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Synthesis and Pharmacological Activity Bicyclic Heterocycles

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ABSTRACT

Heterocyclic compounds, especially pyrido[2,3-d]pyrimidine derivatives, are well-known for their wide range of biological activities and their significant roles in both pharmaceutical and agrochemical fields. The present study describes the synthesis and detailed characterization of a new ruthenium(II) complex formed with a pyridine-based ligand, which was prepared using a modified Krohnke synthesis route. Structural confirmation of both the ligand and its corresponding metal complex was achieved through a variety of spectroscopic techniques, including FT-IR, NMR, UV–Vis, and mass spectrometry. Observed shifts in IR spectra suggested coordination through nitrogen atoms within the heterocyclic framework. Additionally, LC–MS analysis provided a detailed fragmentation profile of the complex. The interaction of the synthesized metal complex with DNA was explored using UV–Vis absorption titration, which demonstrated a notable binding affinity. These findings indicate the potential of such heterocyclic metal complexes in drug discovery, particularly for therapeutic applications involving DNA targeting.

Keywords: Heterocyclic compounds, pyridopyrimidine, ruthenium (II) complex, DNA binding, Krohnke synthesis, spectroscopic analysis

1. INTRODUCTION

Pyrido[2,3-d]pyrimidine-based heterocycles are widely recognized for their significant biological activities and are integral to the core structure of various therapeutic agents. These compounds exhibit diverse pharmacological properties, including antibacterial, antitumor, antimalarial, antihypertensive, antifungal, and kinase inhibitory effects. Their structural versatility makes them valuable in both medicinal and agrochemical applications. Notably, around 70% of agrochemicals introduced in the past two decades contain at least one heterocyclic ring, contributing to improved bioavailability, solubility, and synthetic accessibility. Examples include widely used agents like azoxystrobin and imidacloprid. Heterocyclic scaffolds also serve as effective bioisosteres, enhancing biological efficacy through structural and electronic similarity. Computational studies and structure–activity relationship (SAR) models further support their role in drug design, including targeting specific protein binding sites. Additionally, cyanoacetohydrazide has been employed to synthesize various biologically active heterocycles, categorized by ring size and biological use.

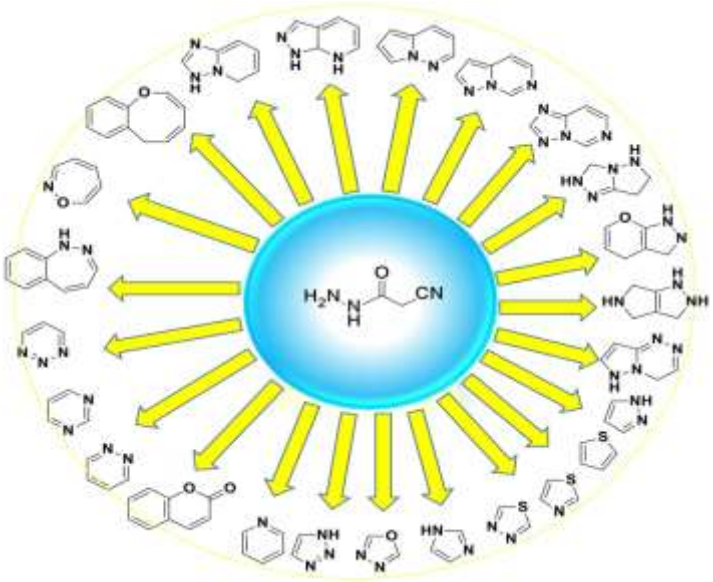


Fig. 1 Summary of various heterocyclic compounds synthesized

Heterocyclic compounds represent one of the most diverse and widely studied families of organic molecules. By replacing carbon atoms in a ring with heteroatoms such as nitrogen, oxygen, sulfur, or even phosphorus, numerous heterocyclic analogues can be synthesized. These compounds are abundant in nature, forming key components of alkaloids, pigments, enzymes, proteins, and nucleic acids. Based on electronic structure, they are classified into saturated (e.g., piperidine, tetrahydrofuran) and unsaturated forms (e.g., pyridine, furan, thiophene), including benzo-fused derivatives like quinoline and indole.

Heterocycles play a crucial role in pharmaceuticals, agrochemicals, and veterinary drugs. Examples include tolazamide (antidiabetic), quetiapine (antidepressant), and herbicides like nicosulfuron. In veterinary use, Bifuran enhances poultry growth. Among these, pyrido[2,3-d]pyrimidine derivatives are notable for their broad biological activities—such as antimicrobial, antitumor, antimalarial, antifolate, and kinase inhibitory effects—making them promising candidates in modern drug development.

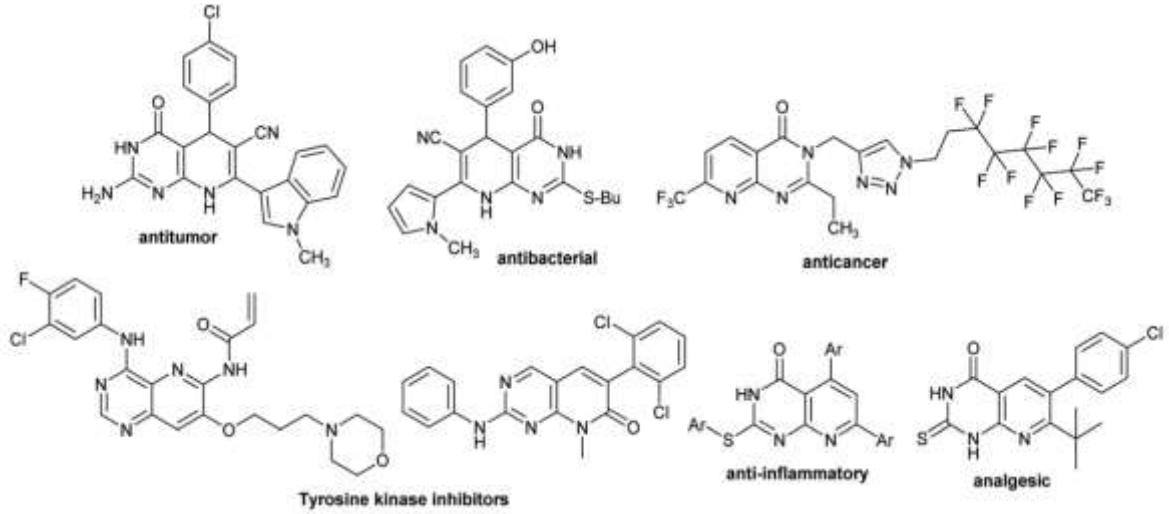


Fig. 2 Structures of bioactive molecules integrated pyridopyrimidine motif.

Different types of heterocyclic compounds

Heterocyclic compounds are classified based on their structure and electronic configuration into aliphatic and aromatic types. Aliphatic heterocycles include saturated rings like cyclic ethers, amides, and amines, while aromatic heterocycles, such as pyrrole and thiophene, follow Hückel's rule and resemble benzene in stability. These rings can range from three to seven members and may contain one or more heteroatoms (e.g., nitrogen, oxygen, sulfur).Three-membered rings include aziridine, oxirane, and thirane, while four-membered examples are azetidine and thiete. Five-membered rings like furan and pyrrole have wide biological significance, and six- and seven-membered rings allow even greater structural diversity. Varying ring size, substituents, and side chains enables the creation of vast molecular libraries with diverse applications.

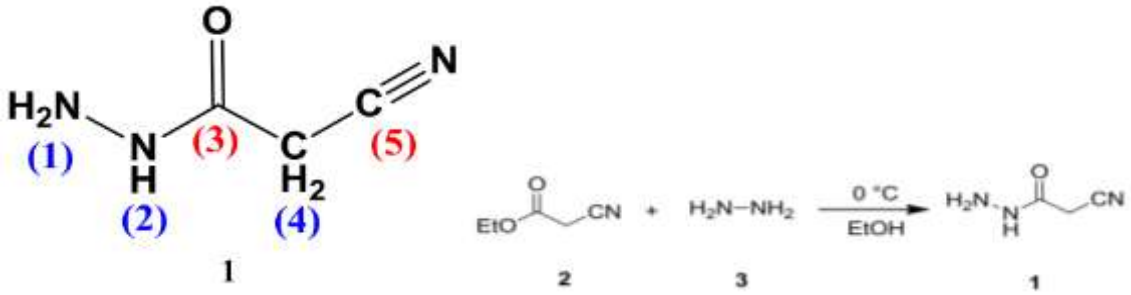


Fig. – 2 Cyanoacetic acid hydrazide (cyanoacetohydrazide)

2. REVIEW OF LITERATURE

Hammouda et al. (2023) highlighted synthetic strategies for pyridopyrimidine scaffolds integrated with heterocycles using nanocatalysts. These compounds exhibit potent biological activities including CDK2 inhibition, apoptosis induction, and anticancer effects. The study confirms the utility of fused heterocyclic cores in targeted drug design.

Rana and Ansari (2023) reviewed the synthesis and pharmacological properties of 7-membered heterocyclic compounds. They emphasized that azepine and its derivatives serve as essential scaffolds in designing CNS-acting agents due to their ring flexibility and tunable functionalization.

Tripathi et al. (2021) described green synthesis routes for biologically relevant heterocycles. They focused on solvent-free approaches that reduce environmental hazards while efficiently producing complex fused ring systems with significant therapeutic potential.

Kaur et al. (2021) provided a comprehensive review on azepine, azepane, and azepinone heterocycles. These seven-membered nitrogen-containing rings exhibit antidepressant, anticonvulsant, and antimicrobial properties. The study also outlines synthetic routes and structure-activity relationships.

Singh et al. (2020) investigated thiazolidinones as bioactive molecules, noting their prominent role in anticancer and antibacterial drug development. The versatility of thiazolidinone stems from the ring's electrophilic centers, which facilitate interactions with biomolecular targets.

Zakharychev et al. (2020) examined pyridine-containing heterocycles in agrochemical applications. These derivatives, often part of fused heterocycles, enhance crop protection by acting as herbicides and insecticides while also being potent antimicrobial agents.

Kaur and Van Humbeck (2020) discussed the growing importance of sp^3 C–H functionalization in heterocyclic frameworks. The study illustrated how catalytic methods enhance scaffold complexity, essential for generating bicyclic molecules with improved pharmacodynamics.

Sharma et al. (2019) reported on bicyclic heterocycles as promising therapeutics. Their data showed that electron-donating substituents on fused systems improve bioavailability and target affinity, supporting the design rationale for thiazolidinone derivatives.

3. MATERIAL AND METHODS

Materials

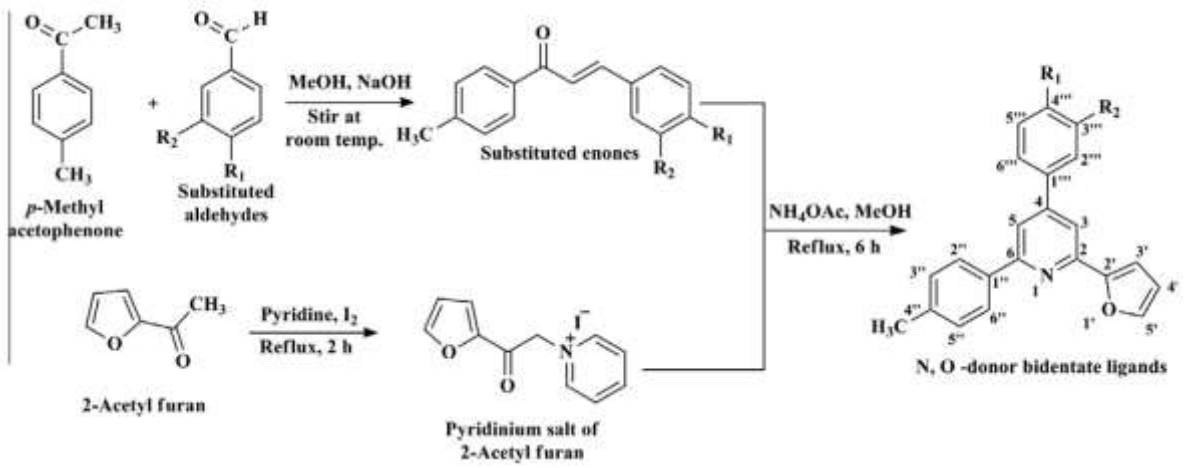
All chemicals used were of analytical grade and sourced from the college laboratory. Key reagents included ruthenium chloride trihydrate, 2-acetylfuran, and various substituted benzaldehydes (chloro, fluoro, and bromo derivatives). Ethidium bromide, bromophenol blue, agarose, and Luria Broth (LB) were also utilized. The pUC19 bacterial strain (MTCC 47) was obtained from a certified institute.

Methods

Elemental analysis was performed using a Perkin–Elmer 240 analyzer. Magnetic susceptibility was measured at room temperature using Gouy's method. FT–IR spectra were recorded on an ABB Bomen MB 3000 spectrophotometer. ^1H and ^13C NMR spectra were obtained using a Bruker Avance 400 MHz spectrometer. UV–Vis spectra were recorded on a Shimadzu UV-160A spectrophotometer.

- **Ligand Synthesis**

Modification of Krohnke pyridine synthesis has been used for the synthesis of ligands [L^1]



Ligands	R_1	R_2
L^1	F	H

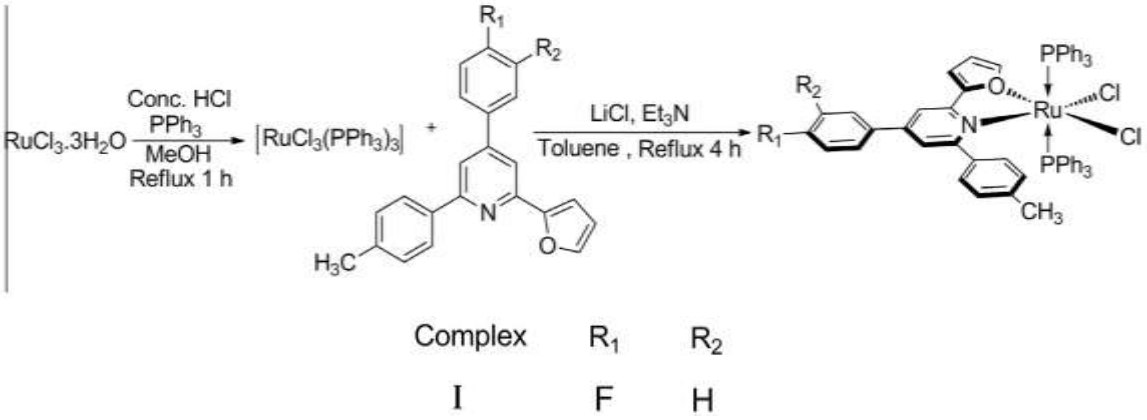
Fig. 1 Scheme(I) General reaction scheme for the synthesis of ligands.

- **Synthesis of 4-(4-fluorophenyl)-2-(furan-2-yl)-6-ptolylpyridine [L^1]**

Substituted enone synthesized by the reaction of *p*-fluorobenzaldehyde and *p*-methylacetophenone, was refluxed with pyridinium salt of 2-acetylfuran in presence of ammonium acetate for 6 h. The reaction mixture was allowed to cool at room temperature.

- **Complex Synthesis**

The ruthenium precursor [$RuCl_3(PPh_3)_3$] was synthesized by refluxing $RuCl_3 \cdot 3H_2O$ with triphenylphosphine (1:3) in methanol containing concentrated HCl for 1 hour. The resulting reddish-brown solid was filtered and vacuum-dried.



Complex	R_1	R_2
I	F	H

Fig. 2 Scheme (II) Reaction scheme for the synthesis of complex.

Synthesis of [$Ru(L^1)(PPh_3)_2Cl_2$] (I):

The complex [$Ru(L^1)(PPh_3)_2Cl_2$] was synthesized by refluxing [$RuCl_3(PPh_3)_3$] (0.1 mmol) in toluene with a methanolic solution of ligand L^1 (0.1 mmol), in the presence of LiCl (0.4 mmol) and Et_3N (0.1 mmol) for 4 hours. The reaction mixture was concentrated, and the product was precipitated using petroleum ether (60:80), washed with methanol and toluene, and vacuum-dried.

- **Yield:** 12.5%; **Melting point:** 272.2 °C
- **Anal. Calcd. for $C_{58}H_{46}Cl_2FNOP_2Ru$ (1025.91):** C, 67.90; H, 4.52; N, 1.37; Ru, 9.85%
- **Found:** C, 67.84; H, 4.53; N, 1.45; Ru, 9.80%
- **UV–Vis (in DMSO):** λ (nm): 550 (ε = 450), 385 (4365), 275 (23,850)
- **Molar Conductance:** 11 Ω^{-1} cm^2 mol^{-1}

IR Spectral Data:

Coordination was confirmed by shifts in ν(C=N) from 1427–1497 cm^{-1} (free ligand) to 1504–1518 cm^{-1} (complex). Aromatic C=C and C–H stretches appeared at 1546–1556 cm^{-1} and 3029–3057 cm^{-1}, respectively. Metal–ligand vibrations were observed at 547–567 cm^{-1} (Ru–N) and 446–464 cm^{-1} (Ru–O)

Sr. no.	$\nu(C{=}N)_{ar}$ (cm^{-1})	$\nu(C{=}C)_{ar}$ (cm^{-1})	$\nu(C{-}H)_{ar}$ (cm^{-1})	$\nu(Ru{-}N)$ (cm^{-1})	$\nu(Ru{=}O)$ (cm^{-1})	PPh_3 (cm^{-1})
(I)	1512	1549	3029	554	446	1450, 1039, 691

Mass spectra

The mass spectrum of complex (I) shows molecular ion peaks at m/z 1025.09, 1027.01, and 1029.05, confirming two chlorine atoms. Fragment peaks at m/z 990.12 and 955.19 indicate stepwise Cl loss. Additional peaks reflect further fragmentation.

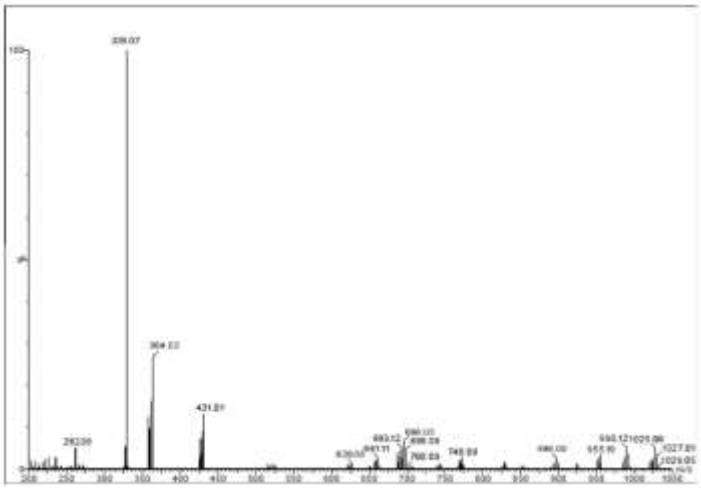


Fig 3 LC–MS spectrum

DNA binding mode study

DNA binding was studied using UV–vis absorption titrations by monitoring changes in ligand-centered and MLCT bands. The binding constant (Kb) was determined from the slope-to-intercept ratio of the [DNA]/(εa–εf) vs [DNA] plot.

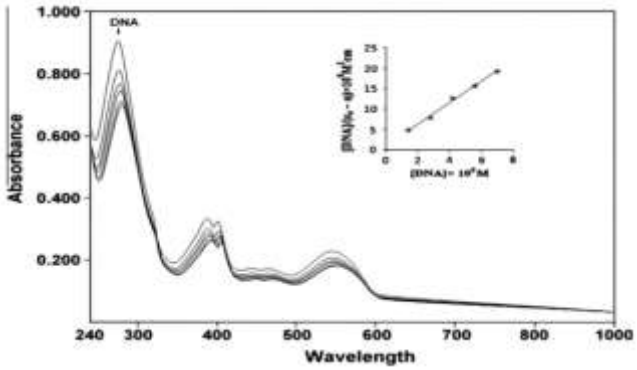


Fig 4 Absorption spectra of complex-I

5. Conclusion

This study synthesized and characterized a new ruthenium(II) complex with a pyridine-based ligand. Spectroscopic analyses confirmed its structure and metal coordination. Strong DNA-binding was observed, highlighting the potential of heterocyclic scaffolds like pyridopyrimidines in developing bioactive metal complexes for pharmaceutical use, especially anticancer and antimicrobial drugs.

REFERENCES

1. Hammouda MM, Rashed MM, Elattar KM, Osman AMA. “Synthetic strategies of heterocycle-integrated pyridopyrimidine scaffolds supported by nano-catalysts” RSC Adv. 2023 Apr 14;13(17):11600-11634.
2. Lamberth C, Dinges J, The significance of heterocycles for pharmaceuticals and agrochemicals, in *Bioactive Heterocyclic Compound Classes – Agrochemicals*, ed. by Lamberth C, Dinges J. Wiley-VCH, Weinheim, pp. 3–20 (2012).
3. Bartlett DW, Clough JM, Godwin JR, Hall, AA, Hamer M, Parr-Dobrzanski B, The strobilurin fungicides. *Pest Manag Sci* **58**:649–662 (2002).
4. Sauter H, Steglich W, Anke T, Strobilurins: evolution of a new class of active substances. *Angew Chem Int Ed* **38**:1328–1349 (1999).
5. Kagabu S, Discovery of imidacloprid and further developments from strategic molecular design. *J Agric Food Chem* **59**:2887–2896 (2011).
6. Jeschke P, Nauen R, Neonicotinoids – from zero to hero in insecticide chemistry. *Pest Manag Sci* **64**:1084–1098 (2008).
7. Koyanagi T, Haga T, Bio-isosterism in agrochemicals, in *Synthesis and Chemistry of Agrochemicals IV, ACS Symposium Series Vol. 584*, ed. by Baker DR, Fenyes JG, Basarab GS. American Chemical Society, Washington, DC, pp. 15–24 (1995).

8. Lamberth C, Dinges J, The significance of heterocycles for pharmaceuticals and agrochemicals, in *Bioactive Heterocyclic Compound Classes—Agrochemicals*, ed. by C Lamberth, J Dinges. Wiley-VCH, Weinheim, pp. 3–20 (2012).

9. Caruso, L.; Musumarra, G.; Katritzky, A. R. "Classical" and "Magnetic" Aromaticities as new Descriptors for Heteroaromatics in QSAR. Part 3 [1]. Principal Properties for Heteroaromatics. *Quant. Struct.-Act. Relat.* **1993**, *12*, 146-151.

10. Langer, T. Molecular Similarity Determination of Heteroaromatics using GRID, CoMFA and Multivariate Data Analysis. *Quant. Struct.-Act. Relat.* **1994**, *13*, 402-405.