysis verified the pyrimidine derivatives sample's high levels of purity.

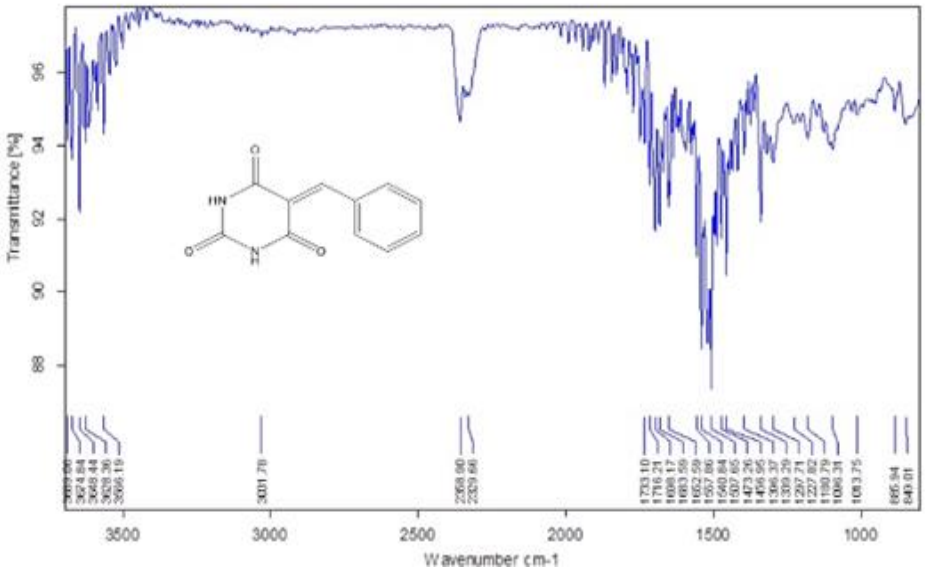


Figure 2: FTIR of 5-Benzylidene barbituric acid

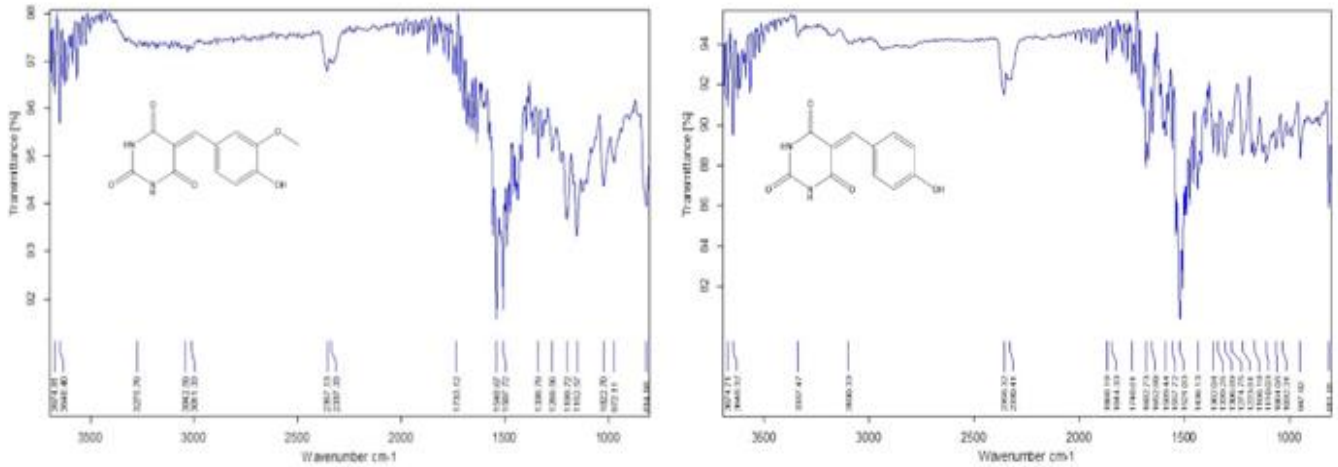


Figure 3: (a) FTIR of 5-(4-Hydroxy-3-Methoxy Benzylidene BA; (b) 5-(4-Hydroxy) Benzylidene BA

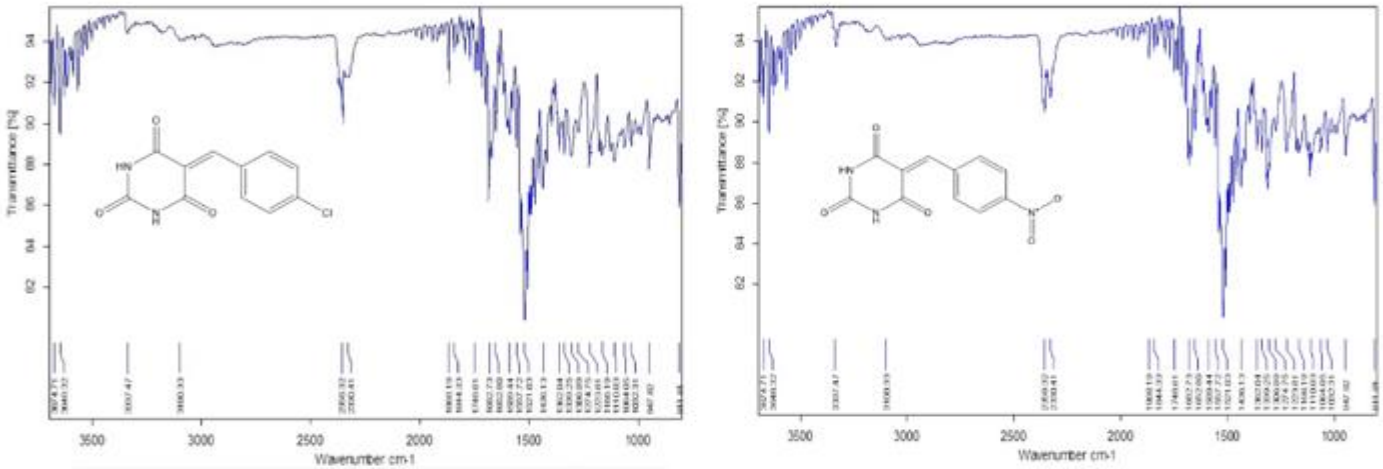


Figure 4: (a) FTIR of 5-(4-Chloro) Benzylidene barbituric acid; (b) 5-(4-Nitro) Benzylidene barbituric acid

Spectroscopy using NMR

In essence, NMR spectroscopy was utilized to verify the compounds purity using 1H spectra acquired using a Bruker AMX 400 MHz spectrometer. The internal reference for the chemical shift of 1H was the DMSO peak at δ 2.50 ppm. The pyrimidine derivatives, 5-benzylidene BA, 5-(4-hydroxy-3-methoxybenzylidene) BA, 5-(4-hydroxybenzylidene) BA, 5-(4-chlorobenzylidene) BA and 5-(4-nitrobenzylidene) barbituric acid, were all structurally intact and showed no discernible deviation from the expected absorption bands that corresponded to their predicted functional groups, according to the NMR spectra. Additionally, NMR analysis verified the pyrimidine derivative samples' high degree of purity.

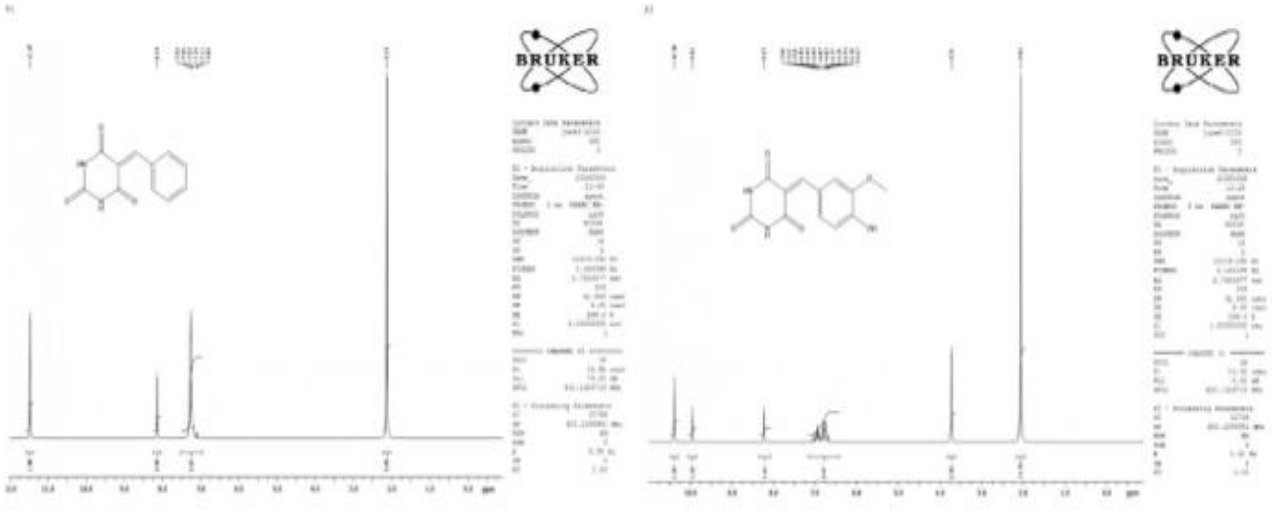


Figure 5: (a) 1H NMR of 5-Benzylidene barbituric Acid; (b) 1H NMR of 5-(4-Hydroxy-3-Methoxy-Benzylidene BA:

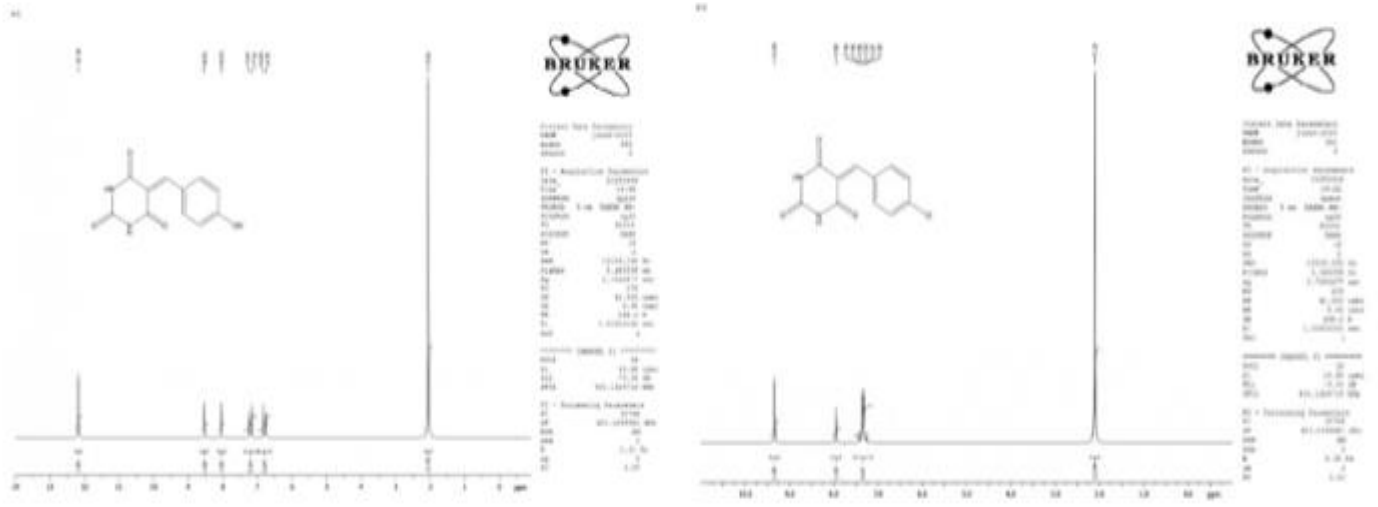


Figure 6: (a)1H NMR of 5-(4-Hydroxy) Benzylidene BA; (b) 1H NMR of 5-(4-Chloro) Benzylidene barbituric acid:

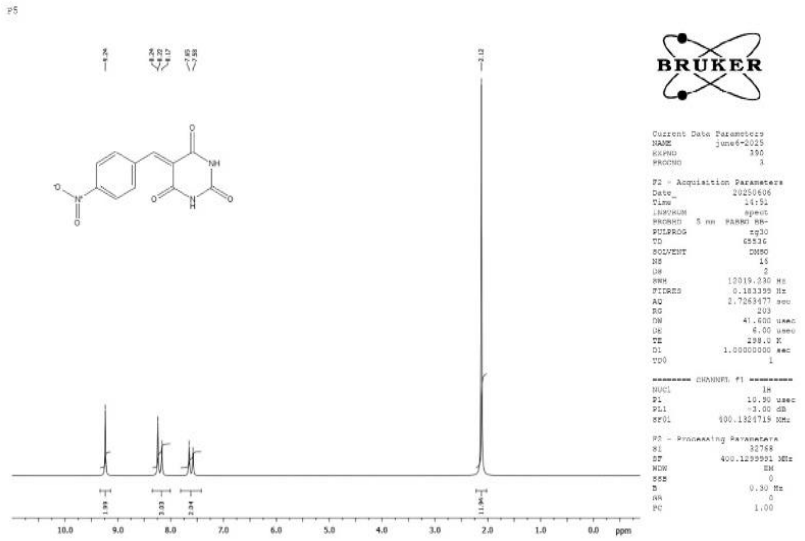


Figure 7: 1H NMR of 5-(4-Nitro) Benzylidene barbituric acid

Mass spectra Analysis: In order to confirm that all of the pyrimidine derivatives, 5-benzylidene BA, 5-(4-hydroxy-3-methoxybenzylidene) BA, 5-(4-hydroxybenzylidene) BA, 5-(4-chlorobenzylidene) BA , and 5-(4-nitrobenzylidene) barbituric acid were all mass to charge ratio intact and did not exhibit any noticeable deviation from the expected absorption bands that matched their predicted functional groups, the mass spectra was used as a crucial analytical tool to identify and quantify molecules based on their mass to charge ratio. Furthermore, the high level of purity within the pyrimidine derivatives samples was confirmed by mass analysis.

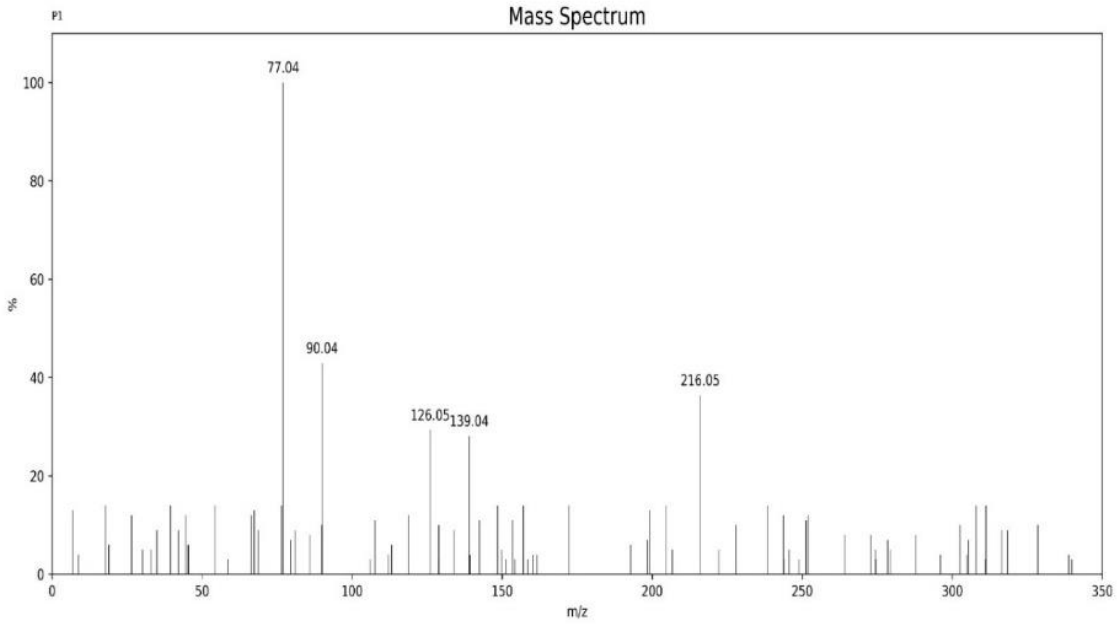


Figure 8: Mass spectra of 5-Benzylidene BA:

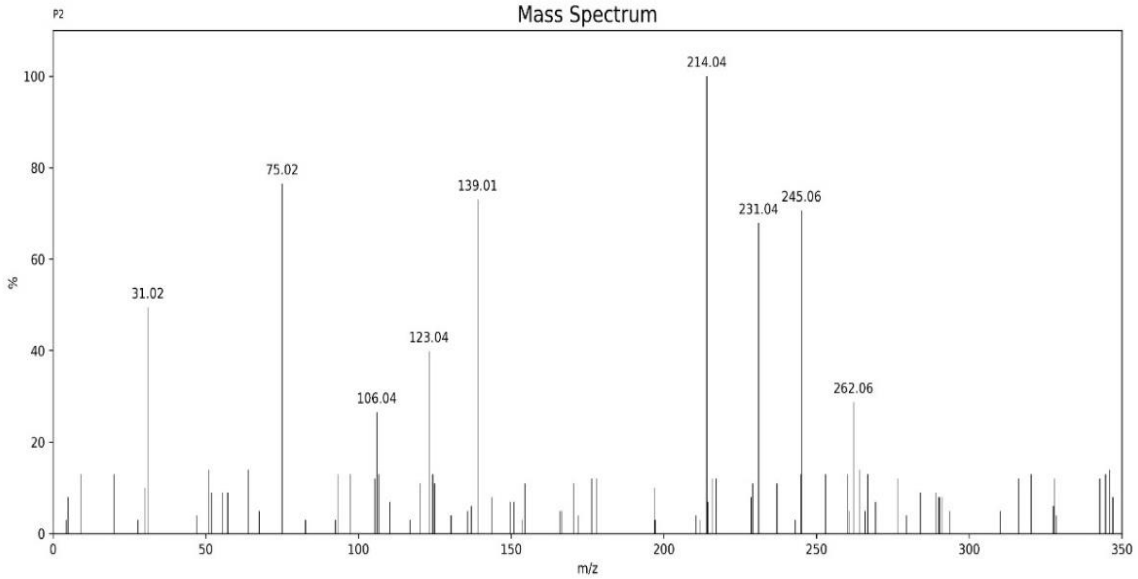


Figure 9: Mass spectra of 5-(4-Hydroxy-3-MethoxyBenzylidene BA:

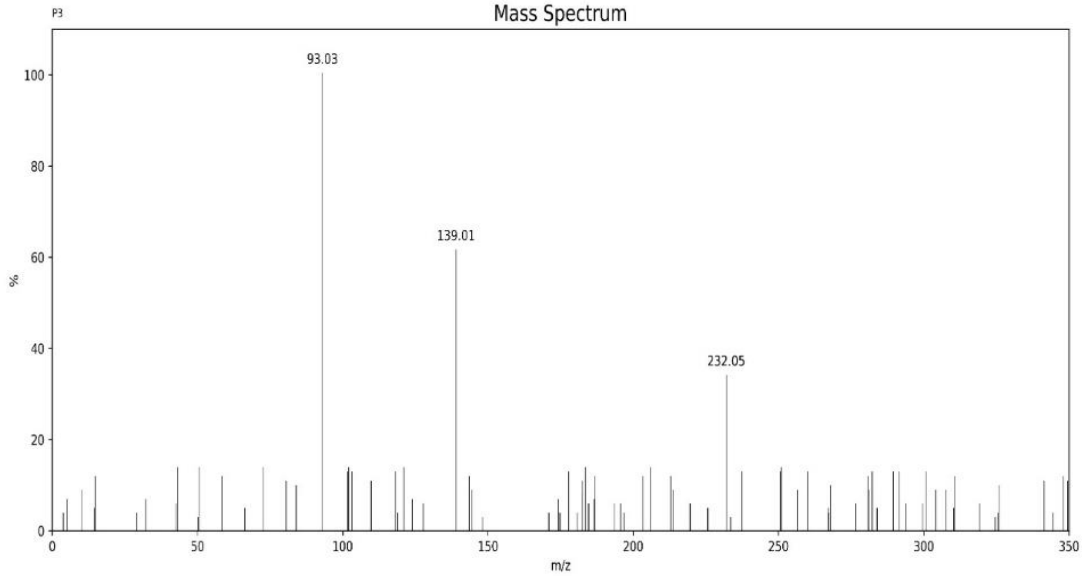


Figure 10: Mass spectra of 5-(4-Hydroxy) Benzylidene barbituric acid:

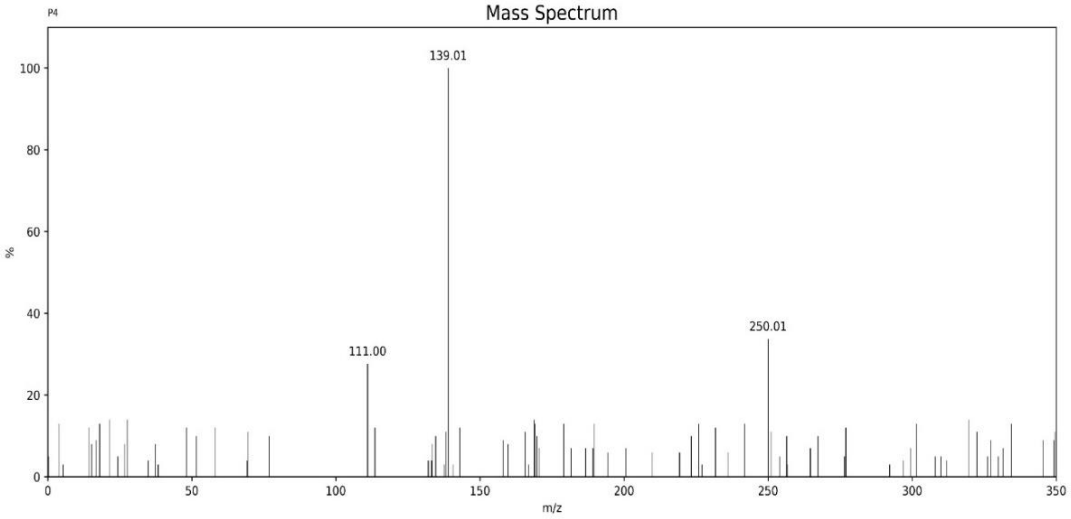


Figure 11: Mass spectra of 5-(4-Chloro) Benzylidene barbituric acid:

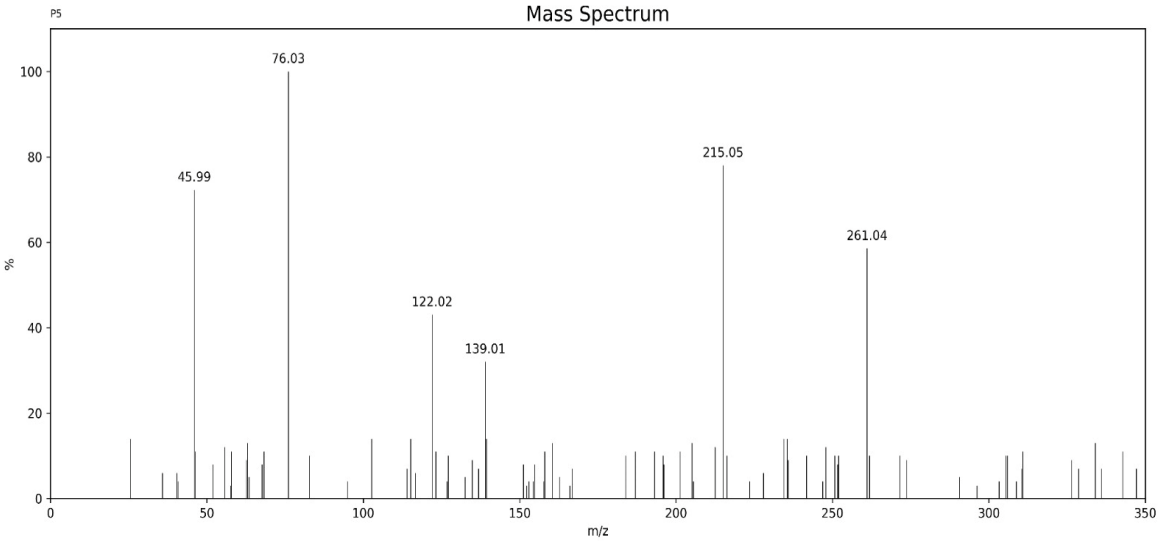


Figure 12: Mass spectra of 5-(4-Nitro) Benzylidene BA:

In Vitro: Kramer & Tisdall's Method for Evaluating Antiurolithiatic activity

A homogeneous precipitation approach was used to determine the in vitro antiurolithiatic efficacy in order to evaluate the production of calcium oxalate stones. In particular, 5-benzylidene BA, 5-(4-hydroxy-3-methoxybenzylidene) BA, 5-(4-hydroxybenzylidene) BA, 5-(4-chlorobenzylidene) BA, and 5-(4-nitrobenzylidene) barbituric acid were examined for their ability to dissolve a specified amount of simulated renal stones (calcium oxalate) that were enclosed in semipermeable membranes. Using farm eggs, eight semipermeable membranes were developed. After being precisely weighed, 10 mg of calcium oxalate and one 100 milligrams of different pyrimidine derivatives were each carefully enclosed in semi-permeable membranes and sutured. The membranes were left to float inside a conical flask filled with 100 milliliters of TRIS buffer at 0.1M. Every conical flask was incubated for two hours at 37 °C, then kept there for another two hours, and finally left undisturbed for seven or eight hours at room temperature. With minor adjustments, the Kramer and Tisdal method was used to estimate the amount of unexpended

calcium oxalate inside the semi-permeable membranes. A persistent light pink tint was achieved by titrating the contents with standard KmnO4 (0.9494N) after they had been treated with 2 milliliters of 1N sulfuric acid. The percentage that consisted of calcium oxalate soluble was calculated after the study was conducted three times (n=3) and the average was determined.

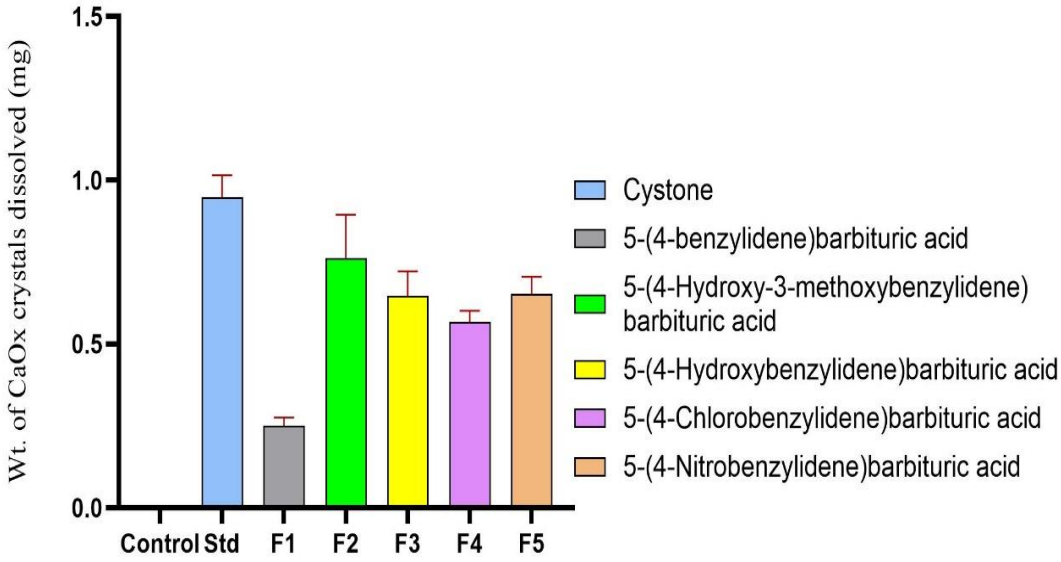


Figure 13: Graphical representation of weight of CaOx dissolved

The capacity of synthetic barbituric acid derivatives for dissolving oxalate of calcium (CaOx) crystals was used to assess their in vitro antiurolithiatic action. In excess of 1.0 mg of CaOx was dissolved by the conventional medication Cystone, demonstrating the maximum dissolution activity and verifying its proven effectiveness. Due to the inclusion of both hydroxyl and methoxy groups, which probably improve the compound's contact with the crystal surface, 5-(4-hydroxy-3-methoxybenzylidene)barbituric acid (F2) exhibited the most substantial dissolution of all the produced compounds, at about 0.9 mg. Both F3 and F5, which have single polar substituents like -OH or -NO_2, respectively, showed moderate activity. Conversely, the least active compounds were F1 (containing a not polar in nature benzylidene group) and F4 (chloro-substituted).

These results imply the fact that the antiurolithiatic capability in these pyrimidine derivatives is largely determined by the amount as well as electronic nature of the substituents in the aromatic ring of the compound.

CONCLUSION: In my study, I have studies series of pyrimidine-based derivatives were successfully synthesized using barbituric acid and various substituted aromatic aldehydes via a Knoevenagel condensation reaction. The substances that have been created have been defined using FTIR, 1H NMR, and MS, which confirmed the formation and purity of the target structures.In the results I have seen that the synthetic pathway is efficient, simple, and reproducible, yielding compounds in good quantities with sharp melting points and confirmed structural integrity. The incorporation of various functional groups, such as hydroxyl, methoxy, chloro, and nitro, was successfully achieved without compromising the reaction efficiency.These compounds are potential candidates for further biological evaluation related

to urolithiasis prevention, as pyrimidine derivatives are known to exhibit significant biological activities. This research lays a strong foundation for future in vitro studies to evaluate the pharmacological potential of these derivatives as anti-urolithiatic agents.

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