Primary amines promote small molecule accumulation in Gram-negative bacteria

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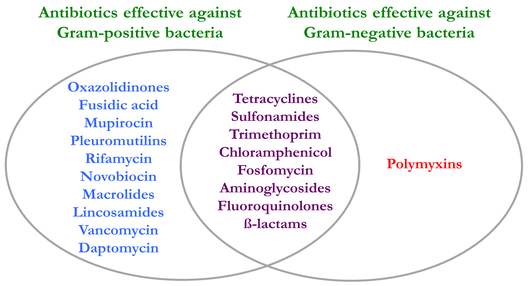
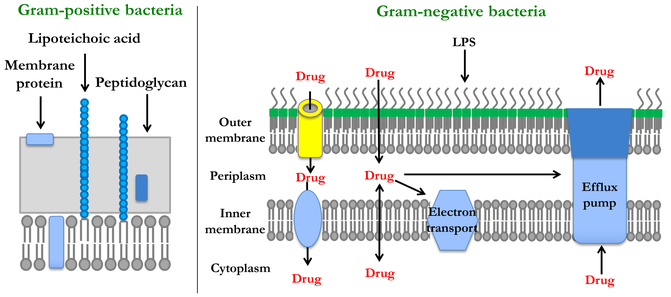
Effective Gram-negative antibiotics are outranked by Gram-positive bacteria



"For drugs targeting Gram-negative pathogens, there has not been a compound approved with a novel mechanism of action in *nearly half a century*"

Clin. Microbiol. Reviews 2011, *24*, 71-106.
CDC Antibiotic Resistance Threats in the United States, 2013.
J. Med. Chem. 2014, *57*, 10144-10161.

Porins and efflux pumps synergistically inhibit small molecule accumulation

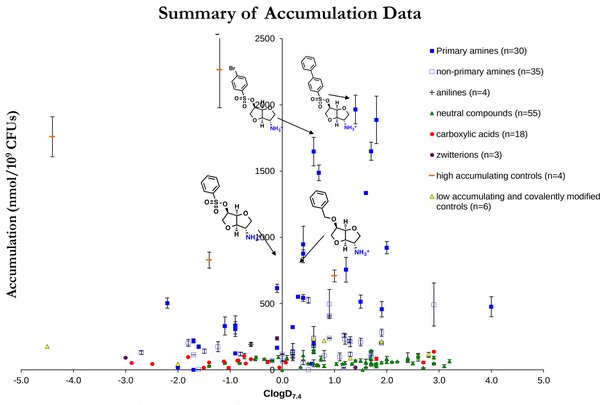


Most small molecules can cross the peptidoglycan layer

The dual membranes and efflux pumps function synergistically to prevent the accumulation of most small molecules

Expert Opin. Drug Discov. 2012, *7*, 633-642.

Studying the properties that enable small molecule accumulation in *E.coli*



145 CtD compounds analyzed for accumulation (including 65 amines)
Observed that primary amines are most likely to accumulate (17 out of 30)
$ClogD_{7.4}$ does not appear to be an important variable

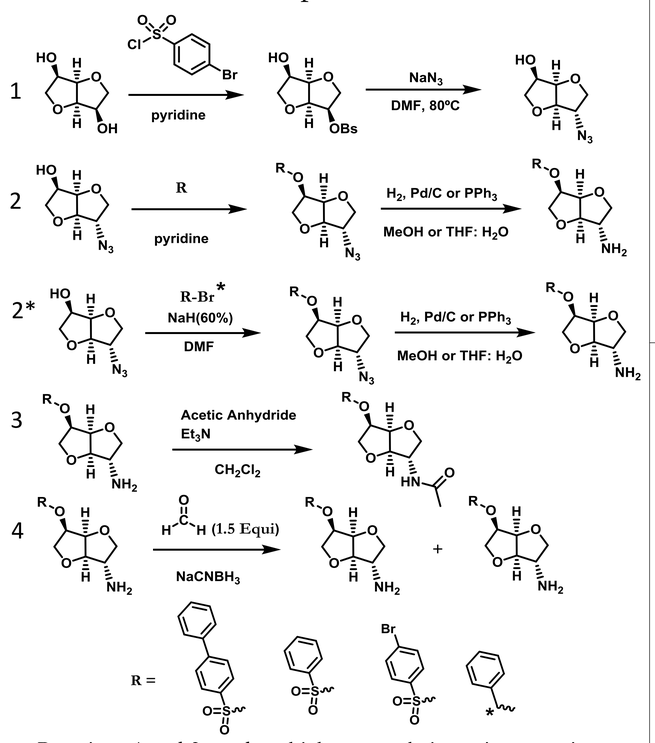
Previous research has shown that primary amine containing small molecules are high accumulators in Gram-negative bacteria.

The four molecules depicted on the diagram were selected for their high accumulation and primary amines .

Structure-activity relationship and accumulation of small molecules within Gram-negative bacteria

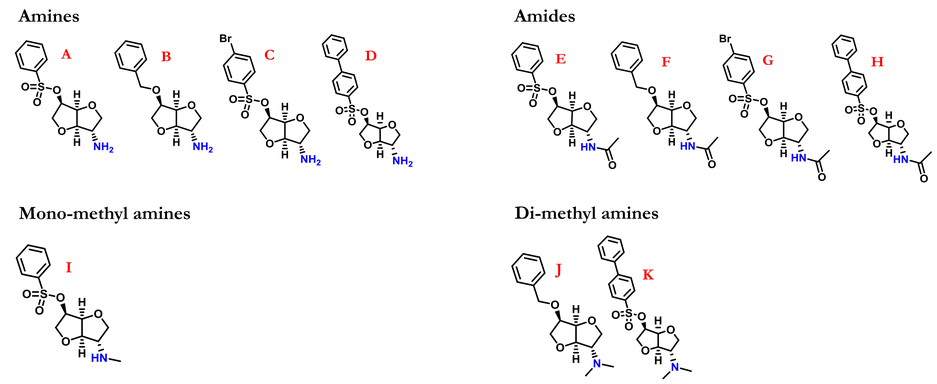
Goal: Understanding how methylation or acylation of the primary amine of high-accumulating isomannide derivatives affects accumulation in Gram-negative bacteria.

Chemical reactions to produce small molecules



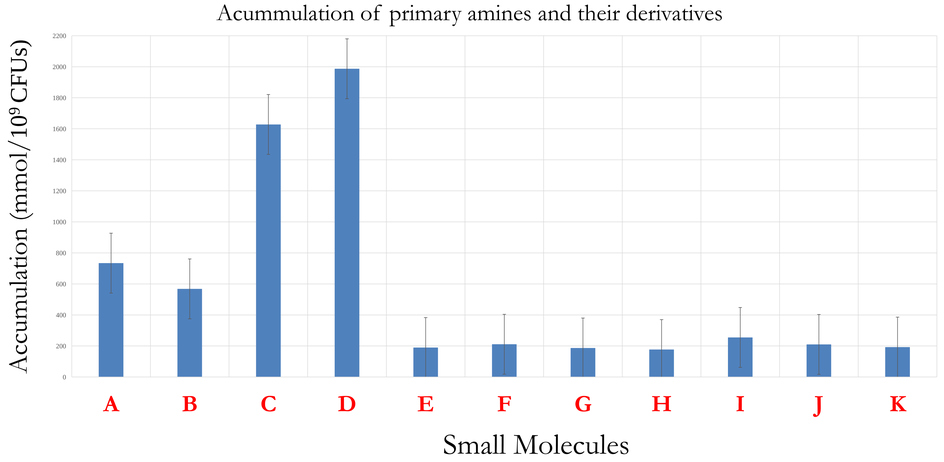
Reactions 1 and 2 produce high-accumulating primary amines. Reactions 3 and 4 create derivatives of the high-accumulation primary amines by ways of methylation or acetylation of the primary amine.

Library of molecules synthesized



Data on accumulation of small molecules

Acummulation of primary amines and their derivatives



Conclusion

- In both cases of methylation and acylation of the primary amine, small molecule accumulation was decreased by as much as 10 fold.
- The data of the primary amines alone seem to suggest that large substituents attached to the molecule increase uptake within Gram-negative bacteria.

Acknowledgements

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