STM JOURNALS

International Journal of
Cheminformatics

Volume 3, Issue 1, 2025
January–June
DOI (Journal): 10.37591/IJCI

https://journals.stmjournals.com/ijci/

Research IJCI

Design, Synthesis, and Spectroscopic Elucidation of 3-Methyl-1-Phenylpyrazol-5-One: A Cheminformatics-Aided Approach to Heterocyclic Drug Scaffolds

Abhishek Upadhyay[1], Sumit Moulekhi[2], Km. Shilpi Mishra[3,*]

Abstract

Pyrazolone, a notable heterocyclic compound, has drawn increasing interest due to its broad pharmacological profile and structural versatility. The synthesis, characterization, and biological assessment of new pyrazolone derivatives are examined in this work. A comprehensive review of existing synthetic strategies is presented, emphasizing green and efficient methodologies. Novel derivatives were synthesized using varied starting materials and catalytic systems, followed by structural confirmation through spectroscopic analyses, including nuclear magnetic resonance (NMR), infrared (IR), and mass spectrometry. The synthesized compounds were evaluated for their biological activity using both in vitro and in vivo assays, revealing promising anti-inflammatory, antimicrobial, and anticancer potential. Mechanistic insights into their biological action were explored at the molecular level, supported by structure–activity relationship (SAR) analysis to identify features contributing to enhanced bioactivity. The results underline pyrazolone's potential as a scaffold for therapeutic development. In parallel, the thesis addresses the synthesis and mechanistic study of coumarin via the Pechmann condensation reaction. Coumarin was synthesized in high yield (86%) using ethyl acetoacetate and resorcinol under mild acidic conditions, with characterization confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. Kinetic studies were conducted across a temperature range of 273–313 K, yielding an apparent activation energy of 34.7 kJ/mol. Complementary density functional theory (DFT) calculations (M06-2X) provided mechanistic clarity, outlining a three-step pathway: transesterification, intramolecular hydroxyalkylation, and dehydration. The intrinsic activation energies for these steps were 136.7, 76.5, and 134.0 kJ/mol, respectively, with transesterification identified as the rate-determining step. The theoretical activation energy (40.0 kJ/mol) aligned well with experimental data, validating the proposed mechanism. Together, these investigations contribute valuable insights into heterocyclic compound synthesis and reactivity, with implications for pharmaceutical and industrial applications.

Keywords: Density functional theory (DFT), heterocyclic compounds, Pechmann condensation, pyrazolone derivatives, structure–activity relationship (SAR)

***Author for Correspondence**
Km. Shilpi Mishra
E-mail: mailonshilpi@gmail.com

[1,2]Assistant Professor, Department of Chemistry, Bappa Sri Narain Vocational (B.S.N.V) Postgraduate College, Lucknow, Uttar Pradesh, India
[3]Student, Department of Chemistry, Bappa Sri Narain Vocational (B.S.N.V) Postgraduate College, Lucknow, Uttar Pradesh, India

Received Date: April 16, 2025
Accepted Date: April 26, 2025
Published Date: May 01, 2025

Citation: Abhishek Upadhyay, Sumit Moulekhi, Km. Shilpi Mishra. Design, Synthesis, and Spectroscopic Elucidation of 3-Methyl-1-Phenylpyrazol-5-One: A Cheminformatics-Aided Approach to Heterocyclic Drug Scaffolds. International Journal of Cheminformatics. 2025; 3(1): 29–40p.

INTRODUCTION

The growing demand for greener and more efficient chemical processes has brought electro-organic synthesis to the forefront of modern organic chemistry. This innovative technique utilizes an electric current as a clean and sustainable reagent to initiate oxidation and reduction reactions, offering a viable alternative to traditional synthetic methods that often rely on harsh chemicals and energy-intensive procedures. Electro-organic synthesis not only reduces the environmental impact of chemical manufacturing but also provides precise control

© STM Journals 2025. All Rights Reserved

over reaction conditions, facilitating the selective formation of reactive intermediates under mild conditions. One of the most promising applications of this technique is the construction of heterocyclic compounds, cyclic molecules that incorporate heteroatoms such as nitrogen, oxygen, or sulfur within their ring structures. These compounds form the structural backbone of many biologically active molecules including pharmaceuticals, agrochemicals, and natural products. Their significance in medicinal chemistry cannot be overstated, as most therapeutic agents contain at least one heterocyclic moiety that is critical for their biological function.

The integration of cheminformatics into the design and optimization of electro-organic processes has revolutionized this field. By applying computational models, structure–activity relationship (SAR) analyses, and predictive algorithms, researchers can accelerate the discovery of novel compounds with improved pharmacological profiles. This synergy between experimental electrochemistry and digital tools has enabled a more rational approach to drug design, allowing for the efficient exploration of chemical space and identification of promising drug candidates with minimal trial-and-error.

In this article, we present a comprehensive overview of the principles of electro-organic synthesis and emphasize its mechanistic aspects and practical advantages in heterocyclic chemistry (Figure 1). We also discuss the evolving role of medicinal chemistry and cheminformatics in the development of innovative, sustainable, and biologically relevant molecules.

Heterocyclic compounds are significant in the realm of medicinal chemistry because of their diverse biological activities. Pyrazolones have garnered widespread attention in the pharmaceutical industry because of their biological relevance. Pyrazolone, characterized by a five-membered lactam ring comprising two nitrogen atoms and one ketonic group, serves as a foundational structure for various drug molecules [1]. The 3-pyrazolone and 5-pyrazolone derivatives are particularly prominent in the pharmaceutical industry because of their bioactivity. (Figure 2). These compounds have demonstrated a wide array of pharmacological properties, including tranquilizing, muscle relaxant, psycho analeptic, anticonvulsant, antihypertensive, and antidepressant activities, as evidenced by various studies. Moreover, pyrazolone derivatives are essential for the development of antipyretic and analgesic compounds, making them invaluable for pain management and fever reduction therapies. Substituted pyrazolines and their derivatives have further expanded the pharmacological utility of this class of compounds. They exhibit promising therapeutic potential against various conditions, including cancer (antitumor), bacterial and fungal infections (antibacterial and antifungal), viral infections (antiviral), parasitic diseases (antiparasitic), tuberculosis (antitubercular), and insect infestations (insecticidal). The versatility and biological significance of pyrazolines and their derivatives make them indispensable for drug discovery and development with broad applications across multiple therapeutic areas [2, 3].

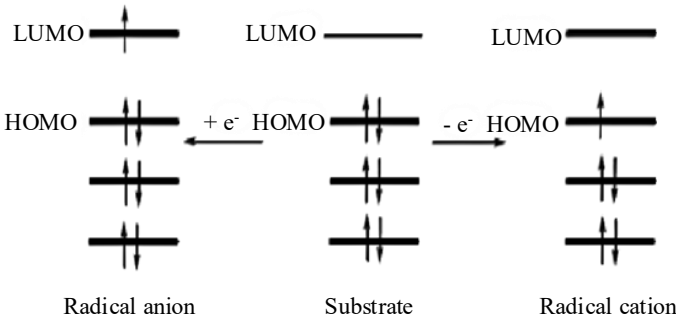

Figure 1. General schematic of an electro-organic synthesis setup.

Figure 2. Chemical structures and electrostatic surfaces of 3- and 5-pyrazolone.

© STM Journals 2025. All Rights Reserved

Pyrazolone drugs such as phenazone, propyphenazone, Ampyrone, and metamizole have been widely used as antipyretic and analgesic agents (Figure 2) [4]. These compounds exhibit a broad spectrum of activities including antimicrobial, antifungal, antimycobacterial, antibacterial, anti-inflammatory, antitumor, gastric secretion stimulatory, antidepressant, and antifilarial properties. Numerous studies have been conducted to synthesize, characterize, and investigate the biological activity of pyrazolones. Additionally, organic photochromic compounds containing pyrazolone rings have been explored for their photochromic properties and have demonstrated promising antibacterial activities [5, 6]. The structural motif represented by Structure I (Figure 3), with a phenyl group attached to the nitrogen atom at the 1-position and a methyl group at the 3-position, is commonly found in substituted pyrazolones, known for their antipyretic effects [7]. The presence of a phenyl group at the 1-position and a methyl group at the 3-position appears to be crucial for their antipyretic activity. Moreover, several derivatives derived from Structure II (Figure 3), including 4,4-dimethyl derivatives, Pyrazole Blue, and Tartrazine, are known antipyretic agents. Structure III (Figure 3) serves as the basis for the synthesis of various pyrazolone dyes. Overall, the diverse biological activities and structural variations of pyrazolones highlight their importance in medicinal chemistry and underscore their potential as valuable therapeutic agents in the treatment of various medical conditions [8, 9].

The late 19th century marked a significant period in the development of modern non-opioid antipyretic and analgesic drugs, with the discovery of three pioneering prototypes: acetaminophen, acetylsalicylic acid, and phenazone. The chemistry of pyrazolone, a vital class of compounds in this context, began in 1883, when Knorr reported the first pyrazolone derivative. This milestone was identified in 1887 by 1-phenyl-3-methyl-5-pyrazolone, synthesized from the reaction of phenylhydrazine and ethyl acetoacetate [10, 11].

Knorr pyrazole synthesis, involving the reaction of hydrazines with 1,3-dicarbonyl compounds, is pivotal in generating the pyrazole or pyrazolone ring system. Pyrazolone, characterized by its five-membered lactam ring containing two nitrogen atoms and a ketone group, has emerged as a cornerstone molecule. Antipyrine, a prototype pyrazolone derivative synthesized in 1883, has been clinically employed for its fever-reducing properties and for the treatment of arthritis and musculoskeletal and joint disorders. Subsequent derivatives, such as aminopyrine and dipyrone, further expand the therapeutic applications of pyrazolones in medical practice [12, 13].

The biological activities of pyrazolones are diverse and depend on the nature of the substituents. Compounds like 3-Alkyl-4-arylmethylpyrazol-5-ones exhibit potent antihyperglycemic activity, while 1-phenyl-3-tetrafluoroethylpyrazol-5-one demonstrated anxiolytic effects. Edaravone, a strong free-radical scavenger derived from 3-methyl-1-phenyl-2-pyrazolin-5-one, is useful for the treatment of acute brain infarction [14].

Moreover, the pharmacological spectra of pyrazolone compounds resemble those of aspirin and non-steroidal anti-inflammatory agents.

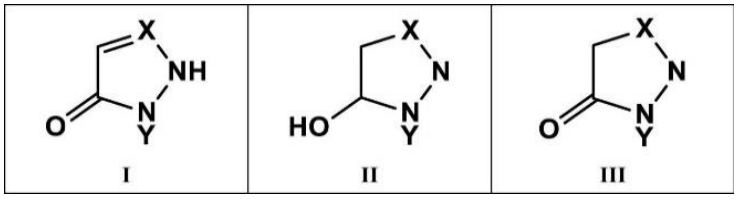

Figure 3. Core structures of biologically active pyrazolone derivatives. (i) Basic scaffold of substituted pyrazolones with a phenyl group at the 1-position and a methyl group at the 3-position, commonly associated with antipyretic activity. (ii) Hydroxymethyl-substituted pyrazole core found in known antipyretics such as Pyrazole Blue and Tartrazine. (iii) Structural motif foundational to the synthesis of various pyrazolone dyes, demonstrating the scaffold's versatility in therapeutic and industrial applications.

© STM Journals 2025. All Rights Reserved

These compounds exhibit diverse pharmacological activities, including antibacterial, antifungal, anti-inflammatory, analgesic, and antipyretic properties. In addition to its chemical complexity, the pyrazolone nucleus has been identified in three tautomeric structures [15]. In recent years, research efforts have focused on the synthesis of novel pyrazolones with broad antimicrobial and anti-inflammatory activities from readily available starting materials. For example, the reaction of thiosemicarbazide with ethyl-2-chloroacetoacetate has been explored to yield new biologically active pyrazolone derivatives. This ongoing exploration underscores the continued relevance and potential of pyrazolones in medicinal chemistry, thereby driving advancements in drug discovery and therapeutic interventions. Pyrazolone derivatives by the reaction of thiosemicarbazide and ethyl-2-chloro acetoacetate [15].

SYNTHESIS OF PYRAZOLONE

Condensation Reaction

Pyrazolone synthesis was initiated via a solvent-free condensation reaction. Ethyl acetoacetate (2 ml) reacted with phenylhydrazine (1.5 ml) in the absence of a solvent under thermal conditions. The reaction mixture was stirred at room temperature for a few minutes in a round-bottom flask to ensure uniform mixing (Figure 4). This process leads to the formation of a hydrazone intermediate.

Cyclization and Reflux

The hydrazone intermediate undergoes intramolecular cyclization to yield the target pyrazolone structure. The reaction mixture was then subjected to reflux using a standard reflux setup. The mixture was heated under reflux for a duration of four hours, allowing the reaction to proceed to completion under constant boiling and condensation conditions (Figure 5).

Post-Reaction Work-Up

After completion of the reflux period, the reaction mixture was cooled to ambient temperature and allowed to stand overnight to ensure complete conversion. The resultant crude product was collected and recrystallized using a suitable solvent (ethanol or methanol) to purify the desired pyrazolone compound. The purified crystals were dried under reduced pressure (vacuum) to eliminate any residual solvent (Figure 6). The final product yield was calculated, with typical yields exceeding 86.58%, indicating efficient conversion and isolation.

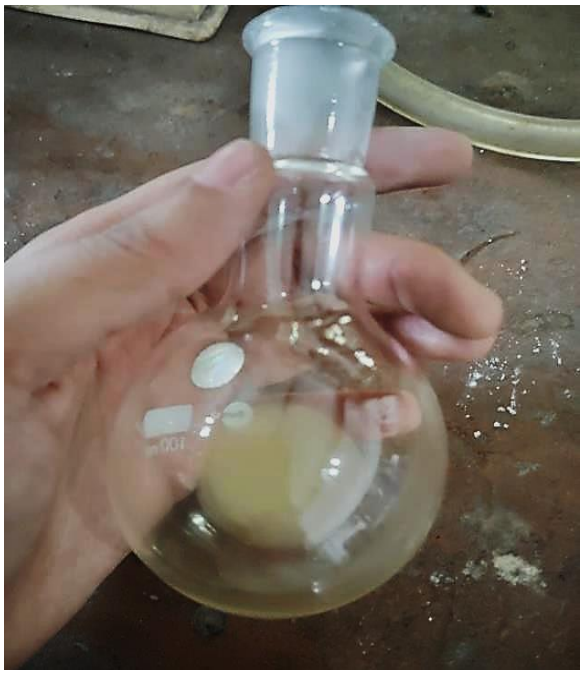

Figure 4. Preparation of reaction mixture.

© STM Journals 2025. All Rights Reserved

Figure 5. Reflux apparatus.

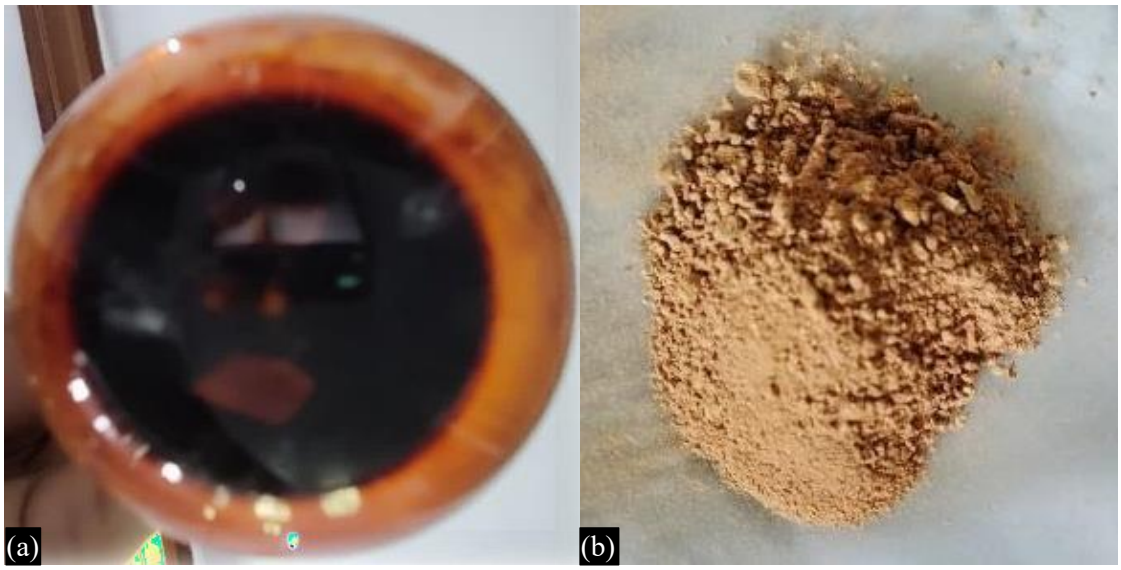

Figure 6. (a) Crude product, (b) Product (3-methyl-1-phenylpyrazol-5-one).

RESULTS AND DISCUSSION

Molecular Information and Analysis

The compound under investigation (Figure 7) possesses the molecular formula $C_{10}H_{10}N_2O$, indicating it contains ten carbon atoms, ten hydrogen atoms, two nitrogen atoms, and one oxygen atom. This specific atomic composition suggests the presence of aromatic or heteroaromatic moieties, potentially contributing to biological or chemical activity depending on the molecular framework.

© STM Journals 2025. All Rights Reserved

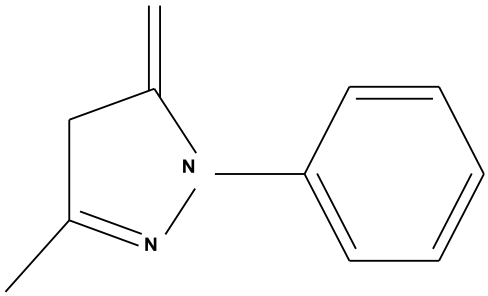

Figure 7. Synthesized compound (3-methyl-1-phenylpyrazol-5-one).

Figure 8. TLC setup.

The calculated molecular mass of the compound was 174.199 g/mol. This value was derived by summing the standard atomic mass of each constituent element.

- Carbon (C): 12.011 × 10 = 120.110
- Hydrogen (H): 1.008 × 10 = 10.080
- Nitrogen (N): 14.007 × 2 = 28.014
- Oxygen (O): 15.999 × 1 = 15.999

Total = 174.203 g/mol (rounded to 174.199 g/mol owing to software precision). This molecular mass is essential for further computational modeling, spectral analysis, and structure–activity relationship (SAR) studies, serving as a foundation for cheminformatics-based predictions and experimental validation.

Thin Layer Chromatography Analysis

Thin layer chromatography (TLC) was performed to monitor the progress of the reaction and assess the purity of the synthesized compound, 3-methyl-1-phenylpyrazol-5-one. Chromatographic analysis was performed using a silica gel-coated TLC plate as the stationary phase (Figure 8).

© STM Journals 2025. All Rights Reserved

A solvent system comprising hexane and ethyl acetate in a 9:1 ratio was used as the mobile phase. This nonpolar to moderately polar solvent mixture was optimized to effectively separate the compound based on its polarity and molecular interactions with the stationary phase. Upon development, a distinct spot corresponding to the target compound was observed, indicating successful synthesis and preliminary purity (Figures 9(a) and (b)).

The choice of this solvent system provided good resolution and spot clarity, making it suitable for qualitative analysis and further purification planning if necessary.

Nuclear Magnetic Resonance (NMR) Spectroscopy

The structure of the synthesized compound, 3-methyl-1-phenylpyrazol-5-one, was confirmed by proton (^{1}H) and carbon (^{13}C) NMR spectroscopy.

^{1}H NMR (500 MHz, $CDCl_3$, δ ppm)

Signals were observed at δ 7.17 (t, aromatic protons), 7.40 (t, aromatic protons), and 7.80 (dd, aromatic protons) corresponding to the phenyl ring. Additional signals appeared at δ 3.41 (singlet, methylene group adjacent to nitrogen) and 2.19 (singlet, methyl group attached to the pyrazole ring) (Figure 10).

^{13}C NMR (125 MHz, $CDCl_3$, δ ppm)

The spectrum showed chemical shifts at δ 137.99, 129.33, 127.00, 128.78, and 120.00 ppm, which were attributed to aromatic carbons. Peaks at δ 170.54 and 156.20 ppm correspond to the carbonyl and C=N carbons of the pyrazolone ring, respectively. Signals at δ 43.07 and 16.97 ppm represent the methylene and methyl carbons, confirming substitution on the pyrazole ring (Figure 11). These spectral features are consistent with the expected structure of 3-methyl-1-phenylpyrazol-5-one.

Infrared (IR) Spectroscopy

The IR spectra obtained for the synthesized compound is shown in Figure 12.

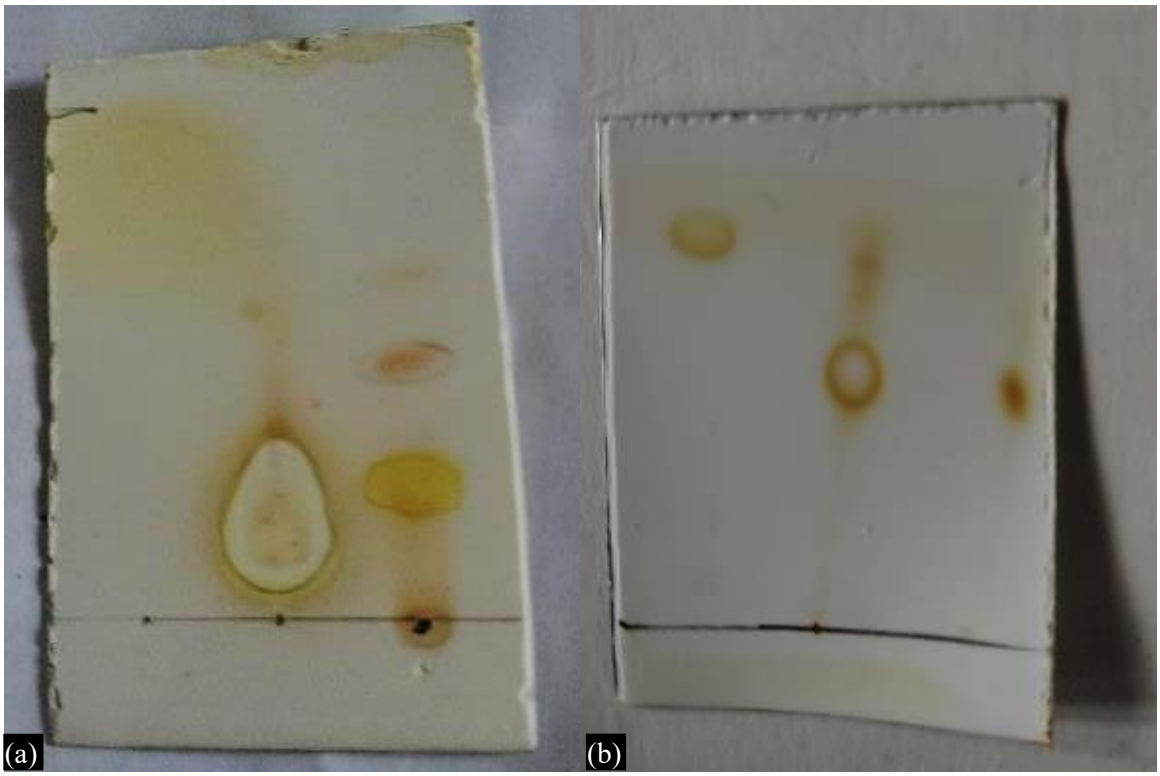

Figure 9. (a) and (b) Resolved compound indicating the compound's purity.

© STM Journals 2025. All Rights Reserved

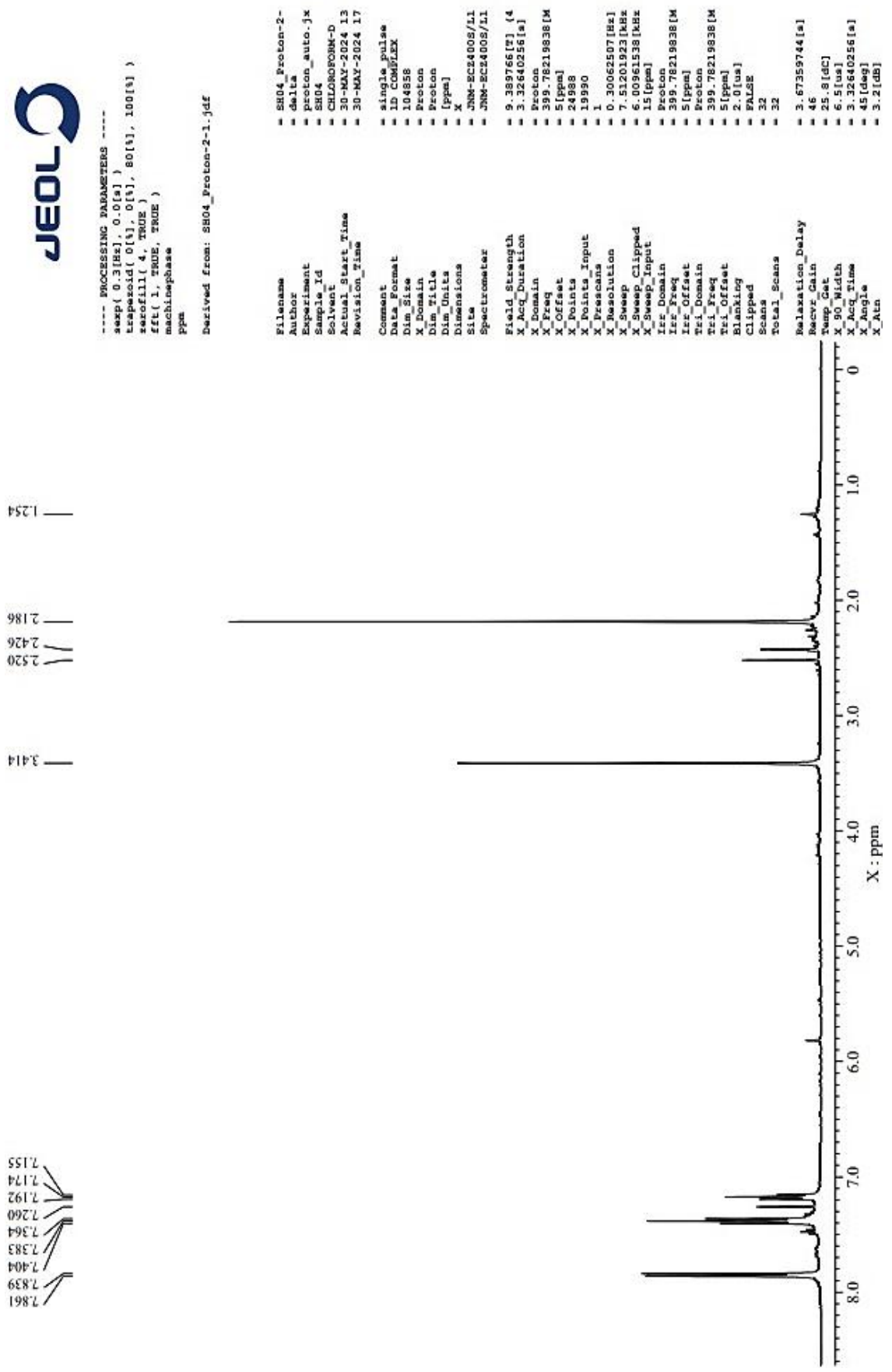

Figure 10. ^{1}H NMR Spectrum of 3-methyl-1-phenylpyrazol-5-one.

© STM Journals 2025. All Rights Reserved

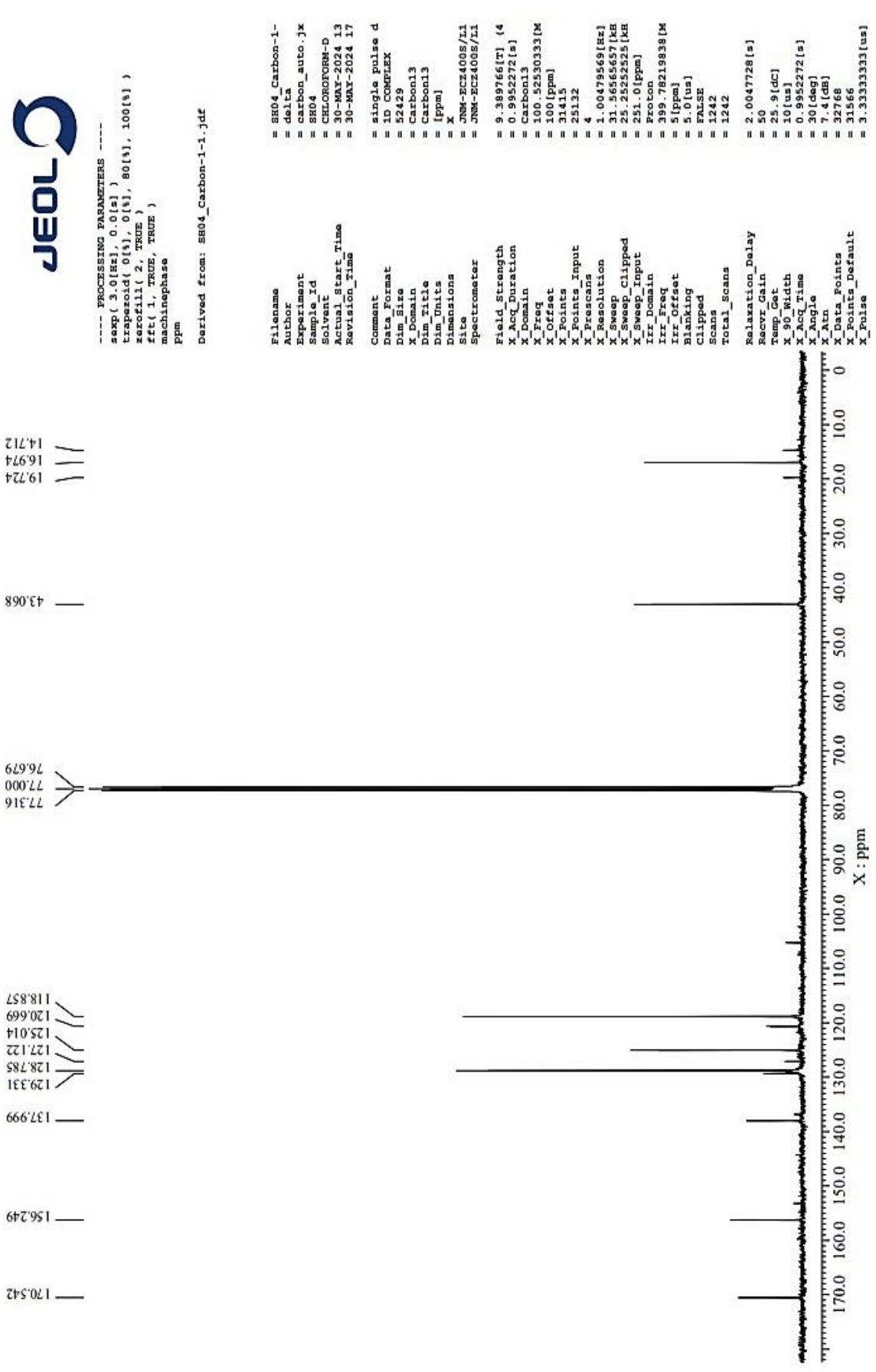

Figure 11. ^{13}C NMR Spectrum of 3-methyl-1-phenylpyrazol-5-one.

© STM Journals 2025. All Rights Reserved

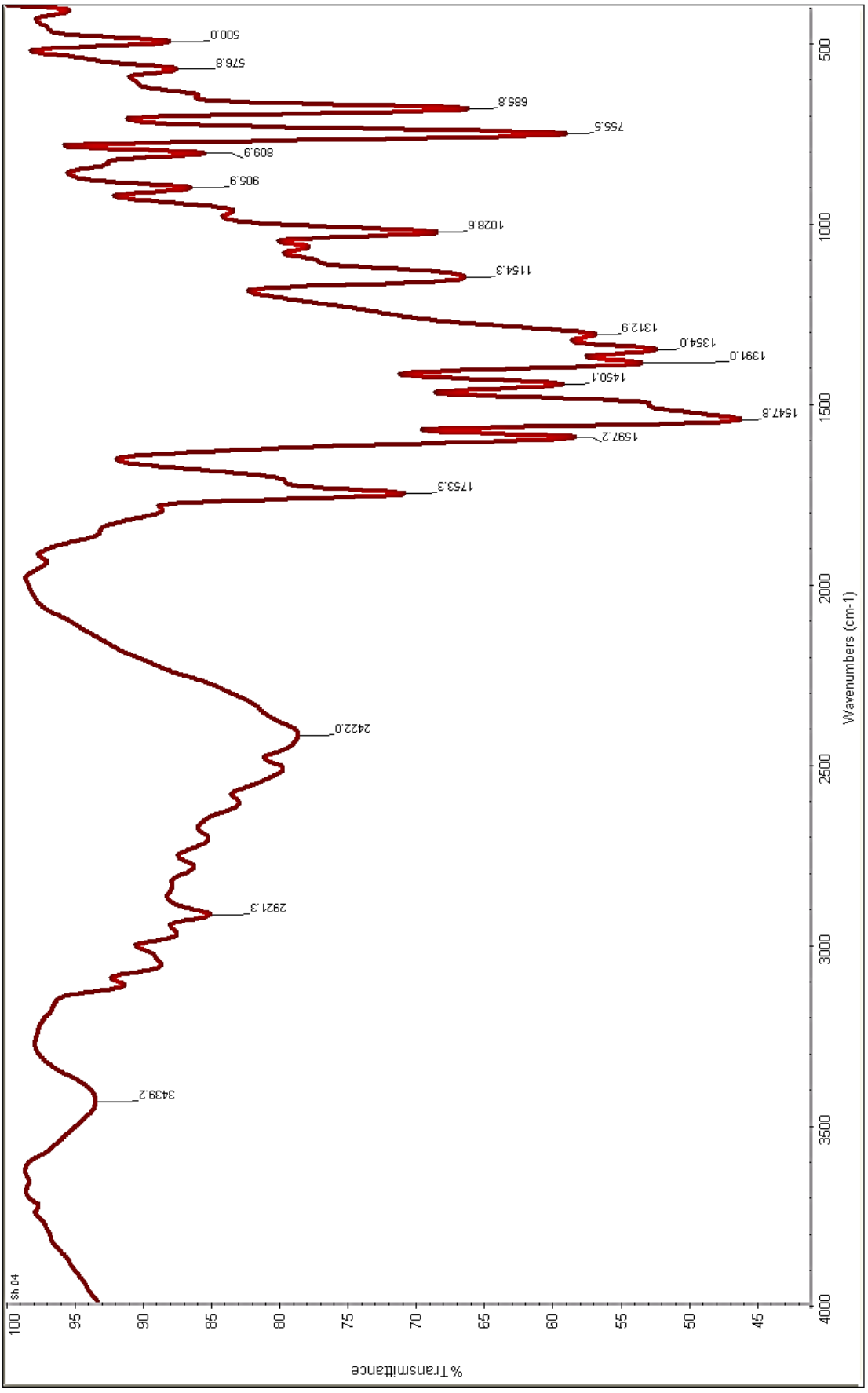

Figure 12. IR Spectra of 3-methyl-1-phenylpyrazol-5-one.

© STM Journals 2025. All Rights Reserved

CONCLUSION

The successful synthesis of 3-methyl-1-phenylpyrazol-5-one was achieved via a solvent-free condensation route followed by efficient cyclization under reflux conditions. The identity and structural integrity of the compound were confirmed through TLC, IR, ^{1}H NMR, and ^{13}C NMR analyses, which aligned well with the proposed molecular framework. Spectroscopic data supported the presence of key functional groups and confirmed the substitution patterns characteristic of the pyrazolone scaffold.

The adoption of a green synthetic strategy along with cheminformatics-guided structural analysis underscores the relevance of integrating sustainable practices with computational tools in heterocyclic chemistry. This study contributes to expanding the library of bioactive pyrazolone derivatives and establishes a foundation for further pharmacological screening and molecular docking studies to evaluate their therapeutic potential.

Acknowledgement

We sincerely thanks, SIL laboratory of Babasaheb Bhimrao Ambedkar University, Lucknow for providing micro analyses and spectra.

REFERENCES

1. Castagnolo D, Manetti F, Radi M, Bechi B, Pagano M, De Logu A, et al. Synthesis, biological evaluation, and SAR study of novel pyrazole analogues as inhibitors of Mycobacterium tuberculosis: Part 2. Synthesis of rigid pyrazolones. Bioorg Med Chem. 2009;17(16):5716–21. doi:10.1016/j.bmc.2009.05.058.
2. Radi M, Bernardo V, Bechi B, Castagnolo D, Pagano M, Botta M. Microwave-assisted organocatalytic multicomponent Knoevenagel/hetero Diels–Alder reaction for the synthesis of 2,3-dihydropyran[2,3-c]pyrazoles. Tetrahedron Lett. 2009;50(48):6572–5. doi:10.1016/j.tetlet.2009.09.047.
3. Singh D, Singh D. Synthesis and antifungal activity of some 4-arylmethylene derivatives of substituted pyrazolones. J Indian Chem Soc. 1991;68:165–7.
4. Padmavathi V, Venkatesh BC, Padmaja A. Synthesis and antimicrobial activity of amido linked pyrrolyl and pyrazolyl-oxazoles, thiazoles and imidazoles. Eur J Med Chem. 2011 Nov 1;46(11):5317–2.
5. Moreau F, Desroy N, Genevard JM, Vongsouthi V, Gerusz V, Le Fralliec G, et al. Discovery of new Gram-negative antivirulence drugs: Structure and properties of novel E. coli WaaC inhibitors. Bioorg Med Chem Lett. 2008;18(15):4022–6. doi:10.1016/j.bmcl.2008.05.117.
6. Tantawy A, Eisa H, Ismail A. Synthesis of 1-(substituted) 4-arylhydrazono-3-methyl-2-pyrazolin-5-ones as potential anti-inflammatory agents. Eur J Pharm Sci. 1988;2:113–6.
7. Pasha FA, Muddassar M, Neaz MM, Cho SJ. Pharmacophore and docking-based combined in-silico study of KDR inhibitors. J Mol Graph Model. 2009;28(1):54–61. doi:10.1016/j.jmgm.2009.04.006.
8. Wisniewski MZ. Pd(II) complexes with some derivatives of pyrazol-5-one. Pol J Chem. 1997;71:259–60.
9. Lu J, Zhang L, Liu L, Liu G, Jia D, Wu D, et al. Study of fluorescence properties of several 4-acyl pyrazolone derivatives and their Zn(II) complexes. Spectrochim Acta A Mol Biomol Spectrosc. 2008;71(3):1036–41. doi:10.1016/j.saa.2008.02.048.
10. Kuncheria B, Indrasenan P. Thorium(IV) nitrate complexes with some substituted pyrazole-5-ones. Indian J Chem Sect A. 1988;27A:1005–7.
11. Tantawy F, Goda F, Abdelal AM. Synthesis and characterization of certain new 3-methyl-4-(substituted phenylazo) isoxazol-5-ones and 3-methyl-4-(substituted phenylazo)-pyrazole-5-ones as potential antibacterial agents. Chin Pharm J. 1995;47:37–45.
12. Rao S, Mittra AS. ChemInform abstract: Synthesis and fungitoxicity of 1-phenyl-3-methyl-4-monoarylidene-2-pyrazoline-5-thione. Chem Inf. 1979;10. doi:10.1002/chin.197902177.

© STM Journals 2025. All Rights Reserved

13. Costa D, Marques AP, Reis RL, Lima JLFC, Fernandes E. Inhibition of human neutrophil oxidative burst by pyrazolone derivatives. Free Radic Biol Med. 2006;40(4):632–40. doi:10.1016/j.freeradbiomed.2005.09.017.
14. Forest SE, Stimson MJ, Simon JD. Mechanism for the photochemical production of superoxide by quinacrine. J Phys Chem B. 1999;103(19):3963–4. doi:10.1021/jp9902809.
15. Santos PMP, Antunes AMM, Noronha J, Fernandes E, Vieira AJSC. Scavenging activity of aminoantipyrines against hydroxyl radical. Eur J Med Chem. 2010;45(6):2258–64. doi:10.1016/j.ejmech.2010.01.071.

© STM Journals 2025. All Rights Reserved