RASĀYAN *J. Chem.*
Vol. 19 | No. 1 | 324-330 | January-March | 2026
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

(*E*)-2-[(2,4-DIHYDROXYBENZYLIDENE)AMINO]-3-HYDROXY PYRIDINE: SYNTHESIS, ANTI-MICROBIAL, ANTIOXIDANT ACTIVITY AND BINDING INTERACTIONS WITH SARS-CoV-2

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ABSTRACT

In the present study, the synthesis, characterisation, and biological evaluation of (*E*)-2-[(2,4-dihydroxybenzylidene)amino]-3-hydroxypyridine were investigated. The title compound was synthesised via a simple condensation reaction between 2,4-dihydroxybenzaldehyde and 2-amino-3-hydroxypyridine, yielding the desired Schiff base in good purity. Structural confirmation and purity of the synthesised compound were established using spectroscopic techniques, including FT-IR and NMR analyses. The biological evaluation revealed that the compound exhibits promising antibacterial activity against selected Gram-positive and Gram-negative bacterial strains, along with antifungal activity against tested fungal species. In addition, the compound demonstrated notable antioxidant potential (IC_{50} value of 57.40 µg/mL, IC_{50} value of *Ascorbic acid* = 42.31 µg/mL), as confirmed by its efficient free radical scavenging ability and protective effect against oxidative stress. Furthermore, molecular docking studies were performed to investigate the binding interactions of the compound with the 2019-nCoV receptor-binding domain (RBD) complexed with ACE2–B0AT1 (PDB ID: 6M17). The docking results indicated favourable binding interactions, suggesting the potential of the synthesised Schiff base as a lead molecule for further biological and antiviral studies with a binding energy of −4.72 kcal/mol and an inhibition constant of 347.06 µM.

Keywords: Schiff Base, 2,4-Hydroxy Benzaldehyde, Antibacterial Activity, Antifungal Activity, Antioxidant Activity, SARS-CoV-2, COVID-19.

INTRODUCTION

The synthesis and utilisation of heterocyclic compounds incorporating *salen*-based Schiff bases have been extensively studied and applied in various fields. These compounds possess unique structural features and exhibit diverse chemical properties, making them highly valuable in numerous applications. Researchers have successfully developed efficient synthetic routes to obtain these heterocyclic compounds, allowing for their systematic investigation and characterisation. Furthermore, their versatile nature enables their utilisation in diverseapplications such as catalysis, therapeutic chemistry, and material science.[1-6] The synthesis and applications of heterocyclic compounds containing *salen*-based Schiff bases continue to be an active area of research, with ongoing efforts aimed at exploring their potential in new and emerging areas. Pyridine Schiff bases are versatile compounds that have found wide-ranging applications in the field of biology. These compounds are derived from the condensation of pyridine aldehydes with primary amines, resulting in the formation of a Schiff base. Pyridine Schiff bases exhibit remarkable structural diversity, making them highly valuable for various biological applications. One of the most significant biological applications of pyridine Schiff bases is their antimicrobial activity. Numerous studies have demonstrated the potent antimicrobial properties of these compounds against a wide range of pathogenic

microorganisms.[1-2] Their competency to constrain the growth and proliferation of bacteria and fungi makes them promising candidates for the progress of new antimicrobial agents.[7-11] Pyridine Schiff bases have also garnered interest for their potential role in cancer therapy. These compounds have shown promising anticancer activity, with researchers exploring their ability to induce apoptosis in cancer cells. Additionally, pyridine Schiff bases have been investigated for their potential to inhibit key enzymes involved in cancer progression, making them valuable components in the development of novel anticancer drugs.[2] Inflammation is a complex biological response that plays a crucial role in various disease processes. Pyridine Schiff bases have been studied for their anti-inflammatory effects, with research indicating their ability to modulate inflammatory pathways and attenuate excessive immune responses. This makes them potential candidates for the expansion of anti-inflammatory medications with enhancedeffectiveness and reduced side effects.[10-12] The antioxidant potential of pyridine Schiff bases has also attracted attention in the field of biological research. These compounds have revealed the competency to scavenge free radicals and mitigate oxidative stress, which plays a crucial role in various diseases and ageing processes. Their antioxidant properties make pyridine Schiff bases compelling candidates for the upgrading of novel healing interventions, levelling oxidative stress-related conditions.[1,6] We synthesised a number of potentially biologically useful Schiff's bases in our earlier work.[13–15] The design and development of multifunctional small molecules with broad-spectrum biological activity remains a major focus in medicinal and pharmaceutical research. Schiff base compounds, owing to their simple synthesis, structural versatility, and rich coordination chemistry, have attracted considerable attention for their diverse biological properties, including antimicrobial, antioxidant, and antiviral activities. In particular, heterocyclic Schiff bases containing hydroxyl and nitrogen donor sites are known to enhance biological efficacy through improved molecular interactions with biomolecular targets. Against this background, the present study focuses on the synthesis of a hydroxyl-functionalized pyridine-based Schiff base, (*E*)-2-[(2,4-dihydroxybenzylidene)amino]-3-hydroxypyridine (2,4-DHBA-3-HP), and explores its multifunctional biological potential. The compound is evaluated for antibacterial, antifungal, and antioxidant activities, alongside molecular docking studies against the 2019-nCoV RBD/ACE2–B0AT1 complex to assess its possible antiviral relevance. The combined experimental and computational approach adopted in this work highlights the significance of Schiff base scaffolds as promising lead structures for the development of new therapeutic agents addressing both microbial infections and emerging viral threats.

EXPERIMENTAL

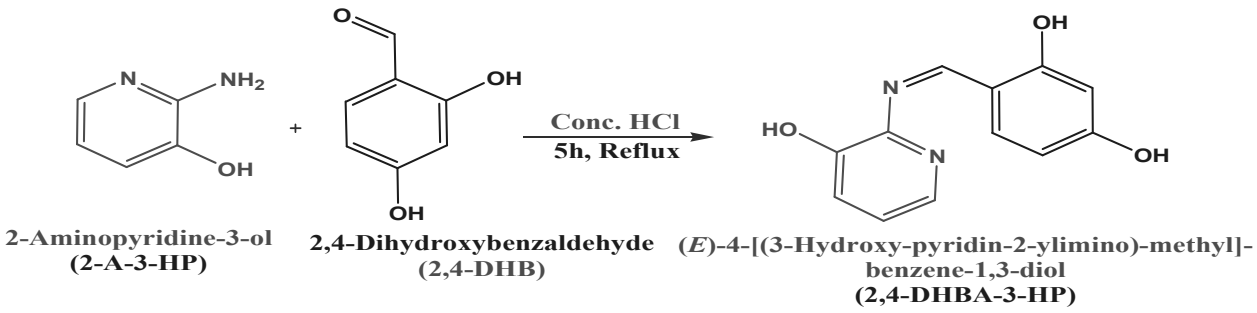
Material and Methods

Reagents and solvents were acquired from Alfa Chemicals, along with 2-Amino-3-hydroxypyridine (2-A-3-HP; ≥98%) and 2,4-Dihydroxy benzaldehyde (2,4-DHB; 98%).

General Procedure

Synthesis of Schiff Base 2,4-DHBA-3-HP

In an RB flask, a simple condensation reaction was used to produce the novel pyridine moiety containing Schiff base compound 2,4-DHBA-3-HP (Scheme 1) by mixing 5 mL of 2,4-Dihydroxy benzaldehyde (2,4-DHB) with 5 mL of 2-Amino-3-hydroxypyridine (2-A-3-HP).[13]



Scheme-1: Synthesis of 2,4-DHBA-3-HP

Brownish Yellow Semi-Solid. FT-IR data (υ in cm^{-1}): 3314, 3182, 1662, 1624, 1574, 1511, 1435, 1289, 1203, 1081, 901, 741. ^{1}H NMR data (δ in ppm, d^6-DMSO): 13.71 (1H, broad singlet, Ar-$OH_{3\text{-HP moiety}}$), 11.58 (1H, singlet, CH=N), 9.92 (1H, singlet, $C^6H_{3\text{-HP moiety}}$), 7.86 (1H, singlet, $C^6H_{2,4\text{-DHB moiety}}$), 7.51 (1H, singlet, $C^3H_{2,4\text{-DHB moiety}}$), 7.44, 7.42 (1H, doublet, $C^4H_{3\text{-HP moiety}}$), 7.30, 7.29 (1H, doublet, $C^5H_{3\text{-HP moiety}}$), 6.73-6.71 (1H, multiplet, $C^5H_{3\text{-HP moiety}}$), 3.57 (1H, broad singlet, Ar-$OH_{2,4\text{-DHB moiety}}$). ^{13}C NMR data (δ in ppm, d^6-DMSO): 167.58 ($ArC^2{}_{3\text{-HP moiety}}$), 165.17 ($ArC^2$ & $ArC^4{}_{2,4\text{-DHB moiety}}$), 160.16 ($C{=}N_{Azomethine}$), 148.19 ($ArC^3{}_{3\text{-HP moiety}}$), 142.88 ($ArC^6{}_{3\text{-HP moiety}}$), 125.30 ($ArC^4{}_{3\text{-HP moiety}}$), 121.78 ($ArC^4{}_{3\text{-HP moiety}}$), 114.79 ($ArC^6{}_{2,4\text{-DHB moiety}}$), 112.77 ($ArC^1{}_{2,4\text{-DHB moiety}}$) 108.98 ($ArC^5{}_{2,4\text{-DHB moiety}}$) 102.15 ($ArC^3{}_{2,4\text{-DHB moiety}}$).

Antimicrobial Activity Technique (Well diffusion method)

Antimicrobial activity is screened for the compound 2,4-DHBA-3-HP against four bacterial pathogens (*S. aureus, E. coli, E. sp* and *K. pneumonia*) and the fungal strain *C. albicans* through the well diffusion method.[13]

Antioxidant Activity Technique (DPPH Method)

The compound 2,4-DHBA-3-HP was employed to its antioxidant activity by measuring its ability to scavenge the stable free radical DPPH (1,1-Diphenyl-2-picrylhyorazyl), following a method similar to the one outlined in a previously published report with some minor adjustments.[13-15]

Docking Method

The three-dimensional crystal structure of the COVID-19 target protein (PDB ID: 6M17, Fig.-1) was retrieved from the RCSB Protein Data Bank. Molecular docking studies were carried out using AutoDock Tools (version 1.5.6), and the binding interactions were visualised using Discovery Studio. Prior to docking, the Schiff base ligand 2,4-DHBA-3-HP was geometry-optimised using Gaussian 09W.[14-17]

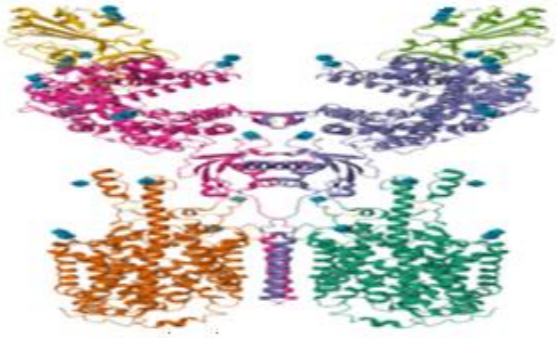


Fig.-1: 3D Structure of the Target Protein (PDB code: 6M17)[13]

RESULTS AND DISCUSSION

Spectral Studies

The amide ($CONH_2$) group of the 2,4-DHB moiety's –NH stretching is responsible for the Schiff base 2,4-DHBA-3-HP observed FT-IR vibrational stretching mode at 3314 cm^{-1}. The stretching peaks for azomethine-CH and aromatic-CH are visible at 3182 cm^{-1}. The carbonyl (C=O) stretching mode of the amide ($CONH_2$) group of the 2,4-DHB moiety is responsible for the peaks at 1662 cm^{-1} and 1624 cm^{-1}. The lower frequency at 1574 cm^{-1} is where the C=N bands were seen, which is a clear indication of the azomethine nitrogen production.[13] The phenolic -OH group in the 2,4-DHB and 3-HP moiety, respectively, are responsible for the two singlet peaks in the ^{1}H NMR spectra of Schiff base 2,4-DHBA-3-HP, which were detected at 3.57 ppm and 13.71 ppm. The two phenolic groups distinct settings were made very evident to them. The production of Schiff base 2,4-DHBA-3-HP is clearly shown by the distinctive peak, which is ascribed to the azomethine (CH=N) group and is detected at 11.58 ppm as a singlet.[13] The aromatic C_6H, C_4H, and C_5H of the 3-HP moiety are responsible for the singlet peak at 9.92 ppm, doublet peak at 7.44, 7.42 ppm, and doublet peak at 7.30, 7.29 ppm that the aromatic protons of the 3-HP moiety displayed, respectively. The aromatic protons (C_6H, C_3H, and C_5H) of the 2,4-DHB moiety are responsible for the peaks that are seen at 7.86 ppm as a singlet, 7.51 ppm as a singlet, and 6.73-6.71

ppm as a multiplet. The appearance of a characteristic signal at 160.16 ppm in the ^{13}C NMR spectrum of the Schiff base 2,4-DHBA-3-HP corresponds to the azomethine (CH=N) carbon, supporting successful Schiff base formation.[13] The phenolic carbons of 2,4-DHB moiety and 3-HP moiety were observed at 165.17 ppm (ArC^2 & $ArC^4{}_{2,4\text{-DHB moiety}}$) and 148.19 ($ArC^3{}_{3\text{-HP moiety}}$) respectively. The aromatic carbons of 3-HP moiety were shown peaks at 142.88 ppm ($ArC^6{}_{3\text{-HP moiety}}$), 125.30 ppm ($ArC^4{}_{3\text{-HP moiety}}$) and 121.78 ppm ($ArC^4{}_{3\text{-HP moiety}}$) and the aromatic carbons of 2,4-DHB moiety were showed peaks at 114.79 ppm ($ArC^6{}_{2,4\text{-DHB moiety}}$), 112.77 ppm ($ArC^1{}_{2,4\text{-DHB moiety}}$), 108.98 ppm ($ArC^5{}_{2,4\text{-DHB moiety}}$), and 102.15 ppm ($ArC^3{}_{2,4\text{-DHB moiety}}$).

Biology

Antibacterial Activity of 2,4-DHBA-3-HP

The antibacterial activity of 2,4-DHBA-3-HP was assessed against Gram-positive (*S. aureus, E. sp.*) and Gram-negative (*E. coli, K. pneumoniae*) bacteria using the agar well diffusion method, with results summarised in Table-1. *Nalidixic acid* and *Chloramphenicol* were used as standard drugs for Gram-positive and Gram-negative bacteria, respectively.

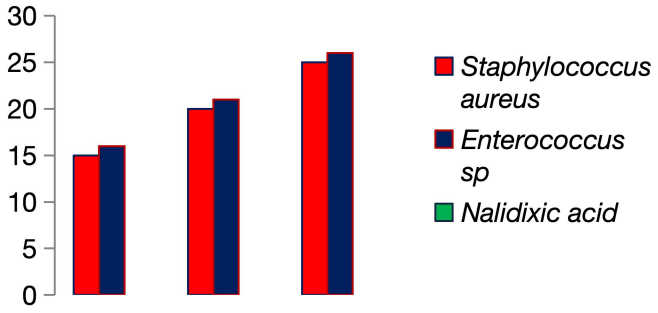


Fig.-2: Antibacterial Activity of 2,4-DHBA-3-HP Against Gram-Positive Bacterial Pathogens (*Staphylococcus aureus* and *Enterococcus sp*)

Table-1: Antibacterial Activity of 2,4-DHBA-3-HP

Type of bacteria/ Standard drug	Bacteria for Test	Concentration (µL/mL)	Zone of Inhibition (mm)
Gram positive	*Staphylococcus aureus*	25	15
		50	20
		100	25
	Enterococcus sp	25	16
		50	21
		100	26
Standard drug	*Nalidixic acid*	50	*NA*[a]
Gram negative	*Escherichia coli*	25	14
		50	18
		100	23
	Klebsiella pneumoniae	25	*NA*[a]
		50	*NA*[a]
		100	*NA*[a]
Standard drug	*Chloramphenicol*	50	*NA*[a]

[a]*No activity*

The synthesised compound 2,4-DHBA-3-HP exhibited remarkable antibacterial activity against the tested Gram-positive strains (*Staphylococcus aureus* and *Enterococcus sp.*) and the Gram-negative strain (*Escherichia coli*) at all tested concentrations (25, 50, and 100 µL/mL; Table-1, Fig.-2), whereas the standard drugs *nalidixic acid* and *chloramphenicol* showed no activity against these pathogens. The

compound 2,4-DHBA-3-HP was showed no antibacterial activity against the *Klebsiella pneumoniae* pathogen only. Against Gram-positive pathogen *Staphylococcus aureus*, the compound 2,4-DHBA-3-HP was showed 15mm of zone inhibition in 25 µL/mL, 20mm of zone inhibition in 50 µL/mL and 25mm zone inhibition in 100 µL/mL. Against Gram-positive pathogen *Enterococcus sp*, the compound 2,4-DHBA-3-HP was showed 16mm of zone inhibition in 25 µL/mL, 21mm of zone inhibition in 50 µL/mL and 26mm zone inhibition in 100 µL/mL(Table-1, Fig.-2). Against the gram-negative pathogen *Escherichia coli*, the compound 2,4-DHBA-3-HP was showed 14mm of zone inhibition in 25 µL/mL, 18mm of zone inhibition in 50 µL/mL, and 23mm zone inhibition in 100 µL/mL. Except for the Gram-negative pathogen *Klebsiella pneumoniae*, the compound 2,4-DHBA-3-HP demonstrated excellent antibacterial activity against all tested pathogens at all concentrations(Table-1, Fig.-3).

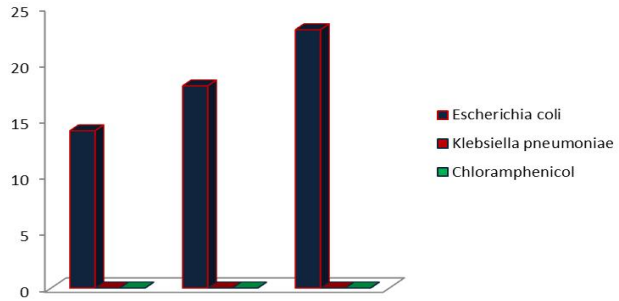


Fig.-3: Antibacterial Activity of 2,4-DHBA-3-HP Against Gram-Negative Bacterial Pathogens (*Escherichia coli* and *Klebsiella pneumonia*)

Antifungal Activity of 2,4-DHBA-3-HP

The antifungal activity of 2,4-DHBA-3-HP was assessed against *Candida albicans* using the agar well diffusion method, with results summarised in Table-2. Fluconazole was used as the standard drug. Neither 2,4-DHBA-3-HP nor *Fluconazole* showed antifungal activity at any of the tested concentrations (25, 50, and 100µL/mL).

Table-2: Antifungal Activityof 2,4-DHBA-3-HP

Compound / Standard drug	*Candida albicans*		
	Zone inhibitions (mm)		
	25	50	100
2,4-DHBA-3-HP [b]	*NA*[c]	*NA*[c]	*NA*[c]
Fluconozole[b]	*NA*[c]	*NA*[c]	*NA*[c]

[b]µL/mL; [c]*No activity*

Antioxidant Activity of 2,4-DHBA-3-HP

The antioxidant activity of the synthesised compound 2,4-DHBA-3-HP was evaluated using the DPPH free radical scavenging assay, and the results are summarised in Table-3. *Ascorbic acid* was used as the standard. The compound exhibited excellent antioxidant activity with an IC_{50} value of 57.40 µg/mL, comparable to that of *ascorbic acid* (IC_{50} = 42.31 µg/mL). At concentrations of 20, 40, 60, 80, and 100 µg/mL, 2,4-DHBA-3-HP showed scavenging activities of 17.94%, 42.31%, 56.41%, 65.38%, and 78.21%, respectively, while *ascorbic acid* exhibited 25.64%, 51.28%, 70.51%, 82.20%, and 98.90% activity at the corresponding concentrations (Table-3, Fig.-4). Overall, the antioxidant activity of 2,4-DHBA-3-HP was found to be comparable to the standard drug.

Table-3: Anti-oxidant Activity of 2,4-DHBA-3-HP

Compound / Standard drug	Percentage of Inhibition(%, µg/mL)					IC_{50}
	20	40	60	80	100	
2,4-DHBA-3-HP[b]	17.94	42.31	56.41	65.38	78.21	57.40
Ascorbic acid[b]	25.64	51.28	70.51	82.2	98.9	42.31

[b]µL/mL

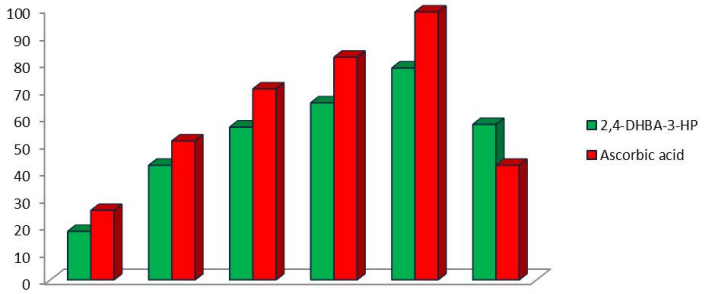


Fig.-4: Antioxidant Activity of 2,4-DHBA-3-HP

Docking Study of 2,4-DHBA-3-HP

The compound 2,4-DHBA-3-HP exhibited favourable binding affinity toward the 2019-nCoV RBD/ACE2–B0AT1 complex (PDB ID: 6M17; Fig.-5 and Table-4), with a binding energy of −4.72 kcal/mol and an inhibition constant of 347.06 μM.

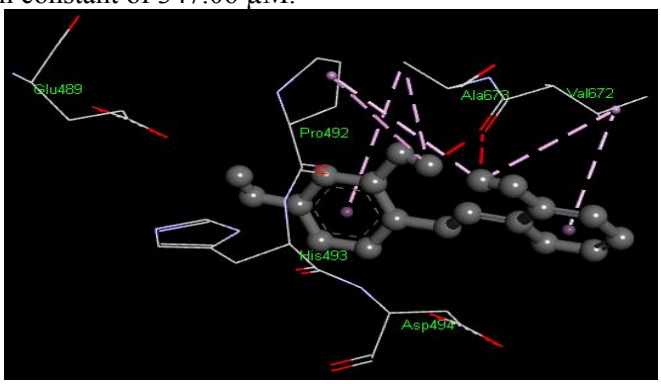


Fig.-5: Binding Mode and Site of 2,4-DHBA-3-HP with the Targeted 2019-nCoV RBD/ACE2-B0AT1 Complex (PDB code: 6M17)

Table-4: Binding Energies, Hydrogen Bonds, Binding Modes and Sites of 2,4-DHBA-3-HP with the Targeted 2019-nCoV RBD/ACE2-B0AT1 Complex (PDB code: 6M17)

Compound	Binding energy (kcal/mol)	Inhibition constant (μM)	No of hydrogen bonds	Hydrogen bonding amino acid residue
2,4-DHBA-3-HP	-4.72	347.06	---	---

CONCLUSION

In conclusion, the present study successfully reports the synthesis and comprehensive biological evaluation of the Schiff base compound (*E*)-2-[(2,4-dihydroxybenzylidene)amino]-3-hydroxypyridine. The compound was efficiently synthesised through a simple condensation reaction, and its structure was unambiguously confirmed by FT-IR and NMR spectroscopic techniques, validating its purity and molecular integrity. Biological investigations demonstrated that the synthesised compound exhibits remarkable antibacterial activity against selected Gram-positive and Gram-negative bacterial strains, while limited activity was observed against fungal pathogens. The antioxidant assessment using the DPPH radical scavenging assay revealed that the compound possesses significant free radical scavenging ability, with activity comparable to the standard antioxidant ascorbic acid. Furthermore, molecular docking studies against the 2019-nCoV RBD/ACE2–B0AT1 complex (PDB ID: 6M17) indicated favourable binding affinity, highlighting its potential as a promising antiviral lead. Overall, the combined experimental and computational results suggest that 2,4-DHBA-3-HP is a biologically active Schiff base with multifunctional properties and may serve as a valuable scaffold for further structural optimisation and development of novel therapeutic agents.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well Being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID IDs, given below:

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Cite this article as: S. M. Rayappan *et al.*, *Rasayan J. Chem.*, 19(1), 324-330(2026), https://doi.org/10.31788/RJC.2026.1919462.

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[RJC-9462/2025]