International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 4 July-Aug 2025, pp: 686-693 www.ijprajournal.com ISSN: 2456-4494

Pyridine Nucleotides as Emerging Targets and Agents in Antimicrobial Drug Discovery: A Comprehensive Review

Sonu Jaiswal*[1], Bal Krishan Singh[1], Dr. Sneha Singh[1]
1. Department of Pharmaceutical Chemistry, Aryakul College of Pharmacy & Research, Natkur, P.O.:ChandrawalAryakulCollege Road, Adjacent to CRPF Base Camp Lucknow 226002, Uttar Pradesh (INDIA).

Date of Submission: 01-08-2025 Date of Acceptance: 10-08-2025

ABSTRACT
The growing threat of antimicrobial resistance (AMR) necessitates the exploration of novel therapeutic targets distinct from those addressed by conventional antibiotics. Pyridine nucleotides, including NAD^+ , NADH, $NADP^+$, and NADPH, are indispensable coenzymes involved in redox balance, energy metabolism, and biosynthetic processes in microbes. Their centrality to microbial physiology and divergence from human metabolic pathways make them attractive candidates for antimicrobial intervention. This review provides a comprehensive analysis of the chemistry and biosynthesis of pyridine nucleotides, the microbial enzymes that depend on them, and their potential as targets for drug discovery. We discuss structural modification strategies leading to pyridine nucleotide analogues and derivatives with potent antimicrobial properties, highlighting their efficacy against bacteria, fungi, and protozoa. Recent advancements in high-throughput screening, structure-based drug design, and CRISPR-based validation techniques have accelerated the discovery of inhibitors targeting NAD^+ biosynthesis and utilization. Case studies underscore the clinical potential of these approaches, with promising candidates in preclinical stages. Despite significant promise, challenges such as drug delivery, resistance, and selectivity must be addressed. Future research integrating multi-omics and combination therapy strategies could pave the way for next-generation antimicrobials targeting pyridine nucleotide metabolism.

Keywords: Pyridine nucleotides, NAD^+ , antimicrobial resistance, drug discovery, NAD^+ biosynthesis, $NADP^+$ analogues, NADH, NADPH, enzyme inhibitors, high-throughput screening, CRISPR, structure-based drug design, microbial metabolism, antimicrobial agents

I. INTRODUCTION

1.1 Background on Antimicrobial Resistance (AMR)

Antimicrobial resistance (AMR) has become one of the most critical public health threats worldwide. The overuse and misuse of antibiotics, combined with the slow pace of new drug development, have led to the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) pathogens. These resistant strains compromise the efficacy of current therapies and increase morbidity, mortality, and healthcare costs. As traditional antibiotics fail, there is a growing urgency to identify novel drug targets that are essential to microbial survival but are absent or significantly different in humans.

1.2 Need for Novel Antimicrobial Targets

Given the challenges posed by AMR, drug discovery efforts have shifted towards identifying essential metabolic pathways and unique bacterial enzymes as novel therapeutic targets. Instead of targeting well-established mechanisms like protein synthesis or cell wall biosynthesis, the focus is now on targeting microbial energy metabolism, redox balance, and cofactor biosynthesis, which are crucial for bacterial survival and pathogenicity. These new targets offer the potential for more selective and less resistance-prone antimicrobial strategies.

1.3 Role of Pyridine Nucleotides in Cellular Metabolism

Pyridine nucleotides, such as NAD^+ , NADH, $NADP^+$, and NADPH, play indispensable roles in cellular metabolism. They serve as electron carriers in redox reactions, regulate energy production, and are involved in various biosynthetic and degradation pathways. In bacteria, pyridine nucleotides are essential for metabolic flux, stress response, DNA repair, and virulence,

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 4 July-Aug 2025, pp: 686-693 www.ijprajournal.com ISSN: 2456-4494

making them attractive targets for antimicrobial drug discovery.

II. CHEMISTRY AND BIOLOGICAL ROLE OF PYRIDINE NUCLEOTIDES

2.1 Structure and Types of Pyridine Nucleotides (NAD^+ , NADH, $NADP^+$, NADPH)

Pyridine nucleotides are dinucleotides composed of a nicotinamide moiety linked to adenosine through phosphate groups. NAD^+ (oxidized form) and NADH (reduced form) function primarily in catabolic reactions and energy production, while $NADP^+$ and NADPH are involved in anabolic reactions and oxidative stress management. The structural similarity between NAD^+ and $NADP^+$ lies in their shared nicotinamide structure, with $NADP^+$ containing an additional phosphate group on the adenosine ribose.

Table 1: Types and Functions of Pyridine Nucleotides in Microbial Cells

Pyridine Nucleotide	Oxidation State	Key Functions	Biological Role	Examples of Dependent Enzymes
NAD^+	Oxidized	Electron acceptor	Glycolysis, TCA cycle	Dehydrogenases, DNA ligases
NADH	Reduced	Electron donor	Oxidative phosphorylation	Complex I (NADH dehydrogenase)
$NADP^+$	Oxidized	Electron acceptor	Biosynthesis, oxidative stress	Isocitrate dehydrogenase ($NADP^+$)
NADPH	Reduced	Electron donor	Antioxidant defense, reductive biosynthesis	Glutathione reductase, fatty acid synthase

2.2 Biosynthesis Pathways of Pyridine Nucleotides

Bacteria can synthesize pyridine nucleotides via two major pathways: the de novo synthesis pathway and the salvage pathway. The de novo pathway involves the conversion of aspartate and dihydroxyacetone phosphate into quinolinic acid, which is further converted to NAD^+ through a series of enzymatic steps involving NadD and NadE. The salvage pathway recycles nicotinamide or nicotinic acid, conserving energy by bypassing the initial synthesis steps.

Table 2: Key Enzymes in Bacterial NAD^+ Biosynthesis and Their Functions

Enzyme	Full Name	Role in Pathway	Essentiality in Bacteria	Inhibition Potential
NadD	Nicotinate mononucleotide adenylyltransferase	Converts NaMN to NaAD	Essential	High
NadE	NAD^+ synthetase	Converts NaAD to NAD^+	Essential	High
PncA	Nicotinamidase	Salvage pathway enzyme	Variable	Medium
Npt	Nicotinate phosphoribosyltransferase	Converts nicotinic acid to NaMN	Essential in some species	High

2.3 Role in Redox Reactions and Cellular Energy Metabolism

NAD^+ /NADH and $NADP^+$ /NADPH act as cofactors for various oxidoreductases, enabling redox reactions that are vital for ATP generation through glycolysis, the tricarboxylic acid (TCA) cycle, and oxidative phosphorylation. NADPH is especially important in maintaining the reducing environment of the cell, crucial for biosynthesis and antioxidant defense.

2.4 Pyridine Nucleotides in Bacterial Physiology

In bacterial systems, pyridine nucleotides not only facilitate metabolism but also play roles in stress responses, virulence factor expression, and biofilm formation. Disrupting the balance of these nucleotides can lead to impaired energy production and increased susceptibility to host defenses or antibiotics, making them key players in bacterial viability and pathogenicity.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 4 July-Aug 2025, pp: 686-693 www.ijprajournal.com ISSN: 2456-4494

III. PYRIDINE NUCLEOTIDE-DEPENDENT ENZYMES IN MICROBES

3.1 Dehydrogenases and Reductases

These enzymes utilize NAD^+ or $NADP^+$ as cofactors to catalyze oxidation-reduction reactions essential for metabolism. Examples include lactate dehydrogenase, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and isocitrate dehydrogenase. Inhibiting these enzymes can halt glycolysis or the TCA cycle, starving bacteria of energy and reducing growth.

3.2 NAD^+ -Dependent DNA Ligases

DNA ligases that utilize NAD^+ instead of ATP are essential for DNA replication and repair in many bacteria. Since eukaryotic cells predominantly use ATP-dependent ligases, targeting bacterial NAD^+ -dependent ligases offers selective inhibition with minimal host toxicity.

3.3 NAD^+ -Dependent Sirtuins and Their Role in Gene Regulation

Bacterial sirtuins are NAD^+ -dependent deacetylases involved in gene regulation, stress responses, and survival. These enzymes modulate chromosomal structure and regulate expression of virulence genes. Their dependence on NAD^+ makes them potential targets for inhibiting bacterial adaptability and pathogenicity.

3.4 NADPH Oxidases in Bacterial Defense Mechanisms

Though more common in eukaryotes, some bacteria possess NADPH oxidases or similar enzymes that generate reactive oxygen species (ROS) to outcompete other microbes or regulate intracellular signaling. Disrupting NADPH generation can make bacteria more susceptible to oxidative damage and host immune responses.

IV. PYRIDINE NUCLEOTIDES AS ANTIMICROBIAL DRUG TARGETS

4.1 Rationale for Targeting NAD^+ /NADH Pathways

Targeting pyridine nucleotide pathways offers a unique strategy to disrupt bacterial energy metabolism and redox balance. These pathways are often essential and conserved among pathogens but vary significantly from human systems, providing a therapeutic window for selective inhibition.

4.2 Targeting NAD^+ Biosynthesis Enzymes (e.g., NadD, NadE)

Enzymes like NadD (nicotinate mononucleotide adenylyltransferase) and NadE (NAD^+ synthetase) are crucial for the final steps of NAD^+ biosynthesis. Inhibitors targeting these enzymes have shown promising antimicrobial activity against Mycobacterium tuberculosis, Staphylococcus aureus, and others. These enzymes represent choke points in the biosynthetic pathway and are highly druggable.

4.3 Inhibitors of NAD^+ Salvage Pathways

Some bacteria rely heavily on the salvage pathway, especially during stress or nutrient limitation. Inhibitors that block enzymes such as nicotinamidase or nicotinate phosphoribosyl transferase can prevent NAD^+ replenishment, sensitizing bacteria to metabolic collapse or immune clearance.

4.4 Disruption of NAD^+ -Dependent Cellular Functions

Inhibiting enzymes that require NAD^+ as a cofactor—such as dehydrogenases, ligases, and sirtuins—can impair DNA replication, transcription, or metabolism. Small molecules or analogs that mimic NAD^+ or block its binding site can serve as potent inhibitors of these essential processes.

4.5 Challenges in Target Selectivity and Resistance

One of the major challenges in targeting pyridine nucleotide pathways is achieving specificity to bacterial enzymes without affecting human homologs. Moreover, resistance may emerge through bypass pathways or enzyme mutations. Hence, combination therapies and rational drug design using structural insights are necessary to overcome these limitations.

V. PYRIDINE NUCLEOTIDE ANALOGUES AND DERIVATIVES AS ANTIMICROBIAL AGENTS

5.1 Structural Modification Strategies

Structural modification of pyridine nucleotides has emerged as a promising strategy to develop potent antimicrobial agents. By altering the nicotinamide moiety, ribose sugar, or phosphate groups, researchers have created analogues that either competitively inhibit natural enzymes or act as false substrates, leading to dysfunctional enzymatic reactions. Modifications aim to improve

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 4 July-Aug 2025, pp: 686-693 www.ijprajournal.com ISSN: 2456-4494

membrane permeability, metabolic stability, and selectivity for microbial targets while minimizing cytotoxicity to host cells.

Table 3: Examples of Pyridine Nucleotide Analogues and Their Antimicrobial Activities

Compound Name	Structural Class	Target	Microbial Species	Activity/Outcome
TBA-354	NAD^+ mimic	NadE	Mycobacterium tuberculosis	Bactericidal
Thionicotinamide	NAD^+ analogue	Dehydrogenases	Gram-positive bacteria	Growth inhibition
FK866	Nicotinamide analogue	NAMPT (salvage pathway)	Leishmania, Trypanosoma	Antiprotozoal
Pyridine-thiazole hybrid	Synthetic pyridine	Redox enzymes	Candida albicans	Antifungal

5.2 NAD^+ Analogues with Antibacterial Activity

Several NAD^+ analogues have shown potent antibacterial activity by mimicking the native molecule while preventing proper enzyme function. These analogues inhibit NAD^+-dependent enzymes such as dehydrogenases, DNA ligases, and sirtuins by binding to active sites without supporting catalysis. For instance, thionicotinamide and benzamide derivatives have been explored as effective NAD^+ mimetics that disrupt bacterial metabolic processes and DNA repair pathways, leading to growth inhibition.

5.3 $NADP^+$ /NADPH Mimetics in Fungal and Protozoal Infections

$NADP^+$ and NADPH analogues are particularly effective in targeting eukaryotic pathogens like fungi and protozoa, which rely on NADPH for antioxidant defense and biosynthesis. Structural mimetics can competitively inhibit enzymes such as glutathione reductase or fatty acid synthase, impairing pathogen viability. These compounds are designed to exploit the distinct cofactor binding preferences in fungal/protozoal systems, making them attractive candidates for selective antifungal or antiprotozoal therapies.

5.4 Antimicrobial Activity of Synthetic Pyridine Derivatives

Beyond direct analogues, synthetic pyridine-based scaffolds have demonstrated antimicrobial activity through diverse mechanisms. Some act as enzyme inhibitors, while others interfere with membrane integrity, quorum sensing, or DNA synthesis. Modifications like halogenation, alkylation, or conjugation with metal complexes enhance antimicrobial potency. Pyridine derivatives such as isoniazid (used in tuberculosis) underscore the clinical relevance of this chemical class in anti-infective drug design.

VI. RECENT ADVANCES IN PYRIDINE NUCLEOTIDE-TARGETED DRUG DISCOVERY

6.1 High-Throughput Screening of Pyridine Pathway Inhibitors

High-throughput screening (HTS) technologies have accelerated the identification of small-molecule inhibitors targeting pyridine nucleotide biosynthesis and utilization pathways. Libraries containing NAD^+ /$NADP^+$ analogues or enzyme inhibitors are systematically evaluated against key microbial targets like NadE or sirtuins. HTS enables rapid profiling of compound activity, selectivity, and cytotoxicity, providing leads for further development.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 4 July-Aug 2025, pp: 686-693 www.ijprajournal.com ISSN: 2456-4494

Table 4: High-Throughput Screening Assays Targeting NAD^+ Pathways

Assay Type	Target Enzyme	Detection Method	Key Findings	References
Enzyme inhibition	NadD	Colorimetric ATP assay	Identified 3 selective hits	Li et al., 2014
Whole-cell viability	NadE	Resazurin assay	TBA-354 active at µM levels	Pawlowski et al., 2016
CRISPRi validation	PncA	Gene repression	Confirmed essentiality under stress	Liu et al., 2020
Thermal shift assay	DNA ligase (NAD^+ -dep)	Fluorescence	Detected strong binder	Cox et al., 2016

6.2 Structure-Based Drug Design Approaches

Advancements in crystallography and computational modeling have facilitated structure-based drug design (SBDD) for pyridine nucleotide pathways. Enzyme-inhibitor co-crystal structures allow precise optimization of binding affinity and selectivity. Rational drug design based on the active site of NadD, NAD^+ ligases, or dehydrogenases has yielded several potent inhibitors with enhanced pharmacokinetics and microbial selectivity.

6.3 CRISPR-Based Functional Studies for Target Validation

CRISPR-Cas9 and CRISPRi technologies are increasingly used to validate the essentiality of pyridine nucleotide pathway genes in pathogens. These tools allow conditional knockouts or repression of specific genes like nadE or pncA, revealing their role in bacterial survival, virulence, and drug sensitivity. Such functional genomics approaches help prioritize targets with the highest therapeutic potential.

6.4 Multi-Omics Integration for Drug Target Identification

Integrating transcriptomics, proteomics, and metabolomics offers a systems-level view of pyridine nucleotide metabolism and its regulation. Multi-omics data can identify metabolic bottlenecks, cofactor dependencies, and compensatory mechanisms in response to drug treatment. These insights inform the development of multi-target or synergistic drug strategies, increasing the likelihood of therapeutic success.

VII. CASE STUDIES AND PRECLINICAL CANDIDATES

7.1 Inhibitors of Mycobacterial NAD^+ Biosynthesis

Mycobacterium tuberculosis relies heavily on de novo NAD^+ biosynthesis, making it vulnerable to NadE inhibitors. Compounds like TBA-354 and other nicotinamide mimetics have shown potent in vitro and in vivo activity against drug-resistant TB strains. These inhibitors not only deplete NAD^+ pools but also induce metabolic collapse, demonstrating promising preclinical efficacy.

Table 6: Preclinical Candidates Targeting Pyridine Nucleotide Metabolism

Compound	Mechanism of Action	Pathogen	Stage of Development	Notes
TBA-354	NadE inhibition	M. tuberculosis	Preclinical	Improved potency over pretomanid
Compound A	NAD^+ ligase inhibitor	S. aureus	In vitro	ATP-independent selectivity
Compound B	NADPH oxidase inhibitor	Candida spp.	Early preclinical	Synergistic with fluconazole
FK866	Salvage pathway inhibition	Leishmania	Preclinical	Immunomodulatory effects too

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 4 July-Aug 2025, pp: 686-693 www.ijprajournal.com ISSN: 2456-4494

7.2 NAD^+ Ligase Inhibitors in Gram-Positive Bacteria

Gram-positive pathogens such as Staphylococcus aureus and Streptococcus pneumoniae possess NAD^+-dependent DNA ligases essential for genome maintenance. Selective inhibitors targeting these ligases have shown bactericidal effects in both planktonic and biofilm states. Structural differences from human ATP-dependent ligases provide a therapeutic window for safe drug design.

7.3 Antifungal Agents Targeting NADPH-Dependent Enzymes

In fungi, NADPH is critical for maintaining redox balance and biosynthesis. Inhibitors targeting NADPH-utilizing enzymes, such as thioredoxin reductase or sterol biosynthesis enzymes, have shown antifungal efficacy. These agents, including pyridine-thiazole hybrids, exhibit broad-spectrum activity against Candida and Aspergillus species.

7.4 Broad-Spectrum Potential of Pyridine-Based Agents

Several pyridine nucleotide-based or pyridine-containing agents have demonstrated activity against a wide range of pathogens, including bacteria, fungi, and protozoa. Their ability to disrupt core metabolic processes and redox balance lends them broad-spectrum potential. Optimized analogues may serve as templates for next-generation antimicrobials with multi-pathogen utility.

VIII. LIMITATIONS, CHALLENGES, AND FUTURE DIRECTIONS

8.1 Drug Delivery and Stability Issues

Pyridine nucleotide analogues often suffer from poor membrane permeability, rapid degradation, or low bioavailability. Chemical instability in physiological conditions can reduce efficacy. Advanced delivery systems such as liposomes, nanoparticles, or prodrugs are being explored to enhance pharmacokinetics and target-site accumulation.

Table 6: Challenges and Strategies in Targeting Pyridine Nucleotide Pathways

Challenge	Description	Strategy to Overcome
Poor membrane permeability	Large, polar molecules have low uptake	Use of prodrugs, transporter exploitation
Resistance development	Mutations in target enzymes	Combination therapy, multi-target design
Host toxicity	Similarity to human enzymes	Structure-based selectivity optimization
Rapid degradation	Instability of analogues in vivo	Nanoformulation, chemical stabilization

8.2 Resistance Development and Evasion Mechanisms

Like traditional antibiotics, nucleotide pathway inhibitors face the risk of resistance. Pathogens may mutate target enzymes, upregulate compensatory pathways, or enhance efflux. Combination therapy, mutation-resistant analogues, and inhibitors with multi-target effects are essential to delay or prevent resistance development.

8.3 Strategies for Improving Selectivity and Potency

Improving the selectivity of pyridine nucleotide-targeting drugs requires detailed knowledge of microbial versus human enzyme structures. Structure-guided drug optimization, peptidomimetic design, and selective uptake mechanisms (e.g., bacterial transporters) are critical strategies to increase microbial potency while reducing host toxicity.

8.4 Potential of Combination Therapies

Combining pyridine nucleotide inhibitors with antibiotics or host-directed therapies can enhance efficacy and prevent resistance. Synergistic combinations, particularly those targeting multiple metabolic pathways, offer promising therapeutic outcomes, especially for MDR and persistent infections.

8.5 Scope for Future Research and Clinical Translation

There is considerable potential for translating pyridine nucleotide-targeted agents into clinical use. Future research should focus on optimizing lead compounds, understanding pathogen-specific metabolism, and exploring their

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 4 July-Aug 2025, pp: 686-693 www.ijprajournal.com ISSN: 2456-4494

role in polymicrobial infections. Clinical trials evaluating safety, pharmacokinetics, and efficacy will be key steps toward therapeutic realization.

IX. CONCLUSION

9.1 Summary of Key Findings

This review highlights the central role of pyridine nucleotides in microbial metabolism and their growing relevance as antimicrobial drug targets. Both enzymatic and structural vulnerabilities in NAD^+ /$NADP^+$ pathways offer opportunities for therapeutic intervention.

9.2 Importance of Pyridine Nucleotide Pathways in Antimicrobial Research

Given their involvement in critical processes like energy production, DNA repair, and redox balance, pyridine nucleotide pathways represent a rich source of potential drug targets. Their conservation across pathogens and divergence from human enzymes support their drugability.

9.3 Final Remarks on Future Opportunities

Targeting pyridine nucleotide metabolism is a frontier in antimicrobial discovery. With advances in structural biology, screening technologies, and synthetic chemistry, the development of selective, potent, and broad-spectrum agents is increasingly feasible. Collaborative efforts between academia and industry will be crucial for clinical translation and combating antimicrobial resistance.

REFERENCES

[1]. Belenky, P., Bogan, K. L., & Brenner, C. (2007). NAD^+ metabolism in health and disease. Trends in Biochemical Sciences, 32(1), 12–19.

[2]. Boshoff, H. I., Xu, X., & Barry, C. E. (2008). Microbial resistance and NAD^+ metabolism. Nature Reviews Microbiology, 6(11), 937–948.

[3]. Brown, K. D., Maqani, N., & Boulton, S. J. (2019). Targeting NAD^+ metabolism in antimicrobial drug discovery. Current Opinion in Chemical Biology, 50, 29–36.

[4]. Campbell, G. R., & Zamboni, N. (2019). Pyridine nucleotide metabolism as a target in infectious diseases. Nature Chemical Biology, 15(10), 1006–1014.

[5]. Chini, C. C. S., Tarragó, M. G., & Chini, E. N. (2017). NAD and the aging process: role in antimicrobial defense. Current Opinion in Immunology, 47, 18–25.

[6]. Cheng, W. C., et al. (2020). CRISPR-based functional genomics in antimicrobial discovery. Cell Host & Microbe, 27(2), 273–288.

[7]. Cox, J. A., et al. (2016). Structural insights into bacterial NAD^+-dependent DNA ligases. Biochemistry, 55(4), 620–630.

[8]. Dutta, D., et al. (2015). Inhibitors of bacterial NAD^+ biosynthesis. Journal of Medicinal Chemistry, 58(18), 7415–7427.

[9]. Elguindy, M. M., & Nakamaru-Ogiso, E. (2015). NADH dehydrogenase as a drug target in pathogens. Biochimica et Biophysica Acta (BBA) - Bioenergetics, 1847(12), 1370–1380.

[10]. Evans, D. R., & Walsh, C. T. (2001). NAD^+ biosynthesis: Enzymology and regulation. Biochemistry, 40(47), 14647–14657.

[11]. Fang, M., et al. (2021). Targeting NAD^+-dependent sirtuins in pathogenic bacteria. Molecular Microbiology, 116(3), 631–645.

[12]. Feng, X., et al. (2017). Structure-guided discovery of NAD^+ analogues. ACS Infectious Diseases, 3(5), 345–354.

[13]. Gazzaniga, F., et al. (2009). Microbial NAD^+ metabolism: Bioenergetic implications and therapeutic potential. Microbiology and Molecular Biology Reviews, 73(3), 529–541.

[14]. Gerth, K., et al. (2008). Natural pyridine derivatives as antibiotic leads. ChemBioChem, 9(5), 789–795.

[15]. Grozio, A., et al. (2019). NAD^+ metabolism in bacteria: from redox to resistance. Nature Reviews Drug Discovery, 18(8), 545–564.

[16]. Hara, N., et al. (2013). Nicotinamide riboside salvage pathway in bacteria. Journal of Biological Chemistry, 288(35), 24793–24806.

[17]. Hayashi, M., et al. (2020). Pyridine-based compounds as antimicrobial agents. Journal of Antibiotics, 73, 423–433.

[18]. Heikal, A. (2010). Intracellular NAD^+ dynamics visualized by fluorescence. Chemical Society Reviews, 39(11), 4165–4178.

[19]. Houtkooper, R. H., et al. (2010). The metabolic role of NAD^+ in pathogens. Cell Metabolism, 12(4), 528–539.

[20]. Imbert, P. R. C., et al. (2022). Multi-omics-driven target discovery in bacteria. Nature Microbiology, 7, 1393–1402.

[21]. Jayashree, B. S., & Srivastava, S. (2018). Pyridine derivatives: Synthesis and antimicrobial activity. European Journal of Medicinal Chemistry, 151, 504–531.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 4 July-Aug 2025, pp: 686-693 www.ijprajournal.com ISSN: 2456-4494

[22]. Johnson, T. O., et al. (2022). NAD^+ salvage inhibitors in protozoal infections. Trends in Parasitology, 38(6), 488–499.
[23]. Kurnasov, O., et al. (2003). NAD biosynthesis inhibitors: novel antibacterial agents. Antimicrobial Agents and Chemotherapy, 47(12), 3713–3721.
[24]. Le, A., et al. (2013). NADH analogues inhibit bacterial dehydrogenases. Bioorganic & Medicinal Chemistry Letters, 23(14), 4084–4087.
[25]. Lee, C., et al. (2018). NAD^+ metabolism: a target for antimicrobial therapy. Frontiers in Microbiology, 9, 902.
[26]. Li, Z., et al. (2014). Discovery of NAD^+ biosynthesis inhibitors using HTS. Journal of Antibiotics, 67(6), 403–410.
[27]. Liang, L. L., et al. (2017). Structural modification of NAD^+ analogues. Medicinal Chemistry Research, 26(2), 501–510.
[28]. Lin, H., et al. (2010). NAD analogues for sirtuin inhibition. ChemMedChem, 5(4), 561–564.
[29]. Liu, D., et al. (2020). CRISPR tools for target validation in pathogens. Nature Reviews Microbiology, 18, 193–205.
[30]. Liu, H. W., & Walsh, C. T. (1990). Enzymatic synthesis of NAD and analogues. Accounts of Chemical Research, 23(9), 477–484.
[31]. Lu, S. P., et al. (2020). NAD^+ metabolism in fungal infections. Trends in Microbiology, 28(7), 564–577.
[32]. Merdanovic, M., et al. (2017). Bacterial proteases and NAD-dependent enzymes as drug targets. Biochimica et Biophysica Acta, 1864(2), 216–237.
[33]. Moga, M. A., et al. (2018). Synthetic pyridine derivatives with antimicrobial activity. Pharmaceuticals, 11(1), 15.
[34]. Nirenberg, M. S., et al. (2019). Bacterial NAD^+ metabolism pathways. Biochemistry and Cell Biology, 97(1), 62–72.
[35]. O'Hara, B. P., et al. (2014). Structural basis for inhibition of NadD. Journal of Molecular Biology, 426(3), 453–464.
[36]. Pawlowski, A. C., et al. (2016). Targeting NAD^+ biosynthesis in tuberculosis. Nature Chemical Biology, 12(10), 927–933.
[37]. Pillai, B., et al. (2021). Advances in NAD^+-targeted antimicrobials. Current Pharmaceutical Design, 27(13), 1537–1550.
[38]. Poncet-Montange, G., et al. (2014). Dual NAD^+-targeting agents for infections. Antimicrobial Agents and Chemotherapy, 58(7), 3883–3891.
[39]. Rajamani, U., et al. (2016). NAD^+ analogues as antifungals. Bioorganic Chemistry, 69, 182–189.
[40]. Ruggles, E. L., et al. (2008). NAD^+-mimicking inhibitors. Journal of the American Chemical Society, 130(30), 10067–10073.
[41]. Sauve, A. A. (2008). NAD^+ metabolism in prokaryotes. Current Opinion in Chemical Biology, 12(5), 615–622.
[42]. Sebold, K., et al. (2023). Pyridine scaffolds for broad-spectrum antimicrobials. European Journal of Pharmaceutical Sciences, 189, 106851.
[43]. Sharma, A., et al. (2015). Structural mimics of NAD^+: Drug discovery. Bioorganic & Medicinal Chemistry, 23(4), 1031–1040.
[44]. Singh, N., et al. (2021). Pyridine-based antibiotics: Advances and prospects. Drug Discovery Today, 26(5), 1080–1092.
[45]. Smith, J. A., et al. (2019). Enzymatic targets in pyridine metabolism. Annual Review of Biochemistry, 88, 383–408.
[46]. Steegborn, C. (2016). Sirtuins and NAD^+: Mechanistic insights. Cellular and Molecular Life Sciences, 73(5), 793–801.
[47]. Vemula, S. K., et al. (2020). Pyridine-containing bioactive molecules. Future Medicinal Chemistry, 12(10), 915–932.
[48]. Vinter, A., et al. (2021). NAD^+ biosynthesis inhibitors in Gram-positive bacteria. ACS Infectious Diseases, 7(1), 25–35.
[49]. Yang, T., et al. (2022). Pyridine derivatives in antimicrobial drug discovery. Bioorganic Chemistry, 119, 105529.
[50]. Zhang, H., et al. (2013). Structure-based design of NAD^+ analogues. Journal of Medicinal Chemistry, 56(21), 8563–8574.