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Antibacterial Activity and Provisional Structure-Activity Relationships of a Thiazole-Schiff Base Hybrid Series Against Drug-Resistant Bacteria

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Abstract

Antimicrobial resistance continues to erode the effectiveness of established antibacterial therapy and places a premium on chemically tractable series that retain activity against clinically relevant resistant organisms. This study examines a ten-member thiazole-Schiff base hybrid series (SJ-1-SJ-10) across methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus faecium (VRE), multidrug-resistant *Escherichia coli*, KPC-producing *Klebsiella pneumoniae* and multidrug-resistant *Pseudomonas aeruginosa*. The available compound records showed isolated yields of 68-84%, melting points of 142-183 °C and HPLC purities of 97.2-99.1%. Broth microdilution data demonstrated a clear within-series potency gradient. SJ-7, labelled as the 4-CF3 analogue in the source dataset, was the most active compound, with MIC values of 2, 4, 16, 16 and 64 µg/mL against MRSA, VRE, MDR E. *coli*, K. *pneumoniae* and P. *aeruginosa*, respectively. SJ-6 and SJ-9 formed a second activity tier, whereas SJ-1 was consistently weaker. For SJ-7, MBC values were two-fold above the MIC across the bacterial panel. The pattern supports a provisional structure-activity relationship in which selected electron-withdrawing para substituents are associated with improved whole-cell activity, although the Gram-negative spectrum remained constrained, particularly against P. *aeruginosa*.

Keywords: Antimicrobial resistance, thiazole-Schiff base, MRSA, VRE, multidrug-resistant bacteria, MIC, structure-activity relationship

1. Introduction

Antimicrobial resistance (AMR) has become a major limitation on the reliability of anti-infective treatment. The global burden of resistant bacterial infection is substantial, and recent priority-setting exercises continue to emphasise the need for new antibacterial agents directed at difficult-to-treat Gram-positive and Gram-negative pathogens (Antimicrobial Resistance Collaborators, 2022; GBD 2021 Antimicrobial Resistance Collaborators, 2024; World Health Organization, 2024) [1, 7, 14]. The discovery challenge is not simply to identify molecules that inhibit bacterial growth. Resistant organisms can combine drug inactivation, target modification, reduced permeability, active efflux and adaptive physiological responses, so a chemically attractive hit may fail when tested in an intact resistant cell (Blair *et al*., 2015; Darby *et al*., 2023) [2, 6].

This problem is particularly acute for Gram-negative bacteria. The outer membrane and restricted porin pathways limit entry, while multidrug efflux can reduce intracellular concentrations even after a compound crosses the envelope. Enterobacterales may also carry beta-lactamases or carbapenemases together with permeability changes, and *Pseudomonas aeruginosa* adds strong intrinsic resistance and adaptive responses (Nikaido, 2003; Li *et al*., 2015) [9, 8]. For early medicinal chemistry, activity across more than one resistance context is therefore more informative than potency against a single susceptible reference strain.

Scaffold-based analogue series offer a practical way to address this complexity. When substituents can be varied systematically around a common core, the resulting structure-activity relationship (SAR) can indicate whether a chemical feature improves potency broadly or only in a particular organism. The same substitution can also alter solubility, lipophilicity, steric demand, membrane passage and efflux liability. Consequently, SAR is strongest when biological activity is interpreted together with synthetic tractability and chemical purity rather than from MIC values alone (O'Shea & Moser, 2008; Breijyeh & Karaman, 2023) [10, 3].

The present study evaluates a ten-member thiazole-Schiff

base hybrid series designated SJ-1 to SJ-10. The numerical records include isolated yield, melting point, mass-spectrometric observations, HPLC purity and replicated MIC/MBC measurements against a five-organism resistant panel. The objectives were to describe the within-series antibacterial spectrum, identify the most promising analogue, and define the SAR that is supported directly by the available data. Because no clinical breakpoints exist for these novel compounds and no matched comparator-antibiotic dataset was supplied, the analysis is intended for comparative lead ranking rather than clinical susceptibility classification.

2. Materials and Methods

2.1 Compound series and available characterisation

Ten compounds, SJ-1 to SJ-10, were recorded under a common thiazole-Schiff base hybrid scaffold. The source dataset labels the substituent series as H, 4-CH3, 4-OCH3, 4-F, 4-Cl, 4-Br, 4-CF3, 3-Cl, 4-NO2 and 3,4-(OCH3)2. The study framework specifies a multi-step synthetic and purification workflow with FT-IR, 1H/13C NMR, mass spectrometry, HPLC and melting-point characterisation. For the present manuscript, only variables available numerically for every compound were analysed: isolated yield, melting point, observed mass-spectrometric m/z and HPLC purity. Numerical FT-IR bands and NMR chemical shifts were not present in the source workbook and were not reconstructed.

2.2 Bacterial panel and susceptibility testing

The test panel comprised MRSA ATCC 43300, vancomycin-resistant Enterococcus faecium 700221, multidrug-resistant *Escherichia coli* EC-17, KPC-producing *Klebsiella pneumoniae* KPC-3 and multidrug-resistant *Pseudomonas aeruginosa* PA-21. This panel was selected to represent distinct resistance and envelope contexts, including clinically important Gram-positive resistance and the permeability-efflux constraints of Gram-negative bacteria.

MIC determination used serial two-fold broth microdilution and was interpreted in accordance with standard dilution-testing principles (Wiegand *et al*., 2008; Clinical and Laboratory Standards Institute, 2024) [13, 5]. Serial two-fold concentrations were used to identify the lowest tested concentration preventing growth under the assay conditions. Growth, sterility, vehicle and reference-antibiotic controls were specified in the study framework. The source workbook contains three replicate entries for each compound-strain combination, with the same MIC endpoint recorded across the three replicates. MBC assessment was performed by subculture from non-growing MIC wells onto drug-free agar, providing a complementary measure of viable recovery after exposure.

2.3 Data analysis and reporting scope

The analysis was descriptive and comparative. Compounds were ranked by MIC within each organism and by the breadth of activity across the panel. Synthetic yield and HPLC purity were used as supporting indicators of tractability and sample fitness. Because replicate MIC entries were identical within each compound-strain combination, no inferential analysis of within-condition MIC variance was attempted. MBC/MIC relationships were interpreted descriptively. No clinical susceptible/resistant designation was assigned to any novel compound.

Data integrity requires a specific qualification. The numerical workbook used for manuscript preparation was supplied as the student's final dataset, but its internal README also describes the records as synthetic demonstration data. The manuscript cannot independently resolve that conflict. In addition, several molecular-formula entries appear inconsistent with the substituent labels, and the source files do not contain numerical FT-IR or NMR assignments. The values below are therefore reproduced exactly as supplied and used for within-series comparison; original laboratory notebooks and instrument files should be used to resolve provenance and structural-record discrepancies before journal submission as primary experimental research.

Table 1: Available chemical and analytical profile of SJ-1 to SJ-10

Compound	Substituent label	Yield (%)	m.p. (°C)	Observed m/z	HPLC purity (%)
SJ-1	H	68	142	313.3673	97.2
SJ-2	4-CH3	72	149	327.3973	97.8
SJ-3	4-OCH3	75	156	343.3973	98.1
SJ-4	4-F	78	161	331.3573	98.5
SJ-5	4-Cl	81	168	347.8173	98.7
SJ-6	4-Br	77	172	392.2673	98.0
SJ-7	4-CF3	84	177	381.3573	99.1
SJ-8	3-Cl	73	164	347.8173	97.6
SJ-9	4-NO2	79	183	358.3673	98.8
SJ-10	3,4-(OCH3)2	70	151	373.4273	97.4

3. Results

3.1 Yield and analytical profile

All ten analogues were represented by a complete set of yield, melting-point, mass-spectrometric and HPLC-purity entries. Isolated yield ranged from 68% for SJ-1 to 84% for SJ-7, with a mean of 75.7%. SJ-5 and SJ-9 also showed relatively high yields of 81% and 79%, respectively. Melting points spanned 142-183 °C. HPLC purity ranged from 97.2% to 99.1% (mean 98.12%), indicating a narrow purity range across the series. SJ-7 combined the highest reported yield with the highest reported HPLC purity. These values support comparative biological testing of the recorded batches, although full structural verification requires the missing spectroscopic records.

3.2 Antibacterial activity across the resistant panel

The MIC matrix showed a consistent potency hierarchy. SJ-7 was the leading analogue against every organism tested. Its MIC was 2 µg/mL against MRSA, 4 µg/mL against VRE, 16 µg/mL against MDR E. *coli* and K. *pneumoniae*, and 64 µg/mL against P. *aeruginosa*. SJ-6 and SJ-9 formed a second tier, each giving MICs of 4 µg/mL against MRSA, 8 µg/mL against VRE and 32 µg/mL against both E. *coli* and K. *pneumoniae*. SJ-5 gave 8 µg/mL against both MRSA and VRE and 32 µg/mL against E. *coli*, whereas SJ-4 and SJ-8 showed intermediate activity. The unsubstituted SJ-1 was the weakest or among the weakest members across the panel.

Activity was systematically stronger against the Gram-positive organisms than against the Gram-negative panel. Even SJ-7 showed an eight-fold difference between its

MRSA MIC and its E. *coli*/K. *pneumoniae* MIC and a 32-fold difference between MRSA and P. *aeruginosa*. P. *aeruginosa* was the least susceptible organism for every analogue, with MIC values of 64-256 µg/mL. The common spectrum gap is consistent with the well-recognised challenge of obtaining sufficient intracellular exposure in Gram-negative bacteria, particularly Pseudomonas, although the dataset does not establish whether reduced penetration, efflux or target biology is responsible.

Table 2: Mean MIC values for the thiazole-Schiff base hybrid series (µg/mL; n = 3 entries per compound-strain combination)

Compound	MRSA	VRE	MDR E. *coli*	K. *pneumoniae*	P. *aeruginosa*
SJ-1	32	64	128	128	256
SJ-2	16	32	128	128	256
SJ-3	16	16	64	128	256
SJ-4	8	16	64	64	128
SJ-5	8	8	32	64	128
SJ-6	4	8	32	32	128
SJ-7	2	4	16	16	64
SJ-8	8	16	64	64	128
SJ-9	4	8	32	32	128
SJ-10	16	32	64	128	256

3.3 MBC relationship and provisional SAR

MBC results tracked the MIC pattern. For SJ-7, MBC values were 4 µg/mL against MRSA, 8 µg/mL against VRE, 32 µg/mL against MDR E. *coli* and K. *pneumoniae*, and 128 µg/mL against P. *aeruginosa*. Thus, the MBC was two-fold above the MIC across the full panel. SJ-9 showed the same two-fold relationship, whereas most other analogues required a larger increase above the inhibitory concentration. These data strengthen the lead ranking of SJ-7 because its advantage was not restricted to growth inhibition.

The substituent labels suggest a coherent provisional SAR. Moving from the unsubstituted SJ-1 to several para-substituted analogues improved Gram-positive activity, and the largest overall gain was associated with the 4-CF3-labelled SJ-7. The 4-Br-labelled SJ-6 and 4-NO2-labelled SJ-9 also performed well. The 3-Cl-labelled SJ-8 was weaker than the corresponding 4-Cl-labelled SJ-5, suggesting that substituent position may matter as well as electronics. Because some formula fields are inconsistent with their substituent labels and definitive FT-IR/NMR assignments are unavailable, these relationships should be viewed as trends in the supplied compound labels rather than final structure-based mechanistic conclusions.

4. Discussion

The central result is the emergence of SJ-7 as the strongest whole-cell antibacterial candidate within a chemically related ten-member series. Its advantage was reproduced across five resistance contexts, which is more informative than a single low MIC against one organism. The compound was four- to sixteen-fold more active than SJ-1 depending on the organism, and its ranking remained favourable when MBC values were considered. This cross-panel pattern makes SJ-7 a rational anchor for subsequent medicinal-chemistry optimisation.

The Gram-positive results are the most compelling part of the profile. MIC values of 2 µg/mL against MRSA and 4 µg/mL against VRE indicate substantial within-series potency. SJ-6 and SJ-9 also showed low single-digit MICs against MRSA, providing nearby comparators that can help define which substituent properties are beneficial. A matched set of active and less active analogues is valuable for follow-up experiments because it allows biological observations to be interpreted against a chemical gradient rather than in isolation.

The Gram-negative data show both progress and limitation. SJ-7 retained measurable activity against MDR E. *coli* and KPC-producing K. *pneumoniae* at 16 µg/mL, whereas the weaker compounds commonly required 64-128 µg/mL. This suggests that the structural features associated with SJ-7 may improve whole-cell exposure or preserve target activity across distinct resistance backgrounds. However, its P. *aeruginosa* MIC remained 64 µg/mL. Gram-negative accumulation depends on a balance of entry, physicochemical properties and efflux, and Pseudomonas imposes particularly demanding envelope constraints (Nikaido, 2003; Li *et al*., 2015) [9, 8]. The present dataset cannot determine which of these factors limits SJ-7, but it identifies a clear question for follow-up accumulation and efflux studies.

The SAR should be interpreted conservatively. The apparent benefit of the 4-CF3, 4-Br and 4-NO2 labels is compatible with a role for electron-withdrawing substituents, but antibacterial SAR is rarely reducible to electronics alone. These groups also change lipophilicity, steric profile, polar surface distribution and membrane interaction. Moreover, the difference between SJ-5 and SJ-8 suggests that positional effects may contribute. A useful next analogue set would therefore separate electronic and positional variables systematically rather than simply adding more strongly electron-withdrawing groups.

The chemical quality data help strengthen the comparison because HPLC purity was high throughout the series and the most active compound also had the highest reported purity. Large potency differences are therefore less likely to be explained solely by gross purity differences. Nonetheless, chromatographic purity does not confirm structure, and the absence of numerical FT-IR and NMR assignments is a material limitation for a medicinal-chemistry paper. Before the structural SAR is treated as definitive, each lead should be reconciled with its original spectra and formula assignment, particularly where the source spreadsheet shows inconsistencies between substituent and molecular-formula fields.

The MIC results should also be interpreted as discovery endpoints rather than clinical breakpoints. Standardised broth microdilution is appropriate for comparative ranking, but novel chemical matter has no established susceptible/resistant thresholds. Comparator antibiotics tested in the same experimental run would improve context and allow readers to judge assay performance more directly. Likewise, independent repeat experiments using freshly prepared compound batches would strengthen the reproducibility of the rank order, particularly because the source workbook records identical MIC values across its three replicate entries.

The current findings therefore support a focused progression strategy rather than a claim of a finished antibiotic

candidate. SJ-7 should be prioritised for complete structure confirmation, repeat MIC/MBC testing, matched comparator studies and deeper profiling of its Gram-negative exposure. SJ-6 and SJ-9 are useful secondary analogues because they preserve strong Gram-positive activity while providing different substituent contexts. Less active compounds such as SJ-1 remain informative because they define the lower end of the SAR and can help distinguish general physicochemical effects from specific structural requirements.

More broadly, the series illustrates why antibacterial lead selection should integrate chemistry and microbiology. A low MIC is valuable only when the test article is well characterised, the result is reproducible and the activity can be placed within a coherent analogue series. This principle is especially important in AMR research, where attrition is driven not only by target potency but also by bacterial exposure, selectivity and resistance biology (Silver, 2011; Tommasi *et al*., 2015; Brown & Wright, 2016) [11, 12, 4]. Within those limits, the present dataset identifies a credible internal lead hierarchy and a clear experimental path forward.

Resistance development should also be considered early. Activity against resistant strains does not mean that a new scaffold is resistant to the evolution of further resistance. Once SJ-7 has been independently confirmed, single-step resistance frequency, serial-passage experiments and cross-resistance testing would help determine whether the lead offers a meaningful barrier to resistance. The value of such work would be greatest if resistant derivatives were paired with sequencing or phenotypic studies capable of distinguishing targ*et al*teration from altered permeability or efflux. This would connect the observed whole-cell SAR with the biological mechanism that ultimately determines durability of activity.

From a medicinal-chemistry perspective, the present series is most useful as a hypothesis-generating platform. The activity gradient suggests that the scaffold can tolerate substantial substituent modification while retaining antibacterial function. Rather than expanding the library broadly, a more efficient next round would use a small, deliberately designed set of analogues that separates steric, electronic and lipophilic effects. Positional isomers around the aryl substituent would be particularly informative because SJ-5 and SJ-8 imply that para and meta substitution are not equivalent. Measurements of aqueous solubility, logD, chemical stability and bacterial accumulation would then allow potency shifts to be interpreted against exposure rather than attributed automatically to target affinity.

These considerations matter because antibacterial discovery frequently fails when early potency is disconnected from the physicochemical and biological properties needed for whole-cell activity. A convincing journal report should therefore make the evidential chain explicit: the structure and purity of the tested batch must be secure; the assay conditions and controls must be reproducible; the activity pattern must be repeatable; and the SAR must remain stable when new analogues are added. The current dataset provides a useful starting point for that chain, but its greatest scientific value lies in defining the confirmatory experiments that would convert a promising internal ranking into a defensible medicinal-chemistry claim.

Finally, the study design would benefit from explicit reporting of independent experimental repeats in addition to technical replicates. Identical triplicate MIC entries can indicate a stable endpoint, but they do not show whether the same ranking persists across separate days, inoculum preparations or compound batches. Independent replication is particularly important when a one-dilution change can alter the apparent order of closely related analogues. A confirmatory programme that repeats the leading compounds under independently prepared conditions would therefore provide a stronger basis for publication and for deciding whether the observed SAR is robust enough to guide further synthesis.

5. Conclusion

The thiazole-Schiff base hybrid series showed a reproducible within-dataset activity gradient across resistant Gram-positive and Gram-negative bacteria. SJ-7 was the strongest member, with MIC values of 2-64 µg/mL across the five-organism panel and an MBC two-fold above the MIC for each organism. SJ-6 and SJ-9 formed a second tier of activity, while P. *aeruginosa* remained the most difficult test organism for the entire series. The substituent pattern supports a provisional SAR favouring selected para electron-withdrawing groups, but complete structural verification is required before that interpretation is considered definitive. Subject to reconciliation of the source-data provenance and the missing spectroscopic records, SJ-7 merits prioritisation for confirmatory antibacterial, exposure and mechanism studies.

6. References

1. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet. 2022;399(10325):629-655. doi:10.1016/S0140-6736(21)02724-0.
2. Blair JMA, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJV. Molecular mechanisms of antibiotic resistance. Nature Reviews Microbiology. 2015;13:42-51. doi:10.1038/nrmicro3380.
3. Breijyeh Z, Karaman R. Design and synthesis of novel antimicrobial agents. Antibiotics. 2023;12(3):628. doi:10.3390/antibiotics12030628.
4. Brown ED, Wright GD. Antibacterial drug discovery in the resistance era. Nature. 2016;529:336-343. doi:10.1038/nature17042.
5. Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. 12th ed. CLSI Standard M07. Wayne (PA): Clinical and Laboratory Standards Institute; 2024.
6. Darby EM, Trampari E, Siasat P, Gaya MS, Alav I, Webber MA, *et al*. Molecular mechanisms of antibiotic resistance revisited. Nature Reviews Microbiology. 2023;21:280-295. doi:10.1038/s41579-022-00820-y.
7. GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990-2021: a systematic analysis with forecasts to 2050. The Lancet. 2024;404(10459):1199-1226. doi:10.1016/S0140-6736(24)01867-1.
8. Li XZ, Plesiat P, Nikaido H. The challenge of efflux-mediated antibiotic resistance in Gram-negative

bacteria. Clinical Microbiology Reviews. 2015;28(2):337-418. doi:10.1128/CMR.00117-14.
9. Nikaido H. Molecular basis of bacterial outer membrane permeability revisited. Microbiology and Molecular Biology Reviews. 2003;67(4):593-656. doi:10.1128/MMBR.67.4.593-656.2003.
10. O'Shea R, Moser HE. Physicochemical properties of antibacterial compounds: implications for drug discovery. Journal of Medicinal Chemistry. 2008;51(10):2871-2878. doi:10.1021/jm700967e.
11. Silver LL. Challenges of antibacterial discovery. Clinical Microbiology Reviews. 2011;24(1):71-109. doi:10.1128/CMR.00030-10.
12. Tommasi R, Brown DG, Walkup GK, Manchester JI, Miller AA. ESKAPEing the labyrinth of antibacterial discovery. Nature Reviews Drug Discovery. 2015;14:529-542. doi:10.1038/nrd4572.
13. Wiegand I, Hilpert K, Hancock REW. Agar and broth dilution methods to determine the minimal inhibitory concentration (MIC) of antimicrobial substances. Nature Protocols. 2008;3:163-175. doi:10.1038/nprot.2007.521.
14. World Health Organization. WHO bacterial priority pathogens list, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. Geneva: World Health Organization; c2024.