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# Bayesian Modeling and Intrabacterial Drug Metabolism Applied to Drug-Resistant *Staphylococcus aureus*

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Fortified by Bayesian modeling and intrabacterial drug metabolism studies

We present the application of Bayesian modeling to identify chemical tools and/or drug discovery entities pertinent to drug-resistant *Staphylococcus aureus* infections. The quinoline JSF-3151 was predicted by modeling and then empirically demonstrated to be active against *in vitro* cultured clinical methicillin- and vancomycin-resistant strains while also exhibiting efficacy in a mouse peritonitis model of methicillin-resistant *S. aureus* infection. We highlight the utility of an intrabacterial drug metabolism (IBDM) approach to probe the mechanism by which JSF-3151 is transformed within the bacteria. We also identify and then validate two mechanisms of resistance in *S. aureus*: one mechanism involves increased expression of a lipocalin protein, and the other arises from the loss of function of an azoreductase. The computational and experimental approaches, discovery of an antibacterial agent, and elucidated resistance mechanisms collectively hold promise to advance our understanding of therapeutic regimens for drug-resistant *S. aureus*.

**KEYWORDS:** Bayesian modeling, *Staphylococcus aureus*, quinoline, intrabacterial drug metabolism ▾

## Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsinfecdis.1c00265>.

- Comparative model external ROC curves; *In vitro* bactericidal activity of JSF-3151; *In vivo* profiling of JSF-3151; IBDM studies of JSF-3151 and its metabolite JSF-3640; JSF-3151 membrane depolarization and NO<sup>•</sup> release assays; Quantification of *yceI* transcription in JSF-3151-resistant strains; Internal Statistics for Bayesian Models; External Statistics for Bayesian Models; *S. aureus* MIC values for top-scoring compounds from MRSA\_1a and MRSA\_1b predictions with the Enamine library; MRSA MIC values for bottom-scoring compounds from MRSA\_1b predictions with the Enamine library; MIC of JSF-3151 versus VRSA and VISA strains; Primers used in this study; Strains and plasmids used in this study; Accumulation metrics for JSF-3151 and JSF-3640 in select strains (PDF)

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## Supplementary Information

### Bayesian Modeling and Intrabacterial Drug Metabolism Applied to *Staphylococcus aureus*

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