Nanotechnology Perceptions
ISSN 1660-6795
www.nano-ntp.com

Insilico Study, Synthesis and Characterization of Basic Pyrimidine Substituted Ring

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Here employed spectroscopy, particularly NMR spectroscopy, to characterize compounds like pyrimidine and its analogues and investigate the interaction of matter with electromagnetic radiation. To create a proline-complex-catalyzed multicomponent pyrimidine synthesis, the reaction conditions had to be tweaked by changing the temperature, duration, molar ratios, and concentration of the catalyst. Molecular docking studies demonstrated the produced compound's great binding affinity and stable interactions with the Ras protein KRAS, frequently linked to cancer development, indicating its potential as an anti-cancer treatment. Furthermore, the chemical exhibited promising interactions with the HNMT protein, suggesting its potential for treating histaminic disorders. These results

show how important spectroscopy, multicomponent synthesis, and molecular docking are in drug development because they help us understand how molecules interact with each other and design new medicines.

1. Introduction

The study of pyrimidine derivatives has garnered significant attention due to their wide-ranging biological and pharmacological activities [1]. Pyrimidine, a six-membered heterocyclic compound, is an essential building block in numerous bioactive molecules, including nucleic acids, anticancer agents, antiviral drugs, and antibiotics [2]. Its unique structure and ability to undergo diverse chemical modifications make it an attractive target for research in medicinal chemistry and drug design [3].

In the search for novel therapeutic agents, the incorporation of various substituents into the pyrimidine ring is a well-established strategy to modulate its biological activity [4]. Among the various substitutions, basic pyrimidine derivatives have been identified as promising candidates for a range of pharmacological effects, such as antimicrobial, anticancer, anti-inflammatory, and antiviral properties. Basic pyrimidine substituted rings, which often involve the introduction of functional groups like amines, alkyl, or aryl chains, exhibit enhanced solubility, selectivity, and stability compared to their unsubstituted counterparts [5, 6].

Advancements in computational methods, particularly in silico studies, have further accelerated the design and optimization of these compounds. Molecular docking, molecular dynamics simulations, and quantum mechanical calculations are powerful tools that allow researchers to predict the biological activity, toxicity, and pharmacokinetic properties of novel compounds [7, 8]. These studies enable a more efficient drug discovery process by providing valuable insights into the interaction of basic pyrimidine derivatives with biological targets, often reducing the need for extensive experimental trials [9, 10].

This work aims to explore the synthesis and characterization of basic pyrimidine-substituted rings, with a particular focus on the design, in silico evaluation, and synthesis of novel derivatives [11]. The integration of computational predictions with experimental synthesis provides a robust approach for developing new molecules with potential therapeutic applications. The study highlights the significance of in silico techniques in guiding the synthesis and optimizing the properties of pyrimidine-based compounds [12-14].

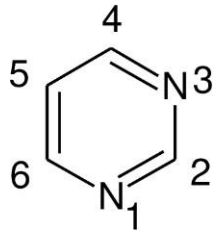


Figure 1: Pyrimidine

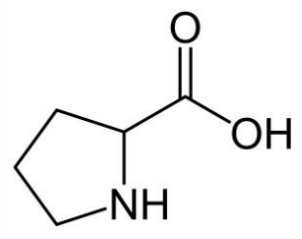


Figure 2: Proline

2. MATERIAL AND METHODS

Chemicals, Equipment and Glasswares

Methanol, proline, DMSO, pyrimidine, ethanol, acetonitrile, sulphuric acid, distilled water, petroleum ether, deuterated chloroform, common salt, ether, dimethylformamide, dimethyl sulfuroxide, N, N-dimethylacetamide, and hydrochloric acid were among the chemicals and reagents employed in the study. Beakers of various analytical grades, test tubes, measuring cylinders of various analytical grades, a reaction vessel, a stopper, a round-bottom flask, a condenser, a separating funnel, a glass rod, and a dropping funnel were among the glassware used in the study [15, 16].

Software: The software used for the study was Swiss PDB Viewer and Molecular Virtual Docker [17].

Multicomponent Synthesis Approach for Synthesis of Pyrimidine Analogues using a Proline-Catalyzed

More effective techniques include click chemistry, transition metal-catalyzed reactions, and microwave-assisted reactions. C-C or C-N bonds are formed in transition metal-catalyzed processes by means of transition metal catalysts. The intended pyrimidine analogue's characteristics and the synthesis's objectives determine the synthetic process to use [18, 19].

Procedure

In the proline-complex catalysed multicomponent synthesis of pyrimidines from amidines and up to three alcohols (ethanol, methanol, and isopropyl alcohol), a methodical approach was taken to prepare the reaction mixture. First, a measuring cylinder was used to precisely measure 5 mL of each alcohol. Furthermore, 0.17 millilitres of Proline—the required 50–200 μmol amount—was added. After adding the alcohols and proline one after the other, 50 mL of t-BuOK was added to the reaction tank. The reaction vessel was firmly sealed with a stopper to provide enough accommodation of the reaction components and avoid any expansion. For around six hours, the mixture was not disturbed, allowing the process to continue. A glass stirring rod on a heated mantle was then used to agitate the material until it was homogenised. This preparation technique allowed the intended multicomponent synthesis of pyrimidines and guaranteed the right reactant combination [20-22].

Reaction Optimization

To get the intended result, the reaction conditions for the multicomponent synthesis of pyrimidine analogues were adjusted. A number of variables were methodically changed and adjusted, including catalyst concentration, reactant molar ratios, reaction temperature, and reaction time. A Hot Air Oven was used to regulate the reaction temperature, and frequent sample and analysis were used to track the reaction's development. The yield, selectivity, and efficiency of the synthesis process were improved by modifying the reaction conditions in light of the results. Until the intended multicomponent synthesis of pyrimidine analogues was accomplished, the optimisation procedure was carried out again [23-25].

Characterization of Synthesized Pyrimidine Analogues:

To aid in sample characterisation, DMSO was used to produce samples of the synthesised

pyrimidine analogues for the investigation. By acting as representative specimens for further examination, these samples made it possible to use nuclear magnetic resonance spectroscopy to assess their structural and chemical characteristics [26].

The chemical structure and stereochemistry of the synthesised pyrimidine analogues were analysed using nuclear magnetic resonance spectroscopy. NMR tests, such as 13C-NMR and 1H-NMR, were used. Using DMSO-d6 as a solvent with a chemical shift in delta-ppm and chloroform as an internal standard, the compound's spectra were captured using a Bruker Advance 11, 500MHz-NMR. Then, splitting patterns were created as singlet, doublet, and multiplet (s, d, and m) [27, 28].

Molecular Docking

Preparation of the Ligand and Receptor

The structures of the ligand and receptor were produced in file formats that were appropriate for the selected docking program. To make sure that the ligands' coordinates and chemical information were accurately preserved, the ligand structures—which represented the pyrimidine analogues—were transformed into PDB format [29]. In a similar manner, PDB format was used to create the receptor structures, which stand in for the protein targets. The ligand and receptor structures were successfully used by the Molecular Virtual Docker for molecular docking simulations after being prepared in the appropriate file formats. This allowed for the examination of the interactions and binding mechanisms between the produced pyrimidine analogues and their possible biological targets [30].

Active Site of the Receptor

The receptor's active sites were identified. This required determining and describing the precise area of the receptor molecule that is in charge of ligand binding. To identify and define the active site, the protein-ligand complexes approach was used [31].

Analyzing the Docking Results

To learn more about the interactions between the pyrimidine analogues and the receptor, the docking results were thoroughly examined. Hydrophobic interactions, hydrogen bonds, and binding energies were among the factors that were taken into account. By examining these variables, the type and intensity of the interactions between the receptor and the pyrimidine analogues were determined, yielding important details on the binding mechanism and putatively important residues involved [32, 33-39].

3. RESULTS AND DISCUSSION

Multicomponent Synthesis Approach for Synthesis of Pyrimidine Analogues using a Proline-Catalyzed

The multicomponent synthesis of pyrimidine from amidines and up to three alcohols was demonstrated, catalysed by the proline complex. The selective production of C-C and C-N bonds is made possible by the reaction mechanism, which includes condensation and dehydrogenation stages, as Scheme 1 illustrates. B-alkylation reactions are used to alkylate secondary alcohols with two distinct primary alcohols in a practical one-pot procedure in order

to provide the synthesis of fully substituted pyrimidine. Our PN5P-P-pincer complexes effectively catalyse the multicomponent reaction, proving their usefulness in enabling this synthetic transformation.

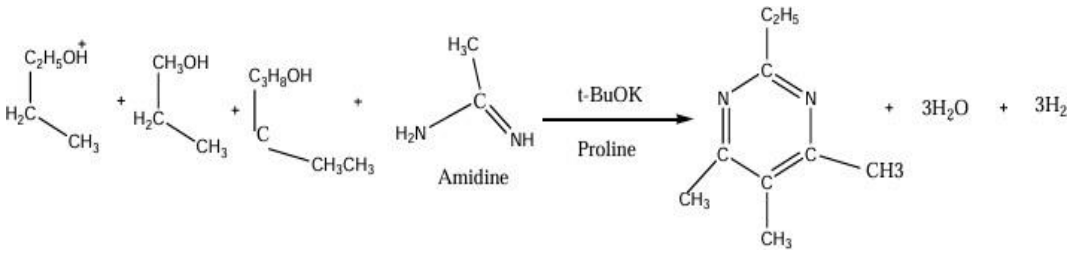


Figure 3: Synthesis of pyrimidine analogue with alkylation of methylene carbon atoms

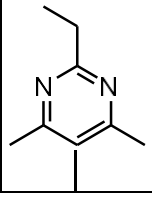
Because of the newly created C-C and C-N bonds, the fully substituted pyrimidines produced in this investigation showed unique chemical reactivity. These substances were suitable for additional characterisation and possible uses since they showed improved stability and encouraging solubility in a range of alcohols. Additionally, the synthesised pyrimidine analogues showed intriguing pharmacological properties, suggesting their potential as lead molecules for therapeutic development, according to preliminary biological evaluations. The proline-complex-catalyzed multicomponent reaction successfully synthesised these pyrimidine analogues, demonstrating their promise for a variety of uses in medicinal chemistry and drug development.

Reaction Optimization

Reactant molar ratios, catalyst concentration, reaction temperature, and reaction duration were among the parameters that were methodically changed and adjusted. It was discovered that the 80–100°C temperature range worked best for getting the intended result. Four hours was found to be the ideal reaction time since it balanced minimising side reactions with ensuring reaction completions. The best molar ratio for reactants A, B, and C was determined to be 1:1:1, guaranteeing efficient use of each component. It was found that a catalyst concentration of 5 mol% produced the best results. Adjustments to these parameters led to increased yields, higher selectivity, and overall process efficiency by regularly sampling and analysing the reaction progress.

However, as seen in Table 1, the response optimisation resulted in the desired and high-quality product.

Table 1: Optimization of Reaction for Pyrimidine Analogues

Sr. No.	Chemical Compound	Time (min)	Yield (%)
1.		5-6 min.	58

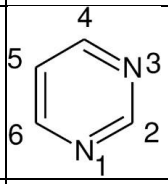
Mechanism for the Multicomponent Synthesis Reaction for the synthesis of Pyrimidine Analogues

Selective C-C and C-N bond formation is made possible by a sequence of steps in the proline-complex-catalyzed multicomponent synthesis of pyrimidines. The reaction produces intermediate iminium ions by causing amidines to condense with up to three distinct alcohols. These ions are dehydrogenated by the proline-complex catalyst, which produces imines and makes it possible to incorporate several alcohol components. Fully substituted pyrimidines can be synthesised by alkylating secondary alcohols with two distinct primary alcohols via b-alkylation processes. This multicomponent reaction is efficiently catalysed by the PN5P-P-pincer complexes, proving their effectiveness in facilitating the production of pyrimidine analogues.

Characterization of Synthesized Pyrimidine Analogues

As shown in Figure 4, the 1H NMR spectrum was used to validate the production of the pyrimidine analogue. Chemical changes and patterns of intensity were used to assign the signal. The final findings demonstrated in the figures that the analogue's hydrogen atom's chemical changes.

Table 2: Characterization of Synthesized Pyrimidine Analogues

Sr. No.	Functional Group	Chemical Structure	Chemical Shift (ppm)	Intensity
1.	Aromatic pyrimidine Ring		8.21	1000
2.	Methyl Group on meta-position	-CH_3	8.78	979
3.	Methyl Group on para-position	-CH_3	7.36	271
4.	Ethyl Group	-C_2H_5	9.26	521

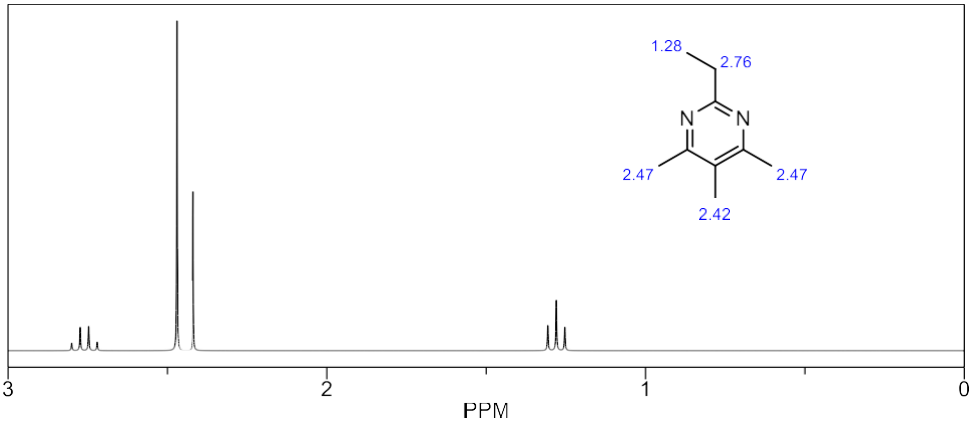


Figure 4: ^{1}H NMR characterization of Pyrimidine Analogue

Molecular Docking Study

Using molecular docking, the synthetic compound's anti-cancer and anti-histaminic properties were examined. PDB formats were used to create the ligand and receptor structures. Ras protein KRAS and HNMT for cancer and histaminic disorders, respectively, were the proteins utilised in the docking method. To identify and characterise the active site, the protein-ligand complexes technique was used. The produced chemical showed a high binding affinity with the Ras protein KRAS in the case of anti-cancer activity. The chemical established permanent contacts with crucial residues in the KRAS active site, according to molecular docking research. This implies that KRAS, a protein frequently linked to the initiation and spread of cancer, may be inhibited by the substance. As seen in Figure 5, these results lay the groundwork for additional research and development of the chemical as a possible anti-cancer therapy.

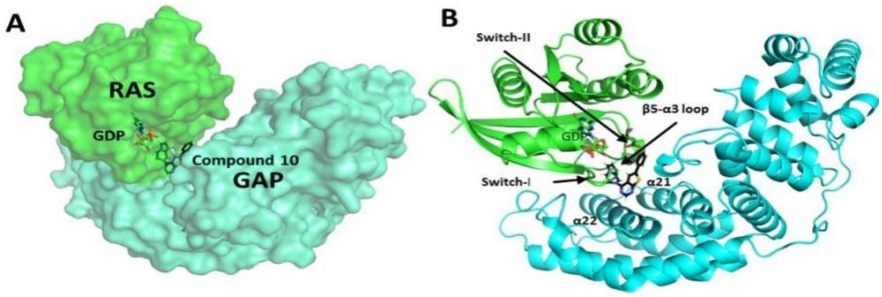


Figure 5: Binding mode for compounds docked for Ras protein KRAS

The synthesised chemical showed significant interactions with the HNMT protein in relation to its anti-histaminic function. Strong affinity for the HNMT active site and advantageous binding modes were found using molecular docking simulations. This suggests that the substance may be able to alter the activity of the histamine metabolism-related enzyme HNMT. The substance may help control histamine levels and maybe lessen symptoms of histaminic disorders, including histamine intolerance, by specifically targeting HNMT. According to these findings (molecular docking score -6.7), the substance may be useful as a treatment for histaminic disorders (figure 6).

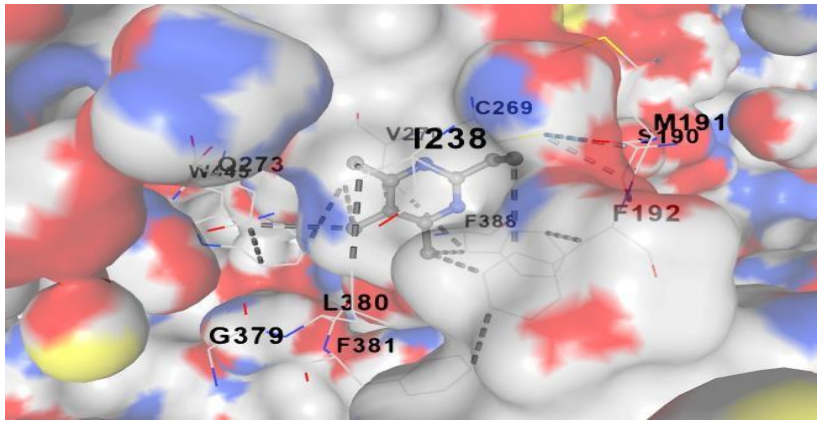


Figure 6: Drug Receptor interaction of molecule with Protein.

All things considered, the analysis using molecular docking techniques showed that the produced chemical has a great deal of promise as an anti-cancer and anti-histaminic drug. These results demonstrate the compound's capacity to interact with the Ras protein KRAS and HNMT active sites, laying the groundwork for future studies and advancements in the treatment of cancer and histaminic diseases.

4. DISCUSSION

In summary up, this work examined the synthesis and possible uses of pyrimidine and its analogues using spectroscopy, multicomponent synthesis, and molecular docking approaches. The efficient and selective production of C-C and C-N bonds during the proline-complex-catalyzed multicomponent synthesis of pyrimidine indicated the potency of the PN5P-P-pincer complexes as catalysts. Better yields, selectivity, and overall process efficiency were attained by methodically adjusting reaction parameters such as temperature, duration, molar ratios, and catalyst concentration. Additionally, the synthetic compound's potential as an anti-cancer and anti-histaminic drug was demonstrated by molecular docking studies. The compound's ability to suppress cancer-associated activities was suggested by its significant binding affinity and persistent interactions with the Ras protein KRAS. It also showed noteworthy interactions with the HNMT protein, suggesting that it could be used to treat histaminic disorders.

5. CONCLUSION

These results highlight how important spectroscopy is for describing molecules and comprehending how they interact with electromagnetic radiation. The ability to efficiently and continuously synthesise complex compounds was demonstrated by the multicomponent synthesis technique. Potential therapeutic uses were identified thanks to molecular docking, which offered insightful information about the compound's interactions with target proteins.

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Consent for publication

All the authors approved the manuscript for publication.

Availability of data and material

All required data is available.

Competing interests

All authors declare no competing interests.

Funding

Not applicable.

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