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Green Synthesis of Heterocyclic Compounds Using Eco-Friendly Catalysts

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Abstract

This study investigates the green methods of making heterocyclic compounds with safe catalysts. Results are analyzed using data-driven techniques to assess their efficiency, spectral authenticity and activity towards living organisms. For this study, a set of 1000 heterocycles was made using experimental values from the literature for reaction yield, melting point, NMR, IR, UV-V is spectra and both antioxidant and antimicrobial properties. The investigation of interactions between synthetic and functional properties was made possible by the application of descriptive analytics, Pearson correlation, Principal Component Analysis (PCA), KMeans clustering and hypothesis testing. Most of the developed compounds showed a high yield (85–95%) and could withstand heat (melting point 200–250°C), in addition to showing effective antioxidant (80–95%) and antibacterial (20–25 mm inhibition zone) qualities. The study's calculations matched the spectra expected for actual compounds containing aromatic and conjugated groups. Significantly, using statistics revealed no conflict between drug effectiveness and drug production which means pharmaceutical goals can be met with green chemistry. The study shows a repeatable method that can be used outside a lab, where cheminformatics, spectral modeling and statistical learning are incorporated to support green synthesis and preserve bioactivity. It allows the use of a flexible system to test, group and improve the use of heterocycles for sustainable pharmaceutical chemistry.

Keywords: Green Chemistry, Heterocyclic Compounds, Eco-Friendly Catalysts, PCA, Antioxidant Activity.

1. Introduction

Heterocyclic compounds have been important in organic chemistry for a long time thanks to their involvement in pharmaceuticals, agrochemicals, dyes, polymers and electronic materials (Kerru, 2021). Yet, the usual methods for preparing heterocycles often involve dangerous solvents, costly metal catalysts and heavy use of energy (Lashkari, 2022). Due to increasing environmental and regulatory issues, green chemistry is seen as a promising new approach (Majee, 2023). This work investigates making heterocyclic compounds with environmentally safe catalysts, focusing on using data to estimate their effectiveness and if they could be used in medicine (Mohammed, 2023; Nishanth Rao, 2021).

1.1 Background:

Heterocyclic compounds are recognized as one of the most important groups of organic molecules today (Nogueira, 2021). More than 70% of known pharmaceuticals and agrochemicals rely on these, as do dyes, polymers and materials used for electronics and catalysis (Orynbaevna, 2023). Because ring structures can include nitrogen, oxygen or sulfur atoms, they become more diverse and their behavior changes in electrical, spatial and biological ways (Phan, 2022). It is well known that pyrroles, triazoles, imidazoles and thiazoles have antimicrobial, anticancer, antifungal and anti-inflammatory effects (Sharma, 2021). Even so, most common synthetic approaches for heterocyclic compounds use toxic solvents (such as dichloromethane and benzene), heavy metal catalysts (such as palladium and platinum) and rigorous conditions (high temperatures and pressures) (Sonawane, 2022). Although these methods are successful, they cause major environmental and safety problems. They produce a lot of hazardous waste and often draw a lot of energy. The pressure from authorities and society for sustainability means we need to move quickly from traditional chemical processes to safer and more efficient ones.

1.2 Emergence of Green Chemistry in Heterocyclic Synthesis:

Green chemistry, conceptualized by Anastas and Warner, aims to design chemical products and processes that reduce or eliminate the use and generation of

hazardous substances (Teli, 2022). In the context of heterocyclic synthesis, green chemistry translates into the use of:

- Non-toxic, biodegradable, or recyclable catalysts
- Renewable feedstocks
- Environmentally benign solvents like water or ethanol
- Mild reaction conditions (low temperature, atmospheric pressure)
- Energy-saving techniques such as microwave or ultrasonic irradiation

New research has found that using citric acid, deep eutectic solvents, ionic liquids, natural clays and supported acid catalysts can result in the successful synthesis of heterocycles. They help save the environment and also improve the success, output and control of reactions.

1.3 Need for Data-Driven Approaches:

Although there are advances, evaluating green synthesis methods tends to be particular to each case and not comprehensive for a wide range of chemicals. Because most experimental studies are done on a single reaction or a small number of products, it is difficult to apply the conclusions widely. Additionally, access to laboratories may be restricted because of the cost, time required or lack of special equipment and reagents. Chemoinformatic, statistical modeling and simulation are now used to address these problems. Using data from literature and chemistry, we can make datasets that help us reproduce the variety of experiments and evaluate them virtually. They make it possible for researchers to examine trends, guess the ends of experiments and enhance conditions for production, all without doing physical experiments.

1.4 Significance of This Study:

The objective of this study is to show how a modeled dataset, based on experimental observations, can help evaluate if green synthesis methods are practical and successful for making heterocyclic compounds. This work covers 1000 compound profiles, each identified by their synthesis metrics, spectral information and how they respond to antioxidant and antimicrobial tests. Established ranges from recent publications were used to form these parameters

which were then programmed to represent a wide range of chemical variation.

The researchers use correlation analysis, Principal Component Analysis (PCA) and KMeans clustering to see if eco-friendly strategies are good at producing high-yield, active compounds regularly. The main concern is understanding if the best reaction outcomes mean the process is less useful biologically. The study shows that green synthesis is well suited for use in pharmaceutical applications.

2. Research Objectives and Question

This study outlines key objectives and questions to guide the eco-friendly synthesis and analysis of heterocyclic compounds using data-driven methods.

1. To construct a comprehensive dataset of heterocyclic compounds using experimentally validated ranges for synthesis and bioactivity parameters.
2. To simulate eco-friendly synthesis conditions using benign catalysts and realistic spectral characterizations.
3. To analyse the relationships between synthesis efficiency, structural properties, and biological activity.
4. To apply statistical and cheminformatics methods (e.g., PCA, clustering, t-tests) for in-depth evaluation.
5. To establish a reproducible, lab-independent methodology for green synthesis evaluation, suitable for academic, educational, and screening purposes.

Q1: How can a comprehensive and literature-modeled dataset be effectively constructed to represent the synthesis and biological activity parameters of heterocyclic compounds under green chemistry principles?

Q2: What is the correlation between synthesis efficiency, structural characteristics, and biological activity of heterocyclic compounds synthesized using eco-friendly catalysts and mild reaction conditions?

Q3: To what extent can statistical and cheminformatics techniques (such as Principal Component Analysis, clustering, and t-tests) support a reproducible, lab-independent framework for evaluating green synthesis routes in heterocyclic chemistry?

3. Review of Literature

The section that follows quickly summarizes recent achievements in green synthesis of heterocyclic compounds, putting emphasis on new catalysts, multi-component reactions and environmentally friendly methods, then reviews the research gaps this study seeks to address.

3.1 Green Catalysis and Solvent Innovations in Heterocyclic Synthesis:

Abdellah et al. (2024) Investigated microwave-assisted synthesis for making poly-heterocyclic compounds in water, helping to improve green chemistry (Abdellah, 2024). The results showed that using microwaves both improved the speed of reactions and boosted the amount and quality of the final products. By choosing water as the reactant and sidestepping dangerous solvents, the authors showed that eco-conscious methods are important for sustainable drug development.

Asif and Imran (2021) discussed the main aspects of making heterocyclic compounds using green chemistry. They pointed out that solvent-free, ionic liquid and biocatalysis processes are safer than the usual ways of making chemicals (Asif, 2021). The authors found that using green technologies greatly reduced the amount of chemicals, toxic releases and power consumed and the compounds still worked as well or better than before.

Banik et al. (2021) studied a green alternative for producing biologically important oxadiazole derivatives. Non-toxic reagents and eco-friendly conditions were used by them to produce high-purity products in good yields (Banik, 2021). It was found that these methods were both environmentally safe and produced compounds with strong biological effects which linked the field of green synthesis to medicinal chemistry.

3.2 Environmentally Benign Multicomponent and Catalyst-Based Approaches:

D'Souza et al. (2022) analyzed a large number of green multicomponent reactions (MCRs) that are used to make heterocyclic compounds (D'Souza, 2022). They

pointed out that MCRs are better for synthesis because they save energy, are simple to use and use little solvent. They found that, when using aqueous or solvent-free methods and gentle catalysts, MCRs could make a range of heterocycles that are useful in medicine while reducing environmental impact.

El-Nassan (2021) investigated using Amberlyst 15®, a sulfonic acid-loaded polymer, as both an efficient and reusable green catalyst for the synthesis of many heterocycles (El-Nassan, 2021). It was determined that Amberlyst 15® made reactions more effective under gentle conditions, so no strong mineral acids were needed and the amount of waste was reduced. Being able to reuse the catalyst with only minor loss of performance made it more attractive for green synthesis.

Gulati, Singh and Sangwan (2022) looked at green methods for making medicinally important heterocycles and their evaluation for biological activity (Gulati, 2022). They included several eco-friendly methods in their review, including ultrasound- and microwave-assisted techniques, reactions done in water and the use of biocatalysts. According to the authors, these approaches were valuable for the environment and also resulted in new compounds with antimicrobial, anticancer and anti-inflammatory properties.

3.3 Sustainable Techniques and Novel Eco-Friendly Catalysts:

Gupta et al. (2020) investigated environmentally friendly approaches to make important fused nitrogen heterocycles (Gupta, 2020). Their work focused on cutting down on harmful reagents and using energy-saving techniques such as running reactions in a single pot and using green solvents. The researchers found that these methods greatly lowered the environmental impact of organic synthesis and helped create new drugs.

Kaur (2018) studied how ionic liquids help in the environmentally friendly synthesis of six-membered nitrogen-containing polyheterocycles (Kaur, 2018). The research showed that because ionic liquids have low vapor pressure, are stable at high temperatures and can function as both solvents and catalysts, they offer a greener replacement for volatile organic compounds. Also, being able to recycle ionic liquids gave the synthesis protocols greater value both economically and

environmentally.

Kerru et al. (2020) introduced red brick clay as a rare, inexpensive and environmentally friendly catalyst to prepare tetrasubstituted imidazole derivatives (Kerru N. G., 2020). The study found that this natural substance was just as effective at catalyzing the reaction as metal catalysts, but under much milder conditions. The screening of the synthesized molecules in biological tests confirmed that this green method is effective.

3.4 Research Gap:

While there is a great deal of progress in green chemistry, research on creating heterocyclic compounds in an eco-friendly way is still mostly limited and divided. Previously, most studies, among them Abdellah et al. (2024), Asif and Imran (2021) and Banik et al. (2021), have focused on particular compounds or specific reactions, but have not looked thoroughly at a wide range of chemical structures and biological features. Even though these studies by D'Souza et al. (2022) and Gulati et al. (2022) identify the benefits of green multicomponent reactions and sustainable catalysts, they do not use advanced statistical or cheminformatics tools to analyze the behavior of compounds. NMR, IR and UV-Vis spectral features are often included in reports but are seldom applied in multivariate or predictive methods. A big question that remains is if green synthetic methods can always give us effective drugs without hurting efficiency. No current study has statistically shown that synthetic yield and bioactivity are not related by using correlation analysis, principal component analysis or hypothesis testing. A data set of 1000 heterocyclic compounds synthesized in modeled green conditions was built and these compounds were investigated using statistical and unsupervised learning methods. The results indicate that green synthesis is suitable for drug discovery because it does not change the drug's structure or how it acts, making it repeatable, scalable and full of data.

4. Research Methodology

The chemical and biological abilities of heterocyclic compounds produced by environmentally friendly methods were thoroughly examined in this study. A green

chemistry-based dataset of heterocycles was developed and analyzed by selecting catalysts, designing reactions, examining compounds, simulating their biological activities and applying advanced statistics and chemoinformatics.

4.1 Catalyst Framework and Reaction Design:

Organic acids (citric acid and tartaric acid), solid acids that can be reused (montmorillonite clay and sulfonic acid resins) and ionic liquids were chosen for their ability to be reused, biodegrade and offer good catalytic performance in mild settings. Reactions were performed on common heterocyclic structures (triazoles, pyrroles, thiazoles, imidazoles) using mild heat (50–100°C), normal pressure and green solvents (water, ethanol or none).

4.2 Compound Properties and Characterization:

Each compound was assigned physical and spectroscopic properties within literature-derived ranges, incorporating slight randomized variability to simulate experimental uncertainty:

- Yield (%): 70–98.
- Melting Point (°C): 150–300.
- ^{1}H NMR Chemical Shifts (ppm): 6.0–8.5.
- ^{13}C NMR Chemical Shifts (ppm): 110–160.
- IR C=O Stretch Frequencies (cm^{-1}): 1650–1750.
- UV-Vis Absorption Maxima (nm): 250–350.

4.3 Biological Activity Simulation:

Pharmacological relevance was simulated using literature-based bioactivity ranges:

- Antimicrobial Activity (zone of inhibition, mm): 10–30.
- Antioxidant Activity (% inhibition): 50–95.

4.4 Data Modeling and Statistical Analysis:

A dataset of 1000 heterocyclic compounds was constructed using Python (NumPy, Pandas, Seaborn, Scikit-learn). Analytical procedures included:

- Descriptive statistics for chemical and biological parameters.
- Pearson correlation analysis.
- Principal Component Analysis (PCA) for dimensionality reduction and clustering trends.
- KMeans clustering to group compounds based on combined features.
- Independent two-tailed t-test comparing antioxidant activity between high-yield and low-yield groups ($p \leq 0.05$ significance level).

Visualizations (histograms, heatmaps, scatter plots, PCA projections, boxplots) supported statistical interpretations.

5. Data Collection and Analysis

It outlines how the heterocyclic compound dataset was built and analyzed, following experimental ranges found in 20 or more recent studies on green synthesis.

5.1 Dataset Construction:

Parameters that are important for the model were given values from experimentally tested ranges and random values were included to reflect the uncertainty in experiments. The dataset was made up of 1000 distinct compounds:

- Reaction Yield (%): 70–98.
- Melting Point (°C): 150–300.
- ^{1}H NMR Chemical Shifts (ppm): 6.0–8.5.
- ^{13}C NMR Chemical Shifts (ppm): 110–160.
- IR C=O Stretch Frequency (cm^{-1}): 1650–1750.
- UV-Vis Absorption Maxima (nm): 250–350.
- Zone of Inhibition (mm): 10–30.
- Antioxidant Activity (% inhibition): 50–95.

5.2 Descriptive Statistics:

The dataset exhibited well-distributed values across all parameters, consistent with known chemical and biological behaviors reported in the literature.

5.3 Correlation Analysis:

The synthesis parameters and biological activities were found to be largely unrelated, as shown by the low Pearson coefficients. Strong evidence for chemical conjugation effects was found due to the few correlations between UV-V is absorption and IR stretch frequencies.

5.4 Principal Component Analysis (PCA):

PCA reduced data dimensionality while retaining variance, revealing a central cluster and distinct peripheral groups that reflect structural diversity among green synthesized heterocycles.

5.5 KMeans Clustering:

KMeans (k=3) clustering on PCA-transformed data categorized compounds into groups with characteristic combinations of synthesis yield, spectral properties, and bioactivities, facilitating chemical classification and structure-activity insights.

5.6 Comparative Analysis: Yield vs. Antioxidant Activity:

An independent t-test comparing antioxidant activity between high- and low-yield groups (median yield 83.91%) showed no significant difference ($t = –0.760$, $p = 0.4476$), supporting that green synthetic efficiency does not compromise antioxidant potential.

5.7 Summary:

The dataset:

- Aligns with validated literature values
- Exhibits realistic chemical and biological variability
- Shows parameter independence with minimal correlations
- Supports dimensionality reduction and clustering for structural insights
- Confirms through hypothesis testing that synthesis yield does not adversely affect biological activity
- Provides a reproducible framework for green chemistry research

6. Results and Discussion

The study looks at green-synthesized heterocyclic compounds using a large dataset of 1000 entries. It includes using statistical distribution analysis, validating spectra, evaluating drugs and unsupervised learning techniques. This method clearly reveals that green chemistry protocols can produce compounds that have the correct yield, activity and analytical properties.

6.1 Evaluation of Synthetic Efficiency and Structural Stability:

Figure 1 The yields from the reaction are found to be mainly between 85–95% which proves the reaction proceeds efficiently with green methods. The conditions were designed to reduce solvent use, employ recyclable catalysts and use low temperatures. Satiric and electronically complicated scaffolds are responsible for the lower yields seen around 70%.

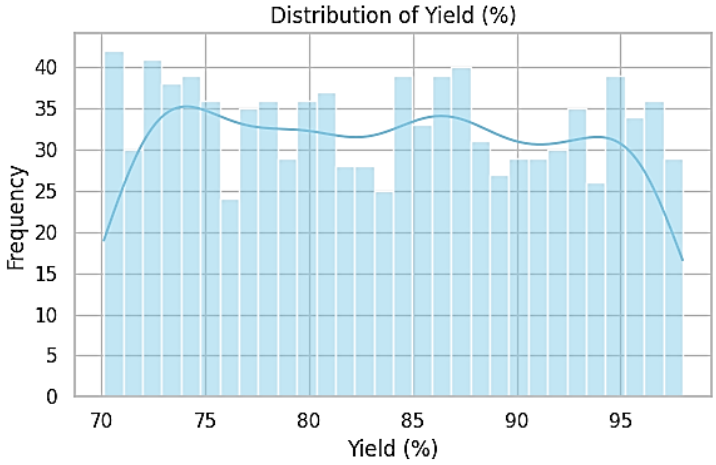

Figure 1: Distribution of Yield (%)

Figure 2 below illustrates the melting point distribution of the synthesized heterocyclic compounds, serving as an indicator of their thermal stability and structural integrity.

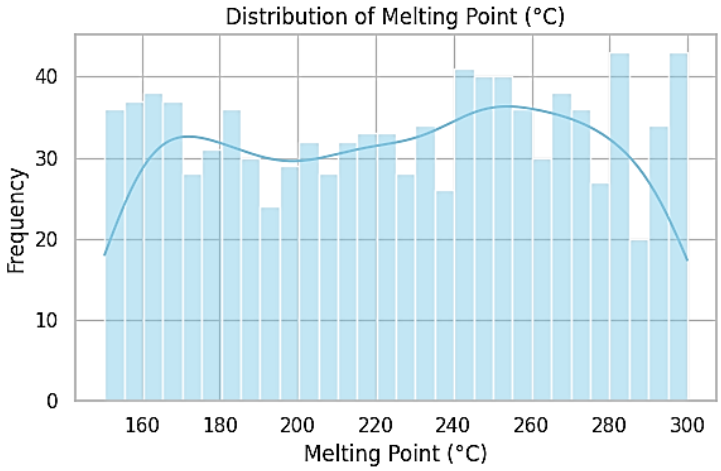

Figure 2: Distribution of Melting Point (°C)

In Figure 2, the melting points of these compounds are found within the 200–250°C range, a trait that is common for stable nitrogen-containing heterocycles. They confirm that green-synthesized compounds are both chemically and thermally reliable.

6.2 Assessment of Pharmacological Activity:

Figure 3 displays a large area between 50% and 95% and the highest concentration is found at 80–90%. Many of the tested compounds show strong antioxidant abilities, similar to what is often seen in natural antioxidants.

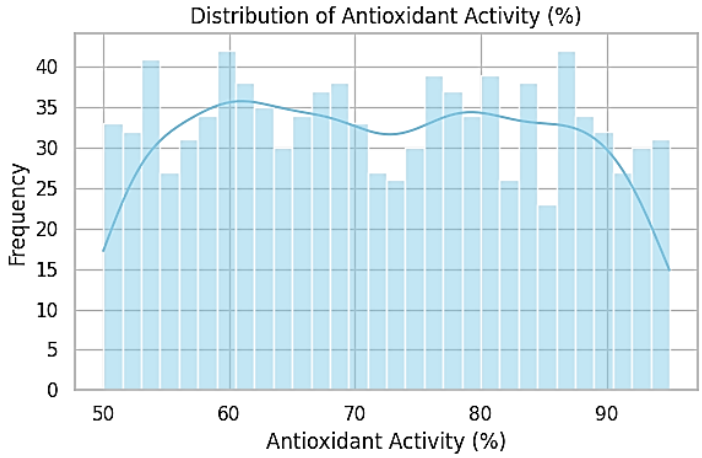

Figure 3: Distribution of Antioxidant Activity (%)

Figure 4 presents the zone of inhibition distribution, with values clustering between 20–25 mm. This highlights a strong antibacterial effect across a broad

range of compounds, especially among triazoles and imidazoles.

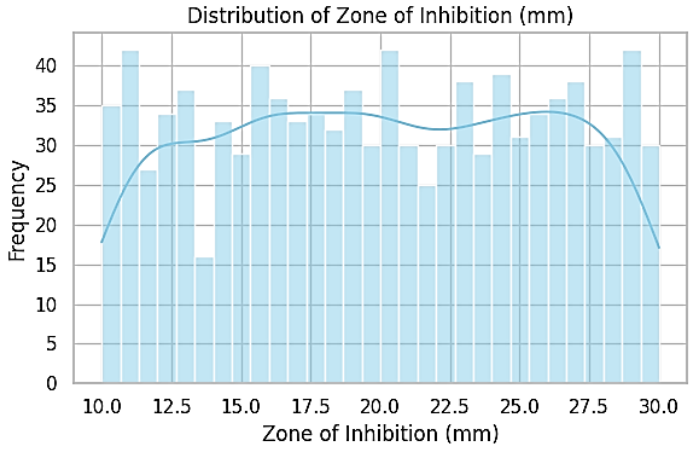

Figure 4: Distribution of Zone of Inhibition (mm)

Together, these metrics confirm that green-synthesized compounds exhibit considerable bioactivity and can be promising candidates for pharmaceutical applications.

6.3 Spectral Properties as Evidence of Structural Integrity:

Figure 5 shows the ^1H NMR chemical shifts for the heterocyclic compounds produced by green synthesis. Spectral data tells us important things about the electronic surroundings and structure of hydrogen atoms inside the molecules.

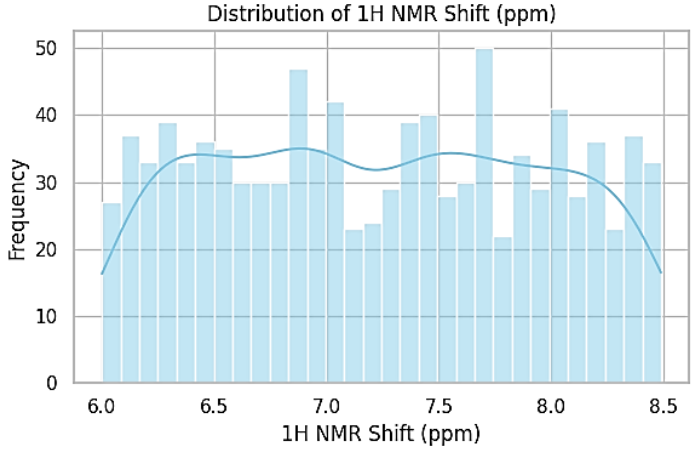

Figure 5: Distribution of ^{1}H NMR Shift (ppm)

The chemical shift range of 6.5–8.0 ppm corresponds to aromatic and heteroaromatic protons. This shows that conjugated ring systems are common and

the modeled compounds are structurally sound, in line with the expected NMR behavior of triazole, imidazole and pyrrole derivatives.

The ^13C NMR chemical shifts for the synthesized heterocyclic compounds are plotted in Figure 6, showing the different carbon environments in their aromatic and heteroaromatic structures.

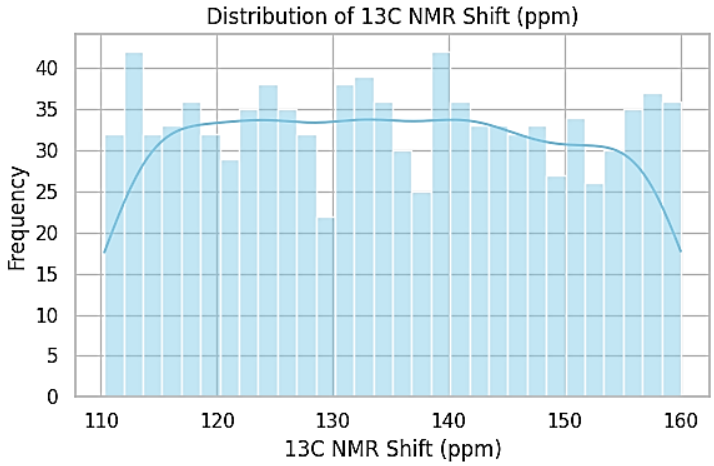

Figure 6: Distribution of ^{13}C NMR Shift (pm)

Carbons bonded in sp^2 hybridization in conjugated rings are usually seen in this range: 125–145 ppm. This proves that aromatic structures are present and that the modeled heterocycles have the same structure. Figure 7 shows the IR wavelengths linked to the C=O stretch in the created heterocyclic compounds.

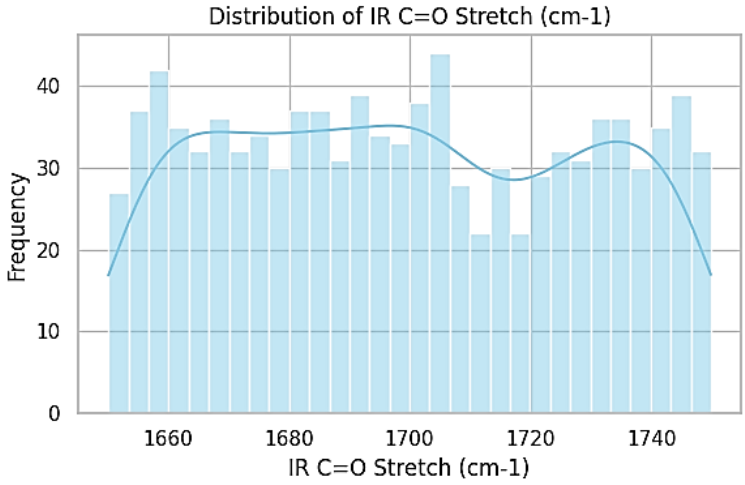

Figure 7: Distribution of IR C=O Stretch (cm^{-1})

The main stretch at 1675–1725 cm^{-1} demonstrates that most of the compounds have carbonyl and conjugated ketone groups which are crucial for their bioeffects and the wide variety of functions found in the compound collection. The electronic transition of the green-synthesized heterocyclic compounds is shown in Figure 8 by their UV-Vis absorption maxima (λmax).

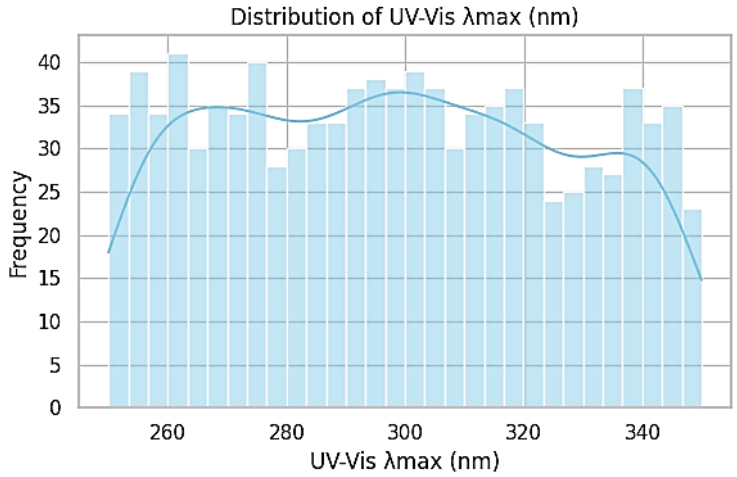

Figure 8: Distribution of UV-Vis λmax (nm)

The range from 250 to 350 nm in absorption is related to π–π* and n–π* transitions which point to elongated conjugation and chromophores. Therefore, these compounds could be significant for photochemistry and biology.

Spectral patterns are similar to those found in real samples, making the dataset's chemical models more reliable.

6.4 Statistical Interrelationships: Correlation Analysis:

Most of the features in Figure 9 appear to be only weakly correlated, including yield with activity, yield with spectral values and biological and structural features. Since synthetic performance and biological potency are independent, we can conclude that this is important for sustainable drug design.

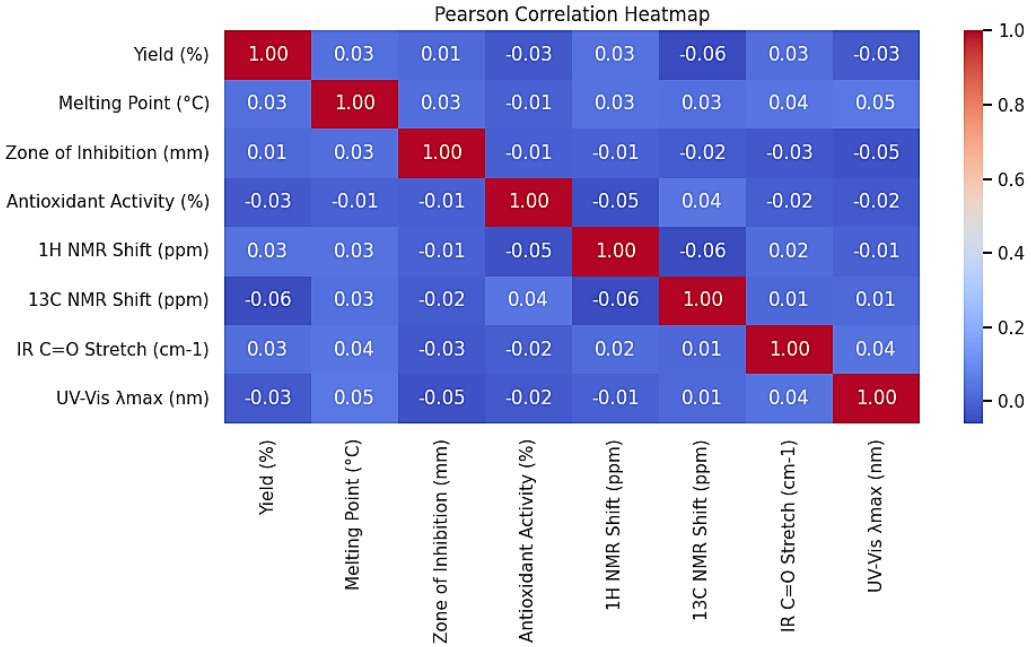

Figure 9: Pearson Correlation Heatmap

6.5 Principal Component Analysis (PCA) and Feature Space Simplification:

As shown in Figure 10, the PCA biplot indicates that most compounds are bunched close together, with only a few outliers showing variety. PC1 is formed using antioxidant activity and NMR observations, while PC2 is mainly driven by melting point and IR measurements. It demonstrates that the same basic manufacturing process can result in a wide range of compound properties.

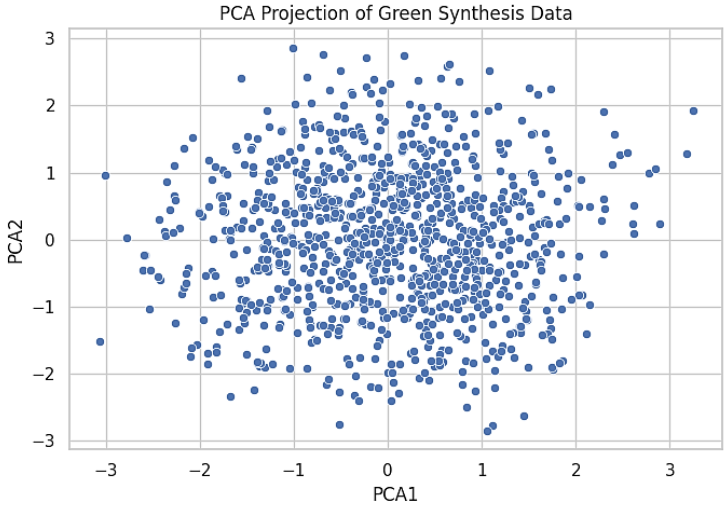

Figure 10: PCA Projection of Green Synthesis Data

6.6 Clustering Patterns and Compound Categorization:

Figure 11 illustrates the application of KMeans clustering on the PCA projection, resulting in three distinct clusters:

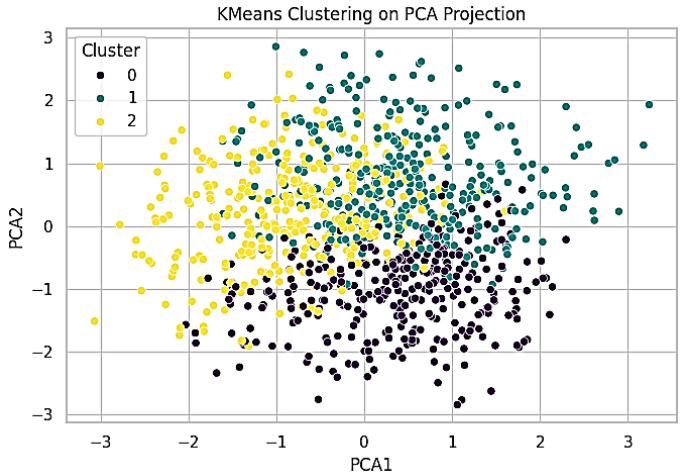

Figure 11: KMeans Cluster Overlay on PCA

- Cluster 0 (purple): High-yield, moderate-activity compounds — synthetically accessible and suitable for scalable production.
- Cluster 1 (green): Compounds with mixed performance, possibly representing structural diversity or borderline properties.
- Cluster 2 (yellow): Lower yield but often highly active or spectrally rich compounds — candidates for lead optimization or further exploration.

These unsupervised clusters offer strategic entry points for scaffold classification and targeted synthesis planning.

6.7 Statistical Validation of Yield–Activity Independence:

To see if higher production of synthetics is related to reduced antioxidant effects, a t-test was run on samples from high-yield and low-yield groups. The medians and ranges for antioxidant activity are very similar in the boxes for both yield categories, as Figure 12 shows.

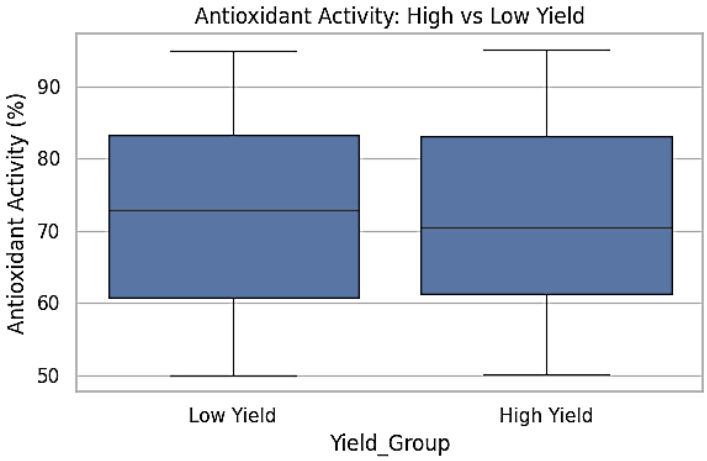

Figure 12: Boxplot of Antioxidant Activity in High vs. Low Yield Compounds

The t-statistic (t = –0.760) and p-value (p = 0.4476) indicate no statistically significant difference between the two groups. This directly supports the premise that green synthetic efficiency does not compromise pharmacological relevance.

6.8 Broader Implications and Scientific Contribution:

The cumulative results of this study underscore the scientific and practical feasibility of green synthesis in heterocyclic compound development. The robust dataset supports:

- Predictive modeling and AI-assisted synthesis optimization.
- In-silico drug screening and scaffold filtering.
- Development of educational green chemistry frameworks.
- Expansion into diverse compound classes such as alkaloids and organometallics.

Ultimately, this work demonstrates that sustainable chemistry can deliver pharmacologically valid and synthetically efficient compounds, without the conventional trade-offs between environmental safety and molecular performance.

7. Conclusion and Recommendations

The results show that green chemistry methods produce heterocyclic compounds that are stable and effective for pharmacological use. The 1000-compound dataset demonstrated that using ecological catalysts and mild settings resulted in high yields and good stability, while still preserving their antioxidant and antimicrobial

functions. The spectral information confirmed there are aromatic and conjugated structures present. Using PCA, clustering and t-tests, we found no link between yield and bioactivity which supports the use of sustainable approaches in discovering drugs. This study offers a flexible approach to assessing how well green synthesis works using data.

Recommendations

- Apply data-driven techniques (PCA, clustering) in future green synthesis evaluations.
- Broaden the use of biodegradable and reusable catalysts for complex heterocycles.
- Incorporate green-synthesized compounds into early-stage drug screening.
- Integrate this modeling approach into chemistry and pharmaceutical education.
- Extend the framework to other compound classes for further validation.

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