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Review Article

Isonicotinic Acid Derivatives as Antimicrobial and Antitubercular Agents: Synthetic Strategies, Structure–Activity Relationships and Drug-Discovery Perspectives

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Abstract

Due to the increasing demand for effective antitubercular agents, and the emergence of drug resistance, structurally diverse heterocyclic compounds have been explored. Isonicotinic acid derivatives are an important subclass of medicinal chemistry scaffolds as they are known to be associated with the drug isoniazid and the possibility of making structural modifications on these scaffolds. This review is an overview of the synthetic approaches, antimicrobial activity and structure–activity relationship of selected derivatives of Isonicotinic acid especially hydrazides and heterocyclic derivatives, particularly that of 1,3,4-oxadiazole derivatives. Results obtained from published studies of the influence of functional group modifications on biological activity and physicochemical properties of the compound are discussed. A special emphasis is laid on reported antibacterial activities, antifungal activities and antitubercular activities, separating general antimicrobial activities from those specifically shown against Mycobacterium tuberculosis. In addition, the utilization of molecular docking and in silico Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) predictions in initial screening of potential compound is explored. Experimental validation, selectivity, drug-like properties and the transfer of computational results to biological efficacy are taken into consideration. This review, by combining synthetic chemistry with the existing pharmacological evidence, aims to pinpoint promising structural elements, expose the existing lacunae and offer a targeted overview for the rational design and development of Isonicotinic acid derivatives as potential antimicrobial and antitubercular agents.

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Introduction

The emergence of antimicrobial resistance (AMR) is a significant global threat and is causing a loss of efficacy of current therapeutic agents and a need for new antimicrobial compounds. Tuberculosis (TB) caused by Mycobacterium tuberculosis is a major public health problem among infectious diseases due to the appearance of multi-drug resistant (MDR) and drug-resistant variants. While there are several antimicrobial and antitubercular drugs available, the problem of resistance, adverse effects, prolonged treatment and diminished therapeutic value of the existing drugs indicates the need of further research on novel chemical entities. In this context, heterocyclic compounds have been the subject of a lot of attention in medicinal chemistry due to the structural diversity, which enables to engender molecules with potentially better biological properties(1) . The Isonicotinic Acid (pyridine-4-carboxylic acid) is an important Heterocyclic Scaffolds in Drug discovery. Its medicinal significance is related to Isoniazid, a first line antitubercular drug, which is a derivative of Isonicotinic acid hydrazide. Its therapeutic relevance has led to the research of its chemical modification for the development of compounds with a variety of pharmacological activities. Modifications of functional groups, their positions and attached heterocyclic rings can affect molecular interactions, physicochemical properties and biological responses. Thus, the systematic modification of the nucleus of Isonicotinic acid gives an opportunity to explore new antimicrobial and antitubercular candidates. The introduction of hydrazide, Schiff base and heterocyclic groups among the different modifications made in structures has been of much interest. Especially, 1,3,4-oxadiazole derivatives are important since this heterocyclic ring has been studied in the design of compounds with various biological activities such as antimicrobial activity. Alternatively, the use of both the Isonicotinic acid-based structural features and such pharmacologically important groups could yield valuable initial options for exploring structure–activity relationships (SARs)(2) . Biological activity, however, has to be proven by experimental means, and structural similarity to known drugs does not by itself prove therapeutic activity. Computational methods are now becoming more and more a part of modern drug-discovery methods and are being used with experimental investigations. Molecular docking could give initial idea about the potential interaction of the candidate molecules with selected biological target, and in silico absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction could help to evaluate the drug like property of the candidate molecules. These techniques will provide guidance for compound prioritisation but will need experimental validation using synthesis, structure determination and relevant biological assays(3) . The synthetic strategies, antimicrobial and antitubercular activity and SAR of some selected Isonicotinic acid derivatives especially those containing hydrazide and 1,3,4-Oxadiazole is discussed. It also covers the role and its restrictions of computational evaluation in the initial phase of drug discovery. The review seeks to tie up the correlation between the chemical modifications and the reported biological results to elucidate the possible promising structural motifs and also to identify the gaps in the present research and give directions for the development of prospective antimicrobial and antitubercular agents(4) .

Chemistry and Synthetic Strategies of Isonicotinic Acid Derivatives

Isonicotinic acid (pyridine-4-carboxylic acid) is an aromatic, heterocyclic chemical compound with one nitrogen atom in the para position with respect to the carboxylic acid group. Structural characteristics open the opportunity to chemical modification and development of derivatives with different biological properties. The pyridine nitrogen can take part in hydrogen-bonding interactions, and the carboxylic acid group can be converted into various other functional groups such as esters, hydrazides, amides and other heterocyclic derivatives. Such changes can impact molecular polarity and solubility, lipophilicity, and interactions with biological targets. Therefore, Isonicotinic acid can be utilized in medicinal chemistry research as a valuable starting scaffold with special emphasis on antimicrobial and antitubercular drug discovery(5) .

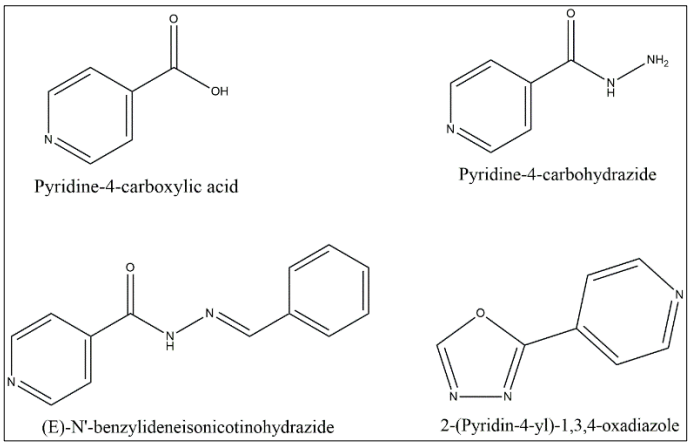


Figure 1 Representative chemical structures of isonicotinic acid and selected derivatives relevant to antimicrobial and antitubercular drug discovery: Isonicotinic acid, isoniazid, (E)-N′-benzylideneisonicotinohydrazide, and a representative pyridine-containing 1,3,4-oxadiazole scaffold.

Among the most significant derivatives of Isonicotinic acid is isoniazid (isonicotinic acid hydrazide). It is known to be a first line therapeutic agent for tuberculosis and has a good pharmacological basis for the investigation of related compounds. The hydrazide functional group, in particular, is useful for further chemical transformations as it can condense with aldehyde and ketone groups to form hydrazones. Such reactions provide variations in structure and enable functional groups such as aromatic rings, heteroaromatic rings, and other functional groups that can affect biological activity to be incorporated. But, antimicrobial activity of these newly synthesized hydrazones has to be individually confirmed by proper biological testing. Another important strategy for modification of the Isonicotinic acid scaffold is esterification. In this method the carboxylic acid group is replaced with an ester group by reacting the carboxylic acid with an appropriate alcohol in suitable conditions. The resulting esters can have different physical and chemical properties from the original acid, and can be used as intermediates for other functionalization's. In the same way, amination can be used to generate a number of amide derivatives by incorporating the appropriate amine containing groups. These changes offer avenues for studying the correlation of functional group changes and biological responses(6) .

Another method used in designing Isonicotinic acid derivatives is the addition of heterocyclic rings. Of these, 1,3,4-oxadiazole is of interest as it has been reported to be of relevance in medicinal chemistry and has the potential to modify the pattern for molecular interaction. The preparations of such derivatives can be carried out by appropriate synthetic pathways using appropriately functionalised precursors. Hydrazide containing intermediates can be subsequently cyclized to oxadiazole derivatives by known cyclization methods depending on substitution pattern desired. The reaction conditions and intermediate selection need to be optimized for every target structure, considering reaction selectivity, yield and purity of products(7) . Further structural variations of this class of compounds can be achieved through the formation of Schiff bases, cyclisation reactions and the incorporation of substituted aromatic groups. The choice of synthetic route will vary according to the desired molecular structure and the compatibility of functional groups, availability of starting materials and the desired substitution pattern at the end of the synthesis. The reproducibility and purification of the compounds is important for the preparation of compounds suitable for further pharmacological investigation. Derivatives are often analyzed after synthesis by physicochemical and spectroscopic methods. Some preliminary information about product characteristics and purity can be obtained from physical appearance, melting point, solubility and thin-layer chromatography (TLC). Infrared (IR) spectroscopy can be used to identify characteristic functional groups, and proton nuclear magnetic resonance (^{1}H NMR) spectroscopy can be used to provide information about the chemical environment of hydrogen atoms. Mass spectrometry can be used to assist the assessment of molecular-mass and to confirm the proposed molecular composition. Other analytical techniques may be necessary to confirm the identity and purity of the compound(s) depending on the structure and research goals. In general, synthetic approach of Isonicotinic acid provides various pathways to obtain structural varieties for antimicrobial research. The chemical foundation and sound chemical characterization coupled with the use of known synthetic transformations lay the groundwork for further biological testing and structure–activity relationship analysis. However, the choice of potential derivatives should rely not only on structural novelty, but also on the availability of proven structural information and the biological activity of the derivative(s) must be confirmed(8) .

Antimicrobial and Antitubercular Activities

Antimicrobial Activity of Isonicotinic Acid Derivatives

Isonicotinic acid derivatives have been studied for their antimicrobial activity; the structural versatility of pyridine-4-carboxylic acid scaffold and the ability to functionalize it with various groups associated with biological activity make the antimicrobial activity of these compounds an interesting target in medicinal chemistry. The different heterocyclic compounds reported to have antibacterial and antifungal properties make it possible to explore the modified Isonicotinic acid derivatives as antimicrobial candidates. But their activity depends on the molecular structure, properties of the substituents, test organism, and experimental conditions used(9) .

Hydrazide derivatives are an important class in this class of chemistry. The therapeutic significance of this structural motif is evident from the well-established use of isoniazid (Isonicotinic acid hydrazide) as an antitubercular agent. In addition to this well-known use, the hydrazide group has been modified to prepare compounds with other physicochemical and biological properties. Hydrazide derivatives with other aromatic and/or heteroaromatic groups can be obtained by condensation of hydrazides with appropriate aldehydes or ketones. These changes could affect molecular lipophilicity, hydrogen-bonding potential, and polarity and interactions with microbial targets. However, it does not always mean that the structural changes will lead to an increase of the antimicrobial activity, and the activity of each derivative must be tested. Another method for the development of compounds with antimicrobial activity is the introduction of heterocycles. Of particular interest are the molecules containing 1,3,4-oxadiazole that have been studied for various biological activities such as antibacterial and antifungal activity. The use of their incorporation into Isonicotinic acid-based structures may offer the opportunity to vary the conformation or patterns of interaction. In a similar fashion, substituted aromatic groups and other nitrogen containing heterocycles can play a role in differential biological responses. It is hence important that structurally related compounds are compared for their effect on activity to identify substituent patterns that are associated with enhanced activity(10) .

In vitro antimicrobial activities are generally examined by standard methods. Agar diffusion assays, such as disc diffusion, can be used to obtain preliminary information concerning inhibition of microbial growth. Broth microdilution methods can be used to define minimum inhibitory concentration (MIC) as the lowest concentration tested that inhibits the visible growth of the microorganism under the conditions of the test. When appropriate, bactericidal activity (minimal bactericidal concentration, MBC) or fungicidal activity (minimal fungicidal concentration, MFC) can be measured to give more information on the concentration that is necessary for killing. Use of test organisms, reference drugs, preparation of inoculum, incubation conditions, and interpretation criteria should be in accordance with appropriate standardized procedures(11) . Care must be taken in making meaningful comparisons between different Isonicotinic acid derivatives, when considering the experimental methodology. However, the diameter of a zone of inhibition cannot always be used to conclude that one compound is more potent than another as diffusion through the agar may be influenced by molecular size, solubility, and other physicochemical properties. Alternatively, MIC values are usually a more direct basis for comparison of inhibitory activity as they are obtained under equivalent conditions. The use of appropriate positive controls, negative controls, biological replicates and the concentrations being tested need to be clearly reported for reliable interpretation. In summary, the antimicrobial activity of Isonicotinic acid derivatives should be judged by structural analysis and the standardized biological testing. Conclusions drawn from published results should be specific to the organisms and experimental conditions investigated, and can help to identify promising chemical modifications. Compounds that demonstrate reproducible activity can then be further evaluated for selectivity, cytotoxicity and other desired characteristics for advancement in antimicrobial development(12) .

Antitubercular Activity of Isonicotinic Acid Derivatives

Tuberculosis still poses significant therapeutic challenges, especially with regard to drug-resistant Mycobacterium tuberculosis, and therefore, research into anti-tubercular drug discovery is still an important area. Due to the known activity of isoniazid, Isonicotinic acid hydrazide is an important structural reference in antitubercular medicinal chemistry. Isoniazid is a prodrug which is activated by the mycobacterial catalase-peroxidase enzyme KatG. It

disrupts the biosynthesis of mycolic acid which is a vital process required to maintain integrity of the mycobacterial cell envelope. This proven mechanism is a good starting point for the investigation of related compounds; however, structural similarity to isoniazid does not imply an identical mechanism of action(13) .

Exploring chemical modification of the Isonicotinic acid scaffold has been explored for new antitubercular candidates. Hydrazide derivatives, hydrazones and derivatives containing other heterocyclic groups may have other biological and physical/chemical properties. Substitution can affect the molecular properties and the permeability, target interactions, and metabolic stability. These effects, however, are structure-dependent and cannot be accurately predicted merely by the presence of a specific functional group. Therefore, the antitubercular activity of each candidate needs to be establish by the appropriate testing on relevant mycobacterial strains(14) .

Methods suitable for the growth characteristics and biosafety requirements of M. tuberculosis must be used to evaluate the potential antitubercular compounds. Susceptibility testing may be performed in vitro and this may result in determination of the minimum inhibitory concentration (MIC) or an equivalent validated measurement of growth inhibition. Studies should specify the strain of bacteria tested, the test protocol, the reference anti-tubercular drug and the criteria for interpretation. If applicable, comparisons of the drug-susceptible and drug-resistant isolates may be used to help evaluate whether the candidate will continue to be active against isolates with known resistance mechanisms. These results need to be considered with care since activity against a small number of isolates does not prove activity against resistant tuberculosis(15) .

Derivatives of known antitubercular drugs are especially significant in regard to resistance mechanisms. Mis-regulation of activation of KatG and the target pathway involving InhA can help develop isoniazid resistance. Depending on the nature of the derivative (chemical structure and biological mechanism), the activity can be retained, lost or modified. Thus, compounds designed to overcome resistance must be tested and not assumed to be effective because of their similarity to isoniazid. Mechanistic studies might be necessary to determine if a candidate is working on the same pathway, or through a different biological target(16) .

Computational approaches can be used to aid prioritization of compounds for synthesis and biological evaluation in the early stages of antitubercular research. Molecular docking could generate hypothesis for potential interaction with targeted mycobacterial proteins and in silico absorption, distribution, metabolism, excretion, and toxicity (ADMET) predictions may help identify potential drug-development liabilities. However, docking scores alone cannot be correlated to antimycobacterial activity and predicted binding does not guarantee target engagement within the bacterial cell. Therefore, the results of the computation should be taken in conjunction with experimental data (table 1)(17) .

Evaluation beyond growth inhibition is needed to develop promising derivatives. Selectivity between microbial inhibition and effect on mammalian cells can be checked using cytotoxicity studies. Other tests can involve resistance development, intracellular activity, pharmacokinetic tests and in vivo efficacy depending on the stage of development. The significance of these studies lies in the fact that in vitro activity does not necessarily mean clinical effectiveness or safety(18) .

To conclude, Isonicotinic acid derivatives are a suitable chemical structure to explore for the investigation of potential antitubercular agents. A systematic relationship between structural modification, validated biological testing, resistance-related investigations, and computational prioritization are needed to support their development. Published evidence can be critically analyzed to find useful structural trends and differentiate between experimentally observed antitubercular activity and preliminary predictions and general antimicrobial studies(19) .

Table 1. Overview of Antimicrobial and Antitubercular Evaluation of Isonicotinic Acid Derivatives

Derivative class	Biological activity investigated	Common evaluation method	Key research objective
Isonicotinic acid hydrazides	Antitubercular	Mycobacterial susceptibility testing	Assess inhibition of M. tuberculosis
Hydrazone derivatives	Antibacterial and antifungal	MIC determination	Investigate the influence of structural

			modifications
1,3,4-Oxadiazole derivatives	Antimicrobial	Agar diffusion and MIC assays	Explore heterocyclic contributions to activity
Substituted Isonicotinic acid derivatives	Antibacterial	Broth microdilution	Establish preliminary structure–activity relationships
Computationally selected derivatives	Predicted target interactions	Molecular docking and ADMET analysis	Prioritize candidates for experimental validation

Structure–Activity Relationships of Isonicotinic Acid Derivatives

Structure–activity relationship (SAR) analysis is a key aspect of medicinal chemistry which studies the effect of structural changes on the biological activity of similar molecules. Changes in the functional group, the pattern of substituents, and the heterocyclic ring systems in Isonicotinic acid derivatives can impact antimicrobial activity and physicochemical properties, as well as interactions with biological targets. These relationships can help to identify the structural features that could be used for further investigations in the development of antimicrobial and antitubercular drugs. Sarah, however, should rely on the comparative experimental data acquired under sufficiently similar conditions and not on the assumptions of structure alone to draw her conclusions for SAR(20) .

The chemical modification of the pyridine-4-carboxylic acid scaffold is a versatile framework. The pyridine N can engage in hydrogen-bonding and the carboxylic acid can be converted to esters, amides and hydrazides. These transformations result in changes in the molecular polarity, ionization behaviour, hydrogen-bonding capacity, and lipophilicity. These properties can affect solubility, membrane permeability and the ability to reach possible biological targets. However, the impact of a specific modification will vary with the whole molecular structure and system being studied(21) .

The hydrazide functionality is especially important as Isonicotinic acid hydrazide, which is also called isoniazid, is an existing antitubercular agent. Condensation reactions can be used to modify this group to give hydrazones with various aromatic and heteroaromatic substituents. These changes can involve the steric, electronic distribution and molecular interactions. While hydrazide containing compounds offer a valuable starting point for antitubercular research, structural similarity to isoniazid is not enough to predict potency and mode of action. Biological evaluation of each derivative required(22) .

Introduction of the heterocyclic rings such as 1,3,4-oxadiazole is another approach for the variation of the biological and physicochemical properties of isonicotinic acid derivatives. Molecular geometry and hydrogen-bonding properties may be altered and the distribution of electron densities may be changed by heterocyclic substitution. R further influences lipophilicity and molecular recognition; additional aromatic substituents will further influence lipophilicity and molecular recognition. Sometimes, the effects of electron-donating and electron-withdrawing groups will be opposite depending on their location and chemical environment. Hence, the effect of individual substituents should be assessed from structurally similar compounds and not from general assumptions regarding their effect(23) .

When the SAR findings are interpreted, the physicochemical properties are also important. Sometimes higher lipophilicity can lead to higher penetration of biological membranes, but higher lipophilicity also can lead to lower aqueous solubility or to higher nonspecific binding. Molecular size and polarity could also affect permeability and interactions with the microbial targets. A desirable balance of these properties is therefore sought in the selection of compounds for further development. Preliminary comparisons can be made using computational descriptors and in silico absorption, distribution, metabolism, excretion and toxicity (ADMET) predictions, but cannot be used alone to establish biological efficacy or safety(24) .

Standardized biological testing, appropriate reference compounds and comparable experimental conditions are necessary for reliable SAR analysis. When the MIC values are obtained by compatible methods and test organisms, the potency of the antimicrobials can be compared. Activity should be differentiated from activity against other bacteria for antitubercular candidates. Observed antimicrobial effects can be further evaluated

using cytotoxicity and selectivity tests to determine if effects were observed at concentrations that may be deemed suitable for further investigation Table 2(25) .

In general, SAR analysis offers a guideline on the correlation of the biological responses with the structural changes of Isonicotinic acid derivatives. Future studies should focus on systematic structural comparisons, reproducible antimicrobial and antitubercular testing and combining computational predictions with experimental data. This strategy could be useful in the identification of promising molecular properties of Isonicotinic acid derivatives as potential antimicrobial agents in the rational approach to their design(26) .

Table 2. Structural Modifications and Their Potential Significance in Isonicotinic Acid Derivatives

Structural modification	Possible influence on molecular properties	Relevance to antimicrobial research
Carboxylic acid to hydrazide conversion	Changes hydrogen-bonding capacity and polarity	Provides a scaffold for investigating antitubercular derivatives
Hydrazide to hydrazone conversion	Introduces additional substituent and conformational diversity	Enables comparative evaluation of antimicrobial activity
Incorporation of 1,3,4-oxadiazole	Alters molecular geometry and electronic properties	Offers an approach for exploring new antimicrobial candidates
Introduction of substituted aromatic groups	May change lipophilicity and steric characteristics	Helps investigate substituent-dependent activity
Modification of polar functional groups	May affect solubility and permeability	Supports preliminary optimization of drug-like properties
Computationally guided structural optimization	Helps prioritize compounds using predicted interactions and ADMET properties	Supports selection of candidates for experimental testing

Molecular Docking and In Silico ADMET Assessment

In the early stages of drug discovery, molecular docking and absorption, distribution, metabolism, excretion and toxicity (ADMET) assessment are common computational methods. These approaches can assist in the investigation of Isonicotinic acid derivatives and help to deliver preliminary data on their potential interactions with biological targets, as well as predicted pharmacokinetic data. Computational methods, in conjunction with synthetic chemistry and biological screening, could be used to prioritize compounds for further investigation, to reduce unnecessary experimental work, and for structural optimization. But their forecasts should be treated with care and confirmed by suitable experiments(27) .

Molecular docking is a computational method that provides an estimate of the preferred orientation of the small molecules within the binding site of selected macromolecules of biological interest. In docking study for Isonicotinic acid derivatives may be planned to explore possible interaction with antimicrobial and antitubercular protein. Selection of targets should be based on sound biology data or a biological hypothesis on a potential mode of action of the compound. For instance, proteins related to crucial mycobacterial functions can be taken into account when searching for potential antitubercular candidates. A target should not, however, be chosen simply because the structure is available for the computation and analysis(28) .

The steps of the docking process are: select an appropriate 3D structure of protein, prepare the protein structure, prepare the ligand structure, specify the binding site and perform docking with validated software. Depending on the target and experimental structure, appropriate treatment of hydrogen atoms, missing residues, water molecules and cofactors can be included within the protein preparation. The preparation of ligands involves the generation of appropriate 3D conformations, and the appropriate protonation states and charges. If possible, it is preferable to validate the docking protocol by redocking a known ligand and compare the predicted docking orientation with the observed orientation. Then the predicted binding scores and interactions can be analysed, such as hydrogen bonds and hydrophobic contacts, and hypotheses can be put forward for possible molecular recognition(29) .

Docking Results are not sufficient to support the antimicrobial activity, target inhibition or specific mechanism of action. Many docking models do not fully

account for cellular permeability, target accessibility, protein flexibility, and other considerations, which may affect the accuracy of docking scores. Therefore, where applicable, the findings obtained from the calculations should be compared with those obtained from the experimental antimicrobial or antitubercular tests(30) .

In silico ADMET assessment can be used in conjunction with molecular docking, allowing additional properties of potential relevance to the suitability of a compound for further development to be predicted. Typical parameters tested include molecular weight, lipophilicity, aqueous solubility, gastrointestinal absorption, membrane permeability, metabolic stability, and potential toxicity. Filters like the Lipinski's rule of five can be used to identify potential physicochemical properties that may be useful for orally active small molecules. However, these guidelines are screening tools and not hard and fast rules; their use will depend on the therapeutic setting in which they are applied(31) .

In the case of the Isonicotinic acid derivatives, ADMET prediction might be useful for detecting compounds with unfavourable solubility, excessive lipophilicity, potential metabolic liability or toxicity alerts. These findings may be used to modify functional groups and substituents in lead optimization. But predicted toxicity does not mean actual toxic effects and apparently favourable computational profiles do not mean human safety(32) .

The molecular docking and ADMET study will help to strategically prioritize Isonicotinic acid derivatives for their synthesis or evaluation in biological systems. The most useful candidates should be chosen taking into account the predicted target interactions, along with the physicochemical properties, synthetic feasibility and available experimental evidence. Finally, computational prediction should be complemented by compound characterization, standardized antimicrobial assays and additional pharmacological studies to ascertain whether the suggested derivatives have a significant therapeutic potential(33) .

Current Challenges and Future Perspectives

Isonicotinic acid derivatives are potential antimicrobial and tuberculostatic agents which could provide an opportunity for medicinal chemistry research; however, there are some scientific and translational research challenges. The need for systematic investigation is due to the occurrence of antimicrobial resistance, variability in biological activity, lack of drug-like properties, and challenges in translating initial research into therapeutic applications. While Isonicotinic acid is a pharmacologically relevant scaffold, it is important to note that structural similarity does not necessarily imply better potency, selectivity or safety. The attention should thus be paid to evidence-based structural modification and rigorous experimental validation of the same in the future(34) .

An important problem is selecting the structural features that seem to be ubiquitous when it comes to improving antimicrobial activity. Modifications in the functional groups, hydrazide substituents and heterocyclic rings like 1,3,4-oxadiazole could affect the molecular interactions and physico-chemical properties. However, they may be different depending on the microbial species and experimental conditions. The structure–activity relationship (SAR) analysis also may be complicated by limited comparability between published studies. Standardization of antimicrobial susceptibility testing method, reference drugs, test organisms and experimental conditions should be done in future investigations. It would help to have the minimum inhibitory concentration (MIC) values, with appropriate controls and biological replicates, to be able to compare between related compounds. A second is related to the difference between general antimicrobial activity and specific antitubercular activity(35) . Activity for common bacterial and fungal strains does not guarantee activity against Mycobacterium tuberculosis. New antitubercular drugs must be evaluated specifically for their activity against mycobacteria and according to biosafety regulations. Also, drug-resistant strains should be studied, if there is a scientific rationale for doing so, especially if the new derivatives are designed to overcome limitations of current drugs. Mechanistic studies can be helpful to determine if any potential compounds offer a known or unknown mode of action. Computational methods such as molecular docking and in-silico absorption, distribution, metabolism, excretion and toxicity (ADMET) predictions can help prioritize the candidate molecules. However, docking scores are only an approximation of biological activity and predicted kinetic or toxicological characteristics do not constitute clinical suitability. In future studies, computational predictions should be combined with experimentally determined antimicrobial activity, cytotoxicity, and target-

engagement data, if available. Future validation of docking protocols and careful selection of biologically relevant targets would also enhance the interpretation of the computational results(36) .

Another key factor is the correlation of the antimicrobial activity and safety. A compound can inhibit the growth of microbes, but can also have an effect on mammalian cells at close to the same concentration. So, the cytotoxicity and selectivity evaluation should go hand in hand with the evaluation of promising candidates. Further solubility, permeability, metabolic stability and resistance development studies may be useful to decide whether a compound is worthy of further preclinical investigation. During lead optimization, synthetic accessibility, reaction reproducibility, purification needs and environmental impact of the chemical procedures should also be taken into consideration. A systematic library of compounds, comparative SAR studies and combination of computational and experimental approaches are desirable for future research into Isonicotinic acid derivatives. These should be considered in particular when hydrazide containing compounds and certain heterocyclic analogues such as 1,3,4-oxadiazole derivatives are involved, with relevant published evidence. Biological testing that can be reproduced with transparency of reporting would greatly help identify promising chemical features and areas of research gaps.In general, Isonicotinic acid derivatives are a promising field for antimicrobial and antitubercular drug discovery which should be explored in a sequential manner to accumulate the proof. Rational molecular design, reliable synthesis, full characterization, validated biological assays, and safety assessment, could aid in the identification of candidates for further investigation. This integrated approach can help in bridging the gap between preliminary chemical research and a development of experimental supported antimicrobial leads(13) .

Conclusion

Isonicotinic acid derivatives are an important field of medicinal chemistry research due to the versatility of the structure and the already known therapeutic value of isoniazid, in the treatment of tuberculosis. Scaffold modifications to the Isonicotinic acid with particular emphasis on hydrazide functionalization, hydrazone formation and addition of various heterocyclic rings like 1,3,4-oxadiazole offer an opportunity for exploring new compounds with potential antimicrobial and antitubercular activity. To understand the structure–property–biology correlation is important for the rational development of these derivatives. The combination of synthetic chemistry, spectroscopic characterization and standardized biological evaluation offers an opportunity to select promising candidates. Priority can also be given to compounds in the early stages of compound prioritization using molecular docking and in silico absorption distribution metabolism excretion and toxicity (ADMET) assessment to gain preliminary insights into possible target interactions and drug-like properties. Computational predictions, however, should be viewed in the context of experimental evidence and biological efficacy cannot be proven solely by structural similarity to already known drugs. Future studies should focus on reproducible synthesis, reliable structural confirmation, comparison of structure–activity relationships and suitable antimicrobial susceptibility testing. Special care should be taken to distinguish between the general antibacterial/antifungal activity and the experimental activity against Mycobacterium tuberculosis. As promising compounds advance through further evaluation, cytotoxicity, selectivity, resistance profiles and relevant pharmacokinetic properties should also be investigated.

Author Contributions

Deepa Yadav: Writing – Original Draft, Investigation, Data Curation, and Formal Analysis.

Devender Kumar Dubey: Supervision, Conceptualization, and Project Administration.

Conflict of Interests

The authors declare that there is no conflict of interest.

Ethics approval and consent to participate

Not applicable

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Data Availability

The information cited and examined in this review comes from earlier publicly accessible published works and can be found in databases, repositories, and cited journals. No original datasets were generated for this work.

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