RESEARCH PAPER

DESIGN, SYNTHESIS & BIOLOGICAL EVALUATION OF OXAZOLE DERIVATIVES FOR ANTIMICROBIAL ACTIVITY

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Abstract

Antimicrobial resistance has increased the demand for compact heteroaromatic scaffolds that combine target engagement with favorable aqueous behavior. Oxazole is a five-membered aromatic ring containing one oxygen and one nitrogen atom and can serve as a polar bioisostere of thiazole. To present a rigorous, journal-style analysis of the design, synthesis, physicochemical behavior, antimicrobial activity, structure–activity relationships, and preliminary safety of 2-aminooxazole carboxamide derivatives. Because the thesis mentioned in the request was not available in the current conversation or accessible file library, no thesis-specific or newly generated data were assumed. The Results section is a transparent secondary analysis of a peer-reviewed matched-isostere dataset comprising 34 newly synthesized derivatives and two previously reported thiazole comparators. Compounds were prepared through cyclocondensation of alpha-bromoketones with urea followed by aroyl chloride coupling, characterized by nuclear magnetic resonance, infrared spectroscopy, high-resolution mass spectrometry, melting point, and ultra-high-performance liquid chromatography, and evaluated by standardized microdilution methods. Antimycobacterial testing included Mycobacterium tuberculosis H37Ra, virulent H37Rv, atypical mycobacteria, and multidrug-resistant clinical isolates. The 2-chloropyridin-4-carbonyl motif and compact subtype-I architecture emerge as credible starting points for further optimization.

Keywords: oxazole; 2-aminooxazole; antimicrobial activity; antimycobacterial; Mycobacterium tuberculosis; bioisostere; minimum inhibitory concentration; FabH; solubility; medicinal chemistry

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1. Introduction

Antimicrobial resistance (AMR) is a convergent biological, clinical, and economic problem. Resistant organisms reduce the probability that empirical therapy will be effective, prolong infectiousness, increase the need for toxic or expensive reserve medicines, and amplify the consequences of weak infection control. A comprehensive global analysis estimated that bacterial AMR was directly responsible for approximately 1.27 million deaths in 2019 and associated with substantially more deaths, establishing resistance as a leading cause of mortality rather than a theoretical future hazard [1]. The World Health Organization (WHO) bacterial priority pathogens framework continues to emphasize drug-resistant Gram-negative bacteria, Staphylococcus aureus, enterococci, and drug-resistant Mycobacterium tuberculosis as organisms for which research and development are urgent [2]. Tuberculosis remains particularly important because long multidrug regimens, intracellular persistence, heterogeneous lesions, and transmission of resistant strains create a high barrier to successful drug discovery [3].

Small heteroaromatic rings are central to antimicrobial medicinal chemistry because they provide precisely located hydrogen-bond acceptors and donors, modulate pKa and dipole moment, and occupy limited steric volume. Among these rings, oxazole is an aromatic 1,3-azole containing oxygen at position 1 and pyridine-like nitrogen at position 3. Its low molecular mass and electron-deficient aromatic character make it useful as a substituent, linker, amide isostere, or pharmacophoric core. Oxazole-containing natural products and synthetic molecules demonstrate that the ring is compatible with high-affinity biological recognition. At the same time, the ring is chemically distinct from imidazole, thiazole, oxadiazole, and isoxazole; results obtained with those heterocycles cannot be transferred to oxazole without direct testing.

Bioisosteric replacement is a rational method for modifying potency, selectivity, metabolism, and physicochemical properties while preserving the spatial arrangement of a lead compound. Classical and non-classical bioisosteres are not expected to be biologically identical; rather, they provide a controlled structural perturbation that can reveal whether activity is constrained by target recognition or by properties

such as solubility and permeability [4]. Replacing sulfur in 2-aminothiazole (2-AMT) with oxygen gives 2-aminooxazole (2-AMO). The replacement reduces atomic size and polarizability, increases polarity, and frequently lowers lipophilicity. It may also alter tautomeric distribution, hydrogen-bonding geometry, and metabolic susceptibility. These changes make a matched thiazole/oxazole series especially informative.

The 2-AMO scaffold has been proposed as a privileged motif in antitubercular medicinal chemistry. Azzali and colleagues demonstrated that 2-aminooxazole derivatives could achieve whole-cell antitubercular activity while providing a useful alternative to more commonly investigated thiazoles [5]. Juhás and co-workers subsequently constructed a matched set of N-(azol-2-yl) heteroaryl carboxamides to isolate the consequences of sulfur-to-oxygen exchange [6]. This dataset is unusually valuable because antimicrobial potency, chromatographic lipophilicity, kinetic solubility, cytotoxicity, resistant-isolate activity, docking, and molecular dynamics were considered within a coherent chemical series.

The present manuscript has three purposes. First, it organizes the chemistry and antimicrobial literature of oxazole derivatives into a mechanistically useful framework. Second, it reconstructs and quantitatively interprets authentic experimental data from the matched-isostere study without representing literature values as newly generated laboratory results. Third, it defines a publication-standard workflow for future synthesis and biological evaluation. The central hypothesis is that 2-AMO is most advantageous when a parent 2-AMT compound is limited by excessive lipophilicity, precipitation, or insufficient effective exposure in the microbial assay. Conversely, when the thiazole analogue already has adequate solubility and potency, oxygen replacement alone is unlikely to guarantee improvement.

2. Literature Review

2.1 Medicinal relevance of oxazole derivatives

Oxazoles occur in bioactive natural products, peptide-derived metabolites, and synthetic screening libraries. Their aromaticity supports pi-stacking and hydrophobic packing, while the ring nitrogen and oxygen can accept hydrogen bonds. Because neither heteroatom is normally protonated at physiological pH, oxazoles often behave as neutral polar fragments. This combination can improve ligand efficiency, although it may also reduce basicity-driven accumulation in organisms in which cation trapping is advantageous. Medicinal utility therefore depends on the entire molecular context rather than on the ring in isolation.

Antimicrobial examples span several target classes. Oxazolyl thiosemicarbazones have produced antitubercular hits, illustrating the ability of the ring to support metal-binding and redox-active pharmacophores [7]. Oxazole-containing fragments were also identified during discovery of bacterial biotin carboxylase inhibitors, supporting compatibility with ATP-dependent enzyme pockets [8]. Benzoxazol-2-amine analogues and bis(azolyl) sulfonamidoacetamides have shown antibacterial or antifungal activity in broader microbial panels [9,10]. These studies collectively establish biological plausibility but do not imply a common mechanism. Whole-cell inhibition can arise from enzyme blockade, membrane effects, metal chelation, redox stress, or a combination of target and exposure determinants.

2.2 Relationship to thiazole-based antimicrobial chemistry

Thiazoles are more heavily represented than oxazoles in antimicrobial discovery. FabH-directed thiazoles have been designed as inhibitors of the initiating condensing enzyme in bacterial fatty-acid biosynthesis [11,12]. 2-Aminothiazole series have also been optimized against M. tuberculosis, and thiazole-containing pyrazinamide hybrids have yielded compounds with useful whole-cell activity [13,14]. These precedents are relevant because oxazole replacement is often undertaken after a thiazole hit has already established an acceptable binding geometry. Related substituted 3-amino-N-(thiazol-2-yl)pyrazine-2-carboxamides have also been evaluated as inhibitors of mycobacterial methionine aminopeptidase 1, illustrating that aminoazole carboxamides can engage more than one antimicrobial target class [29].

Thiazole, however, is not a universally benign scaffold. Some 2-aminothiazoles behave as frequent hitters in biochemical screening, producing apparent activity across unrelated targets [15]. Sulfur-containing drugs can also undergo oxidative bioactivation, and the precise liability depends on substitution, electronic environment, exposure, and metabolic enzymes [16]. Such observations do not justify rejecting every thiazole, but they support early counterscreens and bioisosteric alternatives. Pan-assay interference filters can help flag problematic substructures, although filter alerts are risk indicators rather than proof of artifact [17]. Oxazole substitution is therefore best viewed as a testable design operation rather than a cosmetic change.

2.3 Synthetic strategies for oxazole construction

Oxazoles can be prepared by several established reaction families. Classical routes include cyclodehydration of alpha-acylamino carbonyl compounds, condensation of alpha-haloketones with amides or urea derivatives, oxidative cyclization, and the van Leusen reaction of carbonyl compounds with tosylmethyl isocyanide. Modern variants use transition-metal catalysis, microwave irradiation, continuous flow, or one-pot multicomponent conditions. Route selection should be governed by substitution pattern, functional-group tolerance, regioselectivity, scalability, and purification burden.

For 2-aminooxazoles, cyclocondensation of an alpha-bromoketone with excess urea is operationally simple and directly establishes the exocyclic amino group. In the principal dataset, 2-bromoacetophenone was heated with ten equivalents of urea in dimethylformamide at 120 degrees Celsius for two hours or refluxed in acetonitrile for sixteen hours [5,6]. The resulting 4-phenyloxazol-2-amine was isolated by extraction and flash chromatography. Unsubstituted 2-aminooxazole can be coupled directly with activated heteroaromatic carboxylic acids, whereas 4-phenyl substitution provides a more lipophilic subtype that tests whether the effect of oxygen replacement persists in a larger scaffold.

The final carboxamide bond was formed through acid-chloride chemistry. A heteroaromatic carboxylic acid was treated with excess thionyl chloride and catalytic dimethylformamide at 50–60 degrees Celsius. After removal of volatile reagents, the acid chloride was added to 2-aminooxazole or 4-phenyloxazol-2-amine in dry dichloromethane containing pyridine or N,N-diisopropylethylamine. Overnight reaction at room temperature, basic aqueous work-up, brine washing, drying, concentration, and flash chromatography furnished the target N-(oxazol-2-yl) carboxamides [6]. Although reliable, this sequence uses corrosive and environmentally burdensome reagents. Future process development should compare greener coupling agents, catalytic activation, solvent substitution, and telescoped isolation.

2.4 Structural confirmation and chemical quality

A credible antimicrobial paper requires more than a nominal product and a single spectral signal. Ring formation should be supported by proton and carbon nuclear magnetic resonance spectroscopy, infrared spectroscopy, and accurate mass. For new analogues, high-resolution mass spectrometry should demonstrate agreement between calculated and observed ions, and chromatographic purity should ordinarily exceed 95%. The core study reported greater than 97% purity for most compounds and 95% for one derivative, measured by photodiode-array UHPLC [6]. Melting point and elemental analysis can provide supporting identity, while single-crystal diffraction is valuable when regioisomerism or tautomeric assignment is ambiguous.

2.5 Antimicrobial assay design

Agar diffusion is useful for qualitative screening but is strongly affected by diffusion coefficient, precipitation, inoculum, and medium composition. Minimum inhibitory concentration (MIC) by broth dilution provides a more interpretable concentration-response endpoint. For M. tuberculosis, the microplate Alamar Blue assay (MABA) provides a practical colorimetric or fluorometric readout of metabolic viability and has been validated for clinical isolates [18]. H37Ra is attenuated and can support early screening; most antitubercular drugs show broadly comparable MICs in H37Ra and virulent H37Rv, although lead confirmation in H37Rv remains necessary [19]. Standard bacterial and fungal dilution procedures should follow current CLSI or EUCAST principles, with reference strains, inoculum verification, solvent controls, sterility controls, and appropriate comparators [20,21].

2.6 Physicochemical determinants of whole-cell activity

Whole-cell antimicrobial potency is the integrated result of target affinity, compound stability, free concentration, membrane penetration, efflux, sequestration, and intracellular metabolism. Chromatographic log k'w is an experimentally accessible lipophilicity surrogate obtained by extrapolating reversed-phase retention to an aqueous mobile phase [22]. In silico descriptors, including cLogP, topological polar surface area, and solubility estimates, are useful for prioritization but should not replace measured behavior [23]. Rule-of-five and oral-bioavailability heuristics help identify extreme property profiles [24,25], while experimentally anchored solubility models improve interpretation of compounds that are crystalline or highly aromatic [26]. In microbial screening, apparent inactivity caused by precipitation is especially misleading because it may be mistakenly interpreted as absence of target engagement.

2.7 Target hypothesis: beta-ketoacyl-acyl carrier protein synthase III

FabH, or beta-ketoacyl-acyl carrier protein synthase III, catalyses the initiating condensation in type II fatty-acid biosynthesis. KAS III homologues occupy strategic positions in bacterial metabolism and natural-product pathways [27]. Mycobacterial FabH connects fatty-acid and mycolic-acid precursor metabolism and contains a catalytic region involving Cys112, His244, and Asn274. Structural similarity to reported FabH-directed thiazoles motivated docking of active oxazoles into the mycobacterial enzyme [6,11,12]. Docking is hypothesis-generating: a plausible pose cannot establish that FabH inhibition causes whole-cell activity. Enzyme inhibition, resistant-mutant mapping, target engagement, or chemical-genetic sensitization would be needed to elevate the mechanism from plausible to demonstrated.

2.8 Structure–activity expectations

The aroyl fragment controls electronic distribution, planarity, hydrogen-bonding capacity, and placement of small hydrophobic substituents. Pyridyl and pyrazinyl rings can improve polarity and introduce directional interactions. Meta-position chlorine or methyl groups may occupy hydrophobic subpockets while retaining a compact shape. Quinoxaline increases aromatic surface and can reduce water solubility. A 4-phenyl substituent on the oxazole ring adds conformational and lipophilic load; it may strengthen hydrophobic binding but can mask the solubility benefit of sulfur-to-oxygen replacement. These principles predict a stronger oxazole advantage

in compact subtype-I analogues than in 4-phenyl subtype-II analogues, precisely the pattern observed in the matched dataset [6].

2.9 Comparison with related azole scaffolds

Oxazole should be distinguished from benzoxazole, isoxazole, oxadiazole, and thiazole because ring fusion and heteroatom topology substantially change molecular properties. Benzoxazole contains a fused benzene ring and is generally more lipophilic and planar than oxazole. Isoxazole places oxygen and nitrogen adjacent to one another, producing a different dipole and substitution vector. Oxadiazoles contain an additional nitrogen and are frequently used as amide bioisosteres. Imidazole can be protonated more readily and may coordinate heme iron, a property exploited by many antifungals but also associated with cytochrome P450 interactions. The comparatively neutral 1,3-oxazole ring offers a modest polarity increment without adding a formal charge. This may be advantageous for mycobacteria, whose lipid-rich cell envelope penalizes highly polar molecules but whose intracellular targets still require directional interactions. Direct scaffold hopping among these azoles should therefore compare not only MIC but also pKa, log D at physiological pH, solubility, permeability, efflux ratio, metabolic stability, and plasma-protein binding. A nominally more potent analogue can be a poorer lead when its activity is accompanied by insolubility, aggregation, rapid clearance, or mammalian toxicity. The matched 2-AMT/2-AMO study is informative precisely because it measured several of these dimensions instead of ranking compounds by MIC alone [5,6].

2.10 Synthetic efficiency, sustainability, and scalability

Medicinal-chemistry routes are commonly optimized for speed and analogue coverage rather than process efficiency. The urea cyclocondensation and thionyl-chloride coupling sequence is suitable for milligram-scale discovery but generates excess reagent, acidic gas, halogenated-solvent waste, and chromatographic burden. For a lead series, route development should quantify isolated yield, reaction mass efficiency, process mass intensity, and solvent hazard. Alternatives include activation of carboxylic acids with carbodiimides, propylphosphonic anhydride, or catalytic acyl-transfer systems; however, each alternative must be assessed for difficult-to-remove by-products and compatibility with weakly nucleophilic aminooxazoles. Direct amidation under boron, titanium, or enzymatic catalysis may become attractive at scale. Continuous-flow generation of acid chlorides can limit operator exposure and improve heat and mass transfer. Solvent replacement should prioritize ethyl acetate, 2-methyltetrahydrofuran, acetonitrile, ethanol, or other context-appropriate media over dichloromethane and dimethylformamide when performance permits. Crystallization is preferable to repeated flash chromatography because it improves reproducibility and reduces solvent consumption. These considerations do not alter biological conclusions, but they determine whether a chemical series can progress beyond exploratory synthesis. A publication describing ‘efficient synthesis’ should therefore report mass balance and scale, not only reaction time or percentage yield.

2.11 Assay artifacts, controls, and reproducibility

Heteroaromatic compounds may appear inactive because they precipitate, adsorb to plastic, degrade during incubation, or bind nonspecifically to medium components. Conversely, colored, fluorescent, redox-active, or aggregating molecules can produce false-positive readouts. A rigorous antimicrobial workflow should inspect wells for precipitation before and after incubation, maintain a constant and microbiologically inactive DMSO concentration, confirm compound stability in medium, and repeat active results by an orthogonal endpoint such as optical density, colony counting, or resazurin fluorescence. MIC should be determined in at least three independent biological experiments, with technical duplicates where practical. Reference-strain MICs for control drugs must fall within accepted quality-control ranges [18,20,21]. Minimum bactericidal concentration and time-kill experiments add information that a static MIC cannot provide. For slow-growing mycobacteria, inoculum age, clumping, surfactant concentration, incubation time, and plate sealing are critical variables. Cytotoxicity assays require compound-only blanks when absorbance or fluorescence interference is possible. These controls are especially important when comparing thiazoles and oxazoles because their different solubilities can create an apparent activity difference even if intrinsic target affinity is similar. In the present dataset, the measured solubility and visible precipitation observations substantially strengthen interpretation [6].

3. Materials and Methods

3.1 Study design and data provenance

This article was prepared as a structured secondary research manuscript. The thesis referred to by the requester was not present in the current conversation and no relevant oxazole thesis was identified in the accessible file library. Therefore, no thesis-specific compound codes, yields, spectra, inhibition zones, MICs, or statistical results were invented. Numerical results were transcribed from the peer-reviewed open-access study by Juhás et al. [6], with contextual support from the earlier 2-aminooxazole study by Azzali et al. [5]. The reconstructed dataset contains 36 evaluated structures: 34 compounds reported as newly prepared in the source work and two thiazole comparators (17a and 18a) reported previously. Values containing inequality signs were retained as censored observations.

3.2 Molecular design

Two related subtypes were analyzed. Subtype I comprised compact N-(thiazol-2-yl) or N-(oxazol-2-yl) heteroaryl carboxamides. Subtype II incorporated

an additional phenyl group at the 4-position of the azole. Within matched pairs, code suffix a denotes the thiazole (X = S) and suffix b denotes the oxazole (X = O). Aroyl groups included 2-, 3-, and 4-pyridyl; methyl- and chloro-substituted pyridyl; pyrazinyl; chloropyrazinyl; quinoxalinyl; and phenyl motifs. The matched-pair strategy minimized structural changes outside the sulfur-to-oxygen exchange.

3.3 Representative synthesis

For 4-phenyloxazol-2-amine, 2-bromoacetophenone (1.0 equivalent) was heated with urea (10 equivalents) in dimethylformamide at 120 degrees Celsius for two hours or refluxed in acetonitrile for sixteen hours. The mixture was extracted into ethyl acetate, dried, concentrated, and purified by flash chromatography. Corresponding thiazole intermediates were prepared from alpha-bromoketone and thiourea under ethanolic reflux. For final amide formation, heteroaromatic carboxylic acid (2 mmol) was converted to the acid chloride with thionyl chloride (10 equivalents) and catalytic dimethylformamide at 50–60 degrees Celsius. After evaporation, the residue was dissolved in dry dichloromethane and added under cooling to the selected aminoazole (1.1 equivalents) and pyridine or N,N-diisopropylethylamine (3 equivalents). The reaction was stirred overnight at room temperature, concentrated, partitioned between ethyl acetate and aqueous sodium carbonate at pH 8–9, washed with brine, dried over sodium sulfate, and purified chromatographically [5,6].

3.4 Characterization and purity

Reaction progression was monitored by silica-gel thin-layer chromatography and, where available, TLC-mass spectrometry. Melting points were measured by open capillary. Proton and carbon NMR spectra were obtained at 500/126 or 600/151 MHz, with chemical shifts referenced to residual solvent signals. ATR-FTIR supported functional-group assignment, and heated electrospray high-resolution mass spectrometry provided molecular-formula confirmation. UHPLC-PDA purity was assessed on a C18 column using acetonitrile-water mobile phases and detection at 254 nm. Only structurally confirmed, sufficiently pure compounds were taken forward for biological interpretation [6].

3.5 Experimental lipophilicity and solubility

Chromatographic log k values were measured in several isocratic acetonitrile-water compositions and extrapolated by linear regression to zero percent organic modifier to obtain log k'w. Individual regressions had reported coefficients of determination from 0.953 to 0.999. Kinetic water solubility was evaluated by dissolving 1 mg of compound in the minimum DMSO volume, mixing at 18 degrees Celsius for one hour, diluting with water toward 500 micromolar, filtering through a 0.22-micrometre membrane, and quantifying the dissolved fraction by UHPLC. Experimental molar solubility was converted to log S. Calculated properties were used only as supportive descriptors [6,22-26].

3.6 Antimycobacterial evaluation

Primary activity was measured against M. tuberculosis H37Ra using microplate dilution/MABA principles [18]. Additional organisms included M. smegmatis, M. aurum, M. avium, and M. kansasii. The most active oxazoles, 6b and 7b, were tested against virulent H37Rv and two multidrug-resistant clinical isolates designated IZAK and MATI. The resistant isolates were reported as resistant to streptomycin and most first-line agents, including isoniazid, rifampicin, and pyrazinamide, while retaining ethambutol susceptibility [6,28]. Isoniazid, rifampicin, ciprofloxacin, and ethambutol served as relevant comparators. MIC was defined as the lowest concentration preventing visible or metabolic growth under the assay conditions.

3.7 Antibacterial and antifungal evaluation

The broader screen comprised eight bacterial and eight fungal organisms and used broth microdilution according to EUCAST-aligned procedures. Most compounds were tested to 500 micromolar; selected compounds had lower maximum concentrations because of material or solubility limits. The source report identified low activity against Gram-positive bacteria for 6b, 7b, 15b, and 16b and low antifungal activity for 6b, 7b, and 9b. Best MIC values were 31.25–62.5 micromolar. Exact supplementary organism-by-organism values were not recreated when they were not available in the article body; this prevents false precision [6,20,21].

3.8 Cytotoxicity and selectivity

HepG2 human hepatic cells were used as an early mammalian safety model. Cell viability was quantified with the CellTiter 96 assay, and IC50 values were determined where solubility permitted. The selectivity index (SI) was calculated as HepG2 IC50 in micromolar divided by the H37Ra MIC converted to micromolar. Values preceded by a greater-than sign indicate that 50% inhibition was not achieved at the highest tested concentration. The assay has the same conceptual role as classical tetrazolium viability procedures: metabolic conversion of a reagent provides a quantitative surrogate for viable cells [30].

3.9 Docking and molecular dynamics

MtFabH (PDB 1U6S) was prepared in MOE, including restoration of Cys112, protonation at pH 7.4, and Amber14:EHT charging. Rigid docking used Triangle Matcher placement, London dG prescoring, and GBVI/WSA dG rescoring. Compounds 6b and 15b represented the two structural subtypes. The docked complexes were solvated with TIP3P water in periodic boxes, neutralized with 0.1 M sodium chloride, heated to 300 K, equilibrated, and simulated in three independent 50-ns production runs per ligand in both subunits of the FabH dimer. Stability was

judged by heavy-atom ligand RMSD during the last 5 ns, using 2.0 angstrom as a practical threshold together with visual inspection [6,27].

3.10 Secondary statistical analysis and graph construction

Data were entered into a structured table and independently checked against the source article. Descriptive comparisons were performed without imputing unknown exact values. For graphs, a censored MIC such as at least 500 micrograms per millilitre was plotted at 500 and labelled with its inequality; therefore, apparent fold improvements derived from such bars are minimum estimates. Matched log k'w differences were calculated as thiazole minus oxazole. No inferential p-values were generated because the compounds are designed analogues rather than independent random samples, single experimental property values were reported for some endpoints, and the secondary dataset does not contain replicate-level observations.

Table 1. Integrated experimental framework used in the source dataset and in the present secondary analysis.

Domain	Method	Principal endpoint	Interpretive role
Chemistry	Alpha-bromoketone /urea cyclocondensation; acid-chloride coupling	Isolated oxazole carboxamides	Access matched oxazole/thiazole analogues
Identity and purity	NMR, ATR-FTIR, HRMS, melting point, UHPLC-PDA	Structure confirmation; chromatographic purity	Exclude impurity-driven activity
Physicochemical	RP-UHPLC log k'w; kinetic water solubility	Lipophilicity and dissolved concentration	Distinguish binding from exposure limitations
Antimycobacterial	MABA/microdilution	MIC against H37Ra and additional mycobacteria	Primary whole-cell potency
Resistance panel	H37Rv and MDR clinical isolates	MIC retention or shift	Preliminary cross-resistance assessment
Broader spectrum	Bacterial and fungal broth microdilution	MIC in micromolar	Evaluate non-mycobacterial activity
Mammalian safety	HepG2 CellTiter 96	IC50 and selectivity index	Early cytotoxicity window
Mechanism hypothesis	MtFabH docking and 3 x 50 ns molecular dynamics	Pose, interactions, RMSD	Generate testable target hypothesis

4. Results

4.1 Chemical series and data completeness

The evaluated set covered compact and 4-phenyl-substituted aminoazole carboxamides across six heteroaroyl patterns. All compounds in the main table had experimental log k'w values. HepG2 IC50 was either quantified, reported above the highest tested concentration, or not determined. H37Ra MIC was available for every entry, although several values were right-censored because activity was weaker than the maximum concentration. This completeness permits robust qualitative SAR and physicochemical comparison even though formal population statistics would be inappropriate.

4.2 Lipophilicity reduction by oxazole substitution

Every matched oxazole had a lower log k'w than its thiazole counterpart. In the compact subtype-I pairs, the mean decrease reported by the source study was 0.95 plus or minus 0.09 log unit, corresponding to an approximately 8.87-fold reduction in chromatographic retention-related lipophilicity. In subtype II, the mean decrease was 1.05 plus or minus 0.04 log unit, corresponding to an approximately 11.33-fold shift [6]. Figure 3 places all sixteen matched pairs below the line of identity. This consistency is important: unlike biological potency, which depends on several competing determinants, the direction of the physicochemical effect was uniform.

4.3 Aqueous solubility

Measured solubility confirmed that the lipophilicity shift translated into aqueous behavior. Compound 12a dissolved to only 0.28 micrograms per millilitre, whereas 12b reached 115.65 micrograms per millilitre, a 413-fold improvement. Compound 15a dissolved to 2.10 micrograms per millilitre and 15b to 123.99 micrograms per millilitre, a 59-fold increase. Compound 6a reached 29.93 micrograms per millilitre, while 6b showed no precipitation when challenged at the 500-micromolar test level. These results demonstrate that a one-atom replacement can rescue assayability by several orders of magnitude when crystal packing and aromatic burden are not overwhelmingly unfavorable.

4.4 Primary antimycobacterial activity

Ten compounds produced H37Ra MIC values of 7.81 micrograms per millilitre or lower: 4b, 5b, 6b, 7b, 11a, 11b, 13a, 15a, 15b, and 16a. The most potent exactly quantified derivative was 6b (3.125 micrograms per millilitre), while 7b was active below 3.91 micrograms per millilitre. Compound 5b and both 11 isosteres gave 3.91 micrograms per millilitre. The matched-pair graph shows the greatest oxazole advantages for 2a/2b, 3a/3b, 6a/6b, 7a/7b, 10a/10b, 12a/12b, 17a/17b, and 18a/18b. In contrast, 1b was less active than 1a, 9a/9b and 11a/11b were equipotent, and oxazoles 13b, 15b, and 16b were weaker than their thiazoles. Thus, improved hydrophilicity increased the probability of activity but did not replace the need for favorable molecular recognition.

4.5 Importance of aroyl substitution

The strongest subtype-I oxazoles contained substituted pyridyl aroyl groups. A methyl group in a favorable meta relationship produced 4b and 5b with MICs of 7.81 and 3.91 micrograms per millilitre. The 2-chloropyridin-4-carbonyl motif in 6b produced the best exact MIC, and combined chlorine/methyl substitution in 7b maintained very high potency. Unsubstituted pyridyl orientation mattered: 1b, 2b, and 3b gave 62.5, 31.25, and 15.625 micrograms per millilitre, respectively. The sequence suggests that heteroatom placement controls both ring electronics and binding geometry. Quinoxaline derivatives were generally disadvantaged by high lipophilicity; 19a and 19b were inactive against H37Ra at 500 micrograms per millilitre, although the less lipophilic subtype-I oxazole 10b achieved 15.625 micrograms per millilitre.

4.6 Activity against virulent and multidrug-resistant M. tuberculosis

Compounds 6b and 7b retained MIC values of 6.25 micrograms per millilitre against H37Rv and 3.13 micrograms per millilitre against both MDR isolates. There was no potency loss in the resistant strains; indeed, the measured MIC was two-fold lower than against H37Rv. By comparison, isoniazid shifted from 0.39 micrograms per millilitre against H37Rv to 12.5 micrograms per millilitre against the MDR isolates, consistent with their resistance phenotype. Ethambutol shifted from 0.39 to 1.56 micrograms per millilitre. Retention of oxazole activity is encouraging because it suggests that the compounds are not dependent on the resistance-sensitive pathways targeted by isoniazid or rifampicin. It does not, however, establish an absence of cross-resistance across larger clinical panels.

4.7 Spectrum beyond M. tuberculosis

Compounds 6b, 7b, 11b, and 15b were active across all five standard mycobacterial strains tested in the source study. Compound 19b, despite inactivity against H37Ra, showed notable activity against M. avium, indicating that species-specific permeability, metabolism, or target dependence can invert rank order. In conventional bacterial and fungal panels, activity was weaker. Oxazoles 6b, 7b, 15b, and 16b inhibited selected Gram-positive bacteria at low-to-moderate levels, and 6b and 7b inhibited Candida albicans, Lichtheimia corymbifera, and Trichophyton interdigitale; 9b was active against T. interdigitale. The best reported MIC range was 31.25–62.5 micromolar. Their thiazole counterparts were inactive in those broader panels, supporting a whole-cell exposure advantage for oxazole.

4.8 Cytotoxicity and selectivity

Most compounds did not reduce HepG2 viability by 50% at the highest tested concentration. Compounds 4b, 5b, 6b, 7b, and 11b combined relevant H37Ra potency with SI values exceeding 26, 52, 47.5, 58.3, and 67.8, respectively. Compound 15b had an IC50 of 136.1 micromolar and an SI of 5.2, whereas 15a had an SI of 8.3. Therefore, the additional phenyl group and associated lipophilicity did not necessarily improve safety margin. Solubility-limited IC50 determinations for several thiazoles further illustrate why physicochemical optimization is necessary before a negative cytotoxicity result can be considered conclusive.

4.9 Docking and molecular-dynamics interpretation

Docking placed 6b and 15b near the MtFabH catalytic region. The amide carbonyl accepted hydrogen bonds from backbone NH groups of Cys112 and Ala306, while the pyridyl ring formed an NH-pi interaction with Asn274. Docking scores were -6.4 for 6b and -8.1 for 15b. The stronger computed score of 15b did not translate into stronger whole-cell potency, underscoring the role of solubility, permeability, and entropy. Across six ligand copies/replicas, 6b had last-5-ns RMSDs of 0.86, 1.56, 1.32, 1.69, 4.19, and 0.79 angstrom; 15b had 2.25, 1.49, 2.24, 1.83, 1.30, and 1.98 angstrom. Most trajectories retained the overall pose and the Ala306 hydrogen bond. The simulations support plausibility and pose stability but remain insufficient to assign FabH as the cellular target.

Table 2. Literature-derived physicochemical, cytotoxicity, and M. tuberculosis H37Ra data for the evaluated series [6]. Suffix a = thiazole; suffix b = oxazole; n.d. = not determined. Inequality signs are retained from the source.

Code	Aroyl group	X	log k'w	HepG2 IC50 (µM)	H37Ra MIC (µg/mL)
1a	pyridin-2-yl	S	1.857	>1000	31.25
1b	pyridin-2-yl	O	0.854	>1000	62.5
2a	pyridin-3-yl	S	1.251	>1000	250
2b	pyridin-3-yl	O	0.436	>1000	31.25
3a	pyridin-4-	S	1.306	>1000	250

Code	Aroyl group	X	log k'w	HepG2 IC50 (µM)	H37Ra MIC (µg/mL)
	yl				
3b	pyridin-4-yl	O	0.396	>1000	15.625
4b	5-Me-pyridin-3-yl	O	0.888	>1000	7.81
5b	2-Me-pyridin-4-yl	O	0.714	>1000	3.91
6a	2-Cl-pyridin-4-yl	S	2.013	>250	≥500
6b	2-Cl-pyridin-4-yl	O	1.136	664.1	3.125
7a	2-Cl-6-Me-pyridin-4-yl	S	2.319	>250	≥500
7b	2-Cl-6-Me-pyridin-4-yl	O	1.430	959.4	<3.91
8a	pyrazin-2-yl	S	1.222	n.d.	62.5
8b	pyrazin-2-yl	O	0.154	n.d.	31.25
9a	5-Cl-pyrazin-2-yl	S	1.941	n.d.	31.25
9b	5-Cl-pyrazin-2-yl	O	0.958	n.d.	31.25
10a	quinoxalin-2-yl	S	2.530	>50	≥250
10b	quinoxalin-2-yl	O	1.493	>1000	15.625
11a	pyridin-2-yl	S	3.102	>100	3.91
11b	pyridin-2-yl	O	2.038	883.4	3.91
12a	pyridin-3-yl	S	2.131	>25	≥500
12b	pyridin-3-yl	O	1.118	610.3	125
13a	pyridin-4-yl	S	2.190	>100	7.81
13b	pyridin-4-yl	O	1.163	879.3	31.25
14b	5-Me-pyridin-3-yl	O	1.478	>100	≥250
15a	2-Cl-pyridin-4-yl	S	3.036	102.6	3.91
15b	2-Cl-pyridin-4-yl	O	1.992	136.1	7.81
16a	2-Cl-6-Me-pyridin-4-	S	3.314	n.d.	7.81
16b	2-Cl-6-Me-pyridin-4-yl	O	2.251	n.d.	15.625
17a	pyrazin-2-yl	S	2.365	n.d.	>50
17b	pyrazin-2-yl	O	1.306	>1000	15.625
18a	5-Cl-pyrazin-2-yl	S	3.173	n.d.	>100
18b	5-Cl-pyrazin-2-yl	O	2.073	>100	15.625
19a	quinoxalin-2-yl	S	3.583	n.d.	≥500
19b	quinoxalin-2-yl	O	2.465	n.d.	≥500
20b	phenyl	O	2.090	330.3	62.5

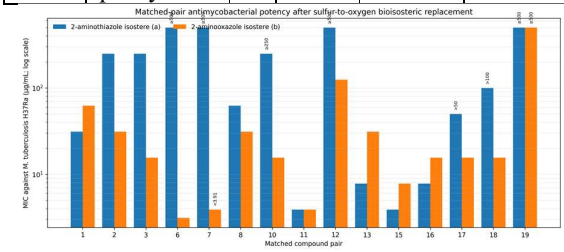

Figure 2. Matched-pair MIC values against M. tuberculosis H37Ra. Values are displayed on a logarithmic axis. Censored observations are plotted at the reported boundary and retain their inequality labels; therefore, visual fold changes involving censored bars are minimum or maximum estimates.

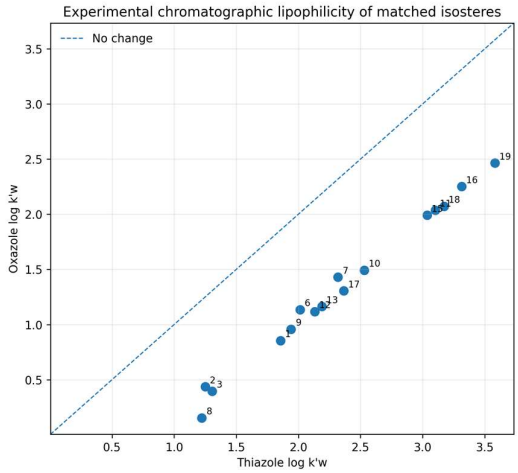

Figure 3. Experimental chromatographic lipophilicity (log k'w) for sixteen matched thiazole/oxazole pairs. Every point lies below the line of identity, demonstrating a uniform decrease after sulfur-to-oxygen replacement.

Table 3. Experimental aqueous solubility of selected matched isosteres [6].

Compound	Solubility (µg/mL)	Relative solubility	Experimental log S
6a	29.93	1	-3.90
6b	No precipitate at test level	Not determined	Not determined
12a	0.28	1	-6.00
12b	115.65	413	-3.36
15a	2.10	1	-5.18
15b	123.99	59	-3.38

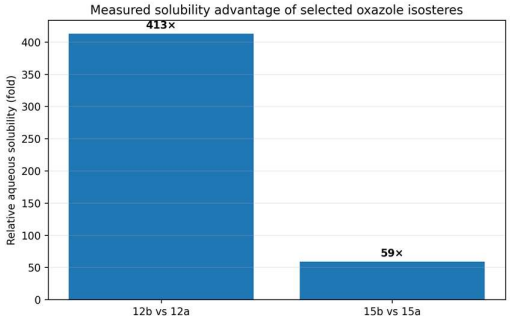

Figure 4. Fold increase in measured aqueous solubility for oxazole derivatives 12b and 15b relative to their matched thiazoles.

Table 4. MIC values of lead oxazoles against virulent and multidrug-resistant M. tuberculosis isolates [6].

Compound	H37Rv	MDR IZAK	MDR MATI
6b	6.25	3.13	3.13
7b	6.25	3.13	3.13
Ciprofloxacin	0.20	0.20	0.20
Ethambutol	0.39	1.56	1.56
Isoniazid	0.39	12.5	12.5 (>12.5 reported for one endpoint)

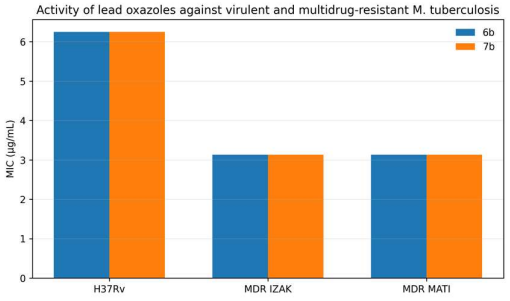

Figure 5. Lead oxazoles 6b and 7b retained activity against virulent H37Rv and two multidrug-resistant clinical isolates. Values are reconstructed from the source study.

Table 5. HepG2 cytotoxicity and antimycobacterial selectivity of the most active compounds [6].

Compound	HepG2 IC50 (µM)	H37Ra MIC (µg/mL)	H37Ra MIC (µM)	Selectivity index
4b	>1000	7.81	38.4	>26.0
5b	>1000	3.91	19.2	>52.0
6b	664.1	3.125	14.0	47.5
7b	959.4	<3.91	<16.5	>58.3
11a	>100	3.91	13.9	>7.2
11b	>1000	3.91	14.7	>67.8
13a	>100	7.81	27.8	>3.6
15a	102.6	3.91	12.4	8.3
15b	136.1	7.81	26.1	5.2

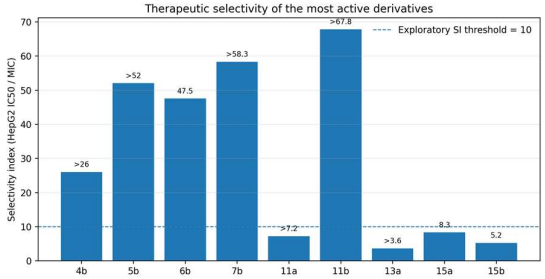

Figure 6. Selectivity indices of active derivatives. Greater-than signs indicate that cytotoxicity IC50 exceeded the highest tested concentration; those bars are minimum selectivity estimates.

Table 6. Consolidated structure–activity relationships derived from the authentic dataset.

Structural/property feature	Observed effect	Design implication
S-to-O replacement in matched aminoazoles	Reduced log k'w by about 1 unit in every matched pair	Use to rescue overly lipophilic or precipitating thiazoles
Compact subtype-I framework	Most consistent gain in H37Ra potency after oxazole substitution	Prioritize low-flexibility leads for bioisosteric rescue
2-Cl-pyridin-4-carbonyl	6b and 7b among the most potent and broad-spectrum derivatives	Retain as an anchor motif during optimization
Meta methyl/chlorine substitution	Improved potency in several pyridyl analogues	Explore small hydrophobic groups systematically
4-Phenyl aminoazole subtype II	Higher absolute lipophilicity;	Avoid adding aromatic bulk without target

Structural/property feature	Observed effect	Design implication
	inconsistent potency advantage	or PK justification
Quinoxalinyl aroyl group	High log k'w and weak H37Ra activity	Reduce fused aromaticity or disrupt crystal packing
Oxazole leads 6b/7b	No loss of activity in two MDR isolates	Advance to larger resistance and intracellular panels
High aqueous solubility alone	Did not guarantee stronger MIC in 15a/15b	Balance exposure with binding and envelope penetration

5. Discussion

5.1 Principal findings

The strongest conclusion from the reconstructed dataset is not that oxazole is universally more antimicrobial than thiazole. Rather, oxygen replacement generated a remarkably consistent physicochemical shift and a context-dependent biological response. All sixteen matched oxazoles were less lipophilic, and selected analogues were tens to hundreds of times more soluble. In compact subtype-I compounds, this often converted weak or censored thiazoles into measurable antimycobacterial leads. In the bulkier subtype-II series, the same lipophilicity reduction did not consistently improve MIC. This is a classic exposure–recognition interaction: once sufficient free compound reaches the cell and target, further polarity changes may help, harm, or have no effect depending on binding and penetration.

The 6a/6b pair is the most persuasive example. The thiazole had log k'w 2.013, solubility 29.93 micrograms per millilitre, and H37Ra MIC at least 500 micrograms per millilitre. The oxazole had log k'w 1.136, no precipitation at the 500-micromolar solubility challenge, and MIC 3.125 micrograms per millilitre. Because the structural change is limited to S-to-O exchange, the at-least 160-fold potency improvement strongly implicates effective exposure. A related pattern occurred in 7a/7b and 10a/10b. Nevertheless, the 1a/1b and 13a/13b pairs demonstrate that lower lipophilicity can reduce potency when a hydrophobic interaction, tautomer distribution, or membrane partitioning is favorable in the thiazole.

5.2 Structure–activity relationship

The aroyl region was a major potency determinant. Pyridin-4-carbonyl analogues generally outperformed pyridin-2-carbonyl analogues in subtype I, and small chlorine or methyl substitution improved activity. The docking model offers a plausible spatial explanation: substituents meta to the carboxamide can project toward a hydrophobic region formed by Ile156, Phe157, Leu207, Ala246, and Asn274. A chlorine atom can increase dispersion and shape complementarity without adding a rotatable bond, while methyl can fill space and tune ring electronics. Combining these effects in 7b preserved potency and broad mycobacterial spectrum.

Quinoxaline illustrates the opposite design pressure. Enlarging the fused aromatic system can improve theoretical stacking but increases planarity, crystal packing, and lipophilicity. Compound 19b remained inactive against H37Ra despite a full log-unit reduction in log k'w relative to 19a, suggesting that its absolute property profile was still unfavorable or that its binding geometry was intrinsically weak. The activity of 19b against M. avium cautions against simplistic deletion of such chemotypes; a species-selective phenotype can reveal uptake or metabolic differences that are valuable for mechanism studies.

The additional 4-phenyl group in subtype II increased aromatic surface and conformational complexity. This series contained potent thiazoles and oxazoles, but matched improvements were inconsistent. Compound 15a was twice as potent as 15b despite the 59-fold solubility advantage of 15b, and the SI of both compounds was modest. This suggests that the thiazole may bind more favorably or partition into the mycobacterial envelope more efficiently. The result also demonstrates why optimization should use multidimensional criteria. Solubility rescue is valuable, but a candidate should not be selected solely because it is easier to formulate.

5.3 Antimicrobial spectrum and resistance relevance

The retained activity of 6b and 7b against two MDR clinical isolates is a high-value observation. The isolates showed the expected loss of isoniazid activity, whereas oxazole MICs did not worsen. A reasonable inference is that the compounds act through a pathway not directly affected by the dominant resistance mechanisms in those isolates. This inference is compatible with FabH inhibition but does not prove it. Larger isolate panels should include diverse resistance genotypes, efflux phenotypes, and lineages. Frequency-of-resistance experiments and whole-genome sequencing of resistant mutants could rapidly identify whether a single target dominates.

The weaker antibacterial and antifungal activity has two interpretations. First, the chemical series appears biased toward mycobacteria, possibly because mycobacterial envelope or fatty-acid metabolism creates a favorable vulnerability. Second, oxazole replacement improved broad whole-cell access enough to reveal low-level activity absent in the thiazoles. The latter supports additional optimization against Gram-positive bacteria or fungi, but current MICs of 31.25–62.5 micromolar are lead-like rather than development-ready. Future analogues should be evaluated against biofilms, intracellular mycobacteria,

dormant or nutrient-starved bacilli, and macrophage infection models.

5.4 Mechanistic interpretation

FabH is a coherent hypothesis because the compounds resemble established FabH-directed thiazoles and dock near the catalytic region. The predicted carbonyl hydrogen bonds and Asn274 interaction are chemically reasonable, and most MD replicas retained the pose. However, docking scores did not correlate simply with MIC; 15b scored better than 6b but was less potent. This discrepancy may reflect whole-cell exposure, imperfect scoring, alternative targets, or multiple mechanisms. Direct biochemical inhibition using purified MtFabH should therefore be paired with counterscreens against related KAS enzymes and unrelated cysteine-containing proteins. Covalent reactivity is not expected from the reported structures, but nonspecific aggregation and redox effects should still be excluded.

Chemical-genetic methods would strengthen target assignment. Overexpression of fabH should shift susceptibility if target engagement is limiting, whereas partial knockdown should sensitize cells. Metabolomic lipid profiling could detect changes in fatty-acid and mycolic-acid precursors. Resistant colonies selected at multiples of MIC could be sequenced for fabH mutations; absence of such mutations would not exclude the target but would guide attention toward uptake, efflux, or polypharmacology. A co-crystal or cryogenic electron microscopy structure would provide definitive binding geometry and enable structure-based optimization.

5.5 Safety and developability

HepG2 data indicate that several leads have an encouraging preliminary selectivity window, especially 5b, 6b, 7b, and 11b. This is necessary but not sufficient. HepG2 cells incompletely reproduce primary hepatocyte metabolism, and a compound can be non-cytotoxic yet cause mitochondrial, genotoxic, cardiotoxic, or idiosyncratic effects. Follow-up should include primary hepatocytes, mitochondrial respiration, hERG or broader cardiac ion-channel assessment, Ames or micronucleus testing, and plasma-protein binding. Because thiazole bioactivation and frequent-hitter behavior motivated the isosteric strategy, comparative metabolite identification and glutathione-trapping studies would be particularly informative [15-17].

The solubility gains are likely to improve formulation flexibility and reduce false-negative assay outcomes. Nevertheless, kinetic solubility at a single temperature does not define thermodynamic solubility, salt behavior, solid-state form, or gastrointestinal dissolution. Crystal polymorphism, pKa, permeability, microsomal stability, and transporter liability should be measured. The oxazole ring is neutral and may reduce nonspecific binding, but excessive polarity could lower passive penetration through the lipid-rich mycobacterial envelope. An optimal property window rather than maximal hydrophilicity is therefore required.

5.6 Methodological strengths

The matched-isostere design is the principal strength of the source dataset. By preserving the aroyl fragment and replacing only S with O, it isolates a chemically meaningful variable. The study also integrated measured rather than merely calculated lipophilicity, direct solubility measurements, several mycobacterial species, virulent and resistant M. tuberculosis, cytotoxicity, and computational hypotheses. Full compound purity and modern spectrometric characterization reduce the risk that activity arose from contaminants. Reporting censored MIC and cytotoxicity values is also preferable to assigning arbitrary exact numbers.

Table 7. Minimum recommended package for converting the present literature-derived lead series into an original, submission-ready experimental study.

Workstream	Required experiment	Decision criterion
Chemistry	Prepare focused 6b/7b analogues; report isolated yield, full NMR/HRMS, and HPLC purity	Reproducible synthesis; purity ≥95%
Primary microbiology	Triplicate H37Rv MIC with independent repeats and MBC/time-kill	MIC ≤2 μg/mL and reproducible bactericidal exposure
Resistance	Test ≥30 resistant clinical isolates; select and sequence resistant mutants	Low MIC shift across genotypes; tractable resistance frequency
Intracellular activity	Macrophage infection assay with host-cell viability	Intracellular potency near broth MIC
Mechanism	Purified MtFabH assay, target engagement, chemical genetics, lipidomics	Concordant evidence for or against FabH causality
Developability	Thermodynamic solubility, permeability, microsomal stability, protein binding	Unbound exposure capable of exceeding MIC
Safety	Primary	Selectivity

Workstream	Required experiment	Decision criterion
	hepatocytes, mitochondrial function, genotoxicity, cardiac channels	margin appropriate for in vivo dosing
In vivo proof	Rodent PK and acute TB efficacy with exposure-MIC analysis	Dose-dependent bacterial burden reduction

6. Conclusion

The oxazole nucleus is a scientifically credible antimicrobial scaffold and a particularly useful bioisostere of 2-aminothiazole. In the authentic matched dataset analyzed here, sulfur-to-oxygen replacement lowered experimental lipophilicity by approximately one log unit in every matched pair and produced major solubility gains, including 413-fold and 59-fold improvements for selected analogues. Biological consequences were structure-dependent. Compact oxazoles bearing substituted pyridyl carboxamides frequently gained antimycobacterial potency, and leads 6b and 7b retained low-microgram-per-millilitre activity against virulent and multidrug-resistant M. tuberculosis. Several leads also demonstrated broad mycobacterial activity, limited antibacterial and antifungal activity, and encouraging HepG2 selectivity.

The data support a disciplined interpretation: 2-aminooxazole can rescue compounds whose apparent inactivity is caused by excessive lipophilicity or precipitation, but it does not automatically improve target affinity. The strongest design signal is the combination of a compact aminooxazole core with 2-chloropyridin-4-carbonyl or related meta-substituted heteroaroyl groups. FabH is a plausible target hypothesis supported by docking and molecular dynamics, yet biochemical and genetic validation is required. Future work should integrate measured solubility, intracellular activity, resistant-isolate breadth, target engagement, primary-cell safety, and pharmacokinetics. With these additions, oxazole carboxamides could progress from informative whole-cell hits to mechanism-supported antimicrobial leads.

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