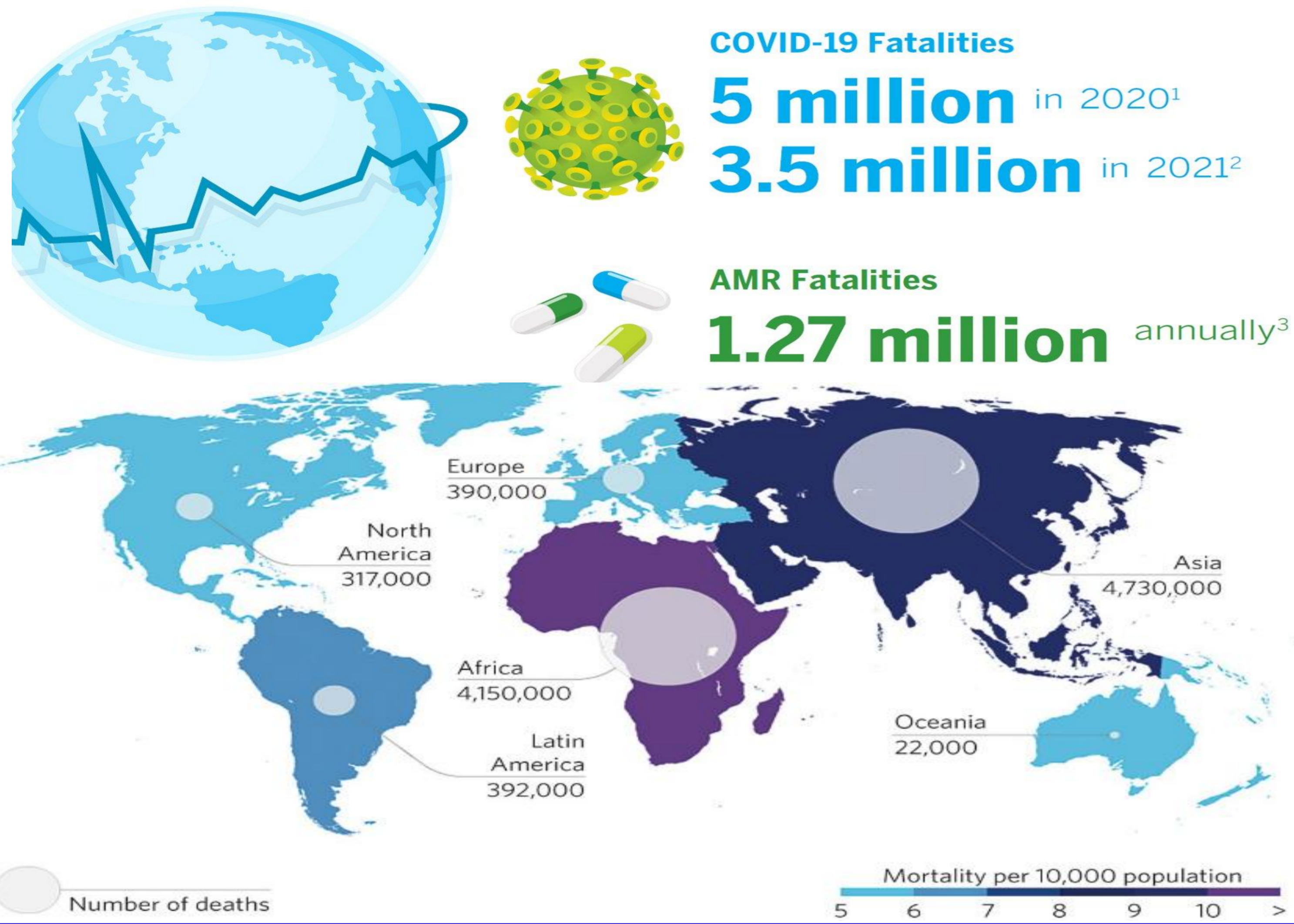


Background

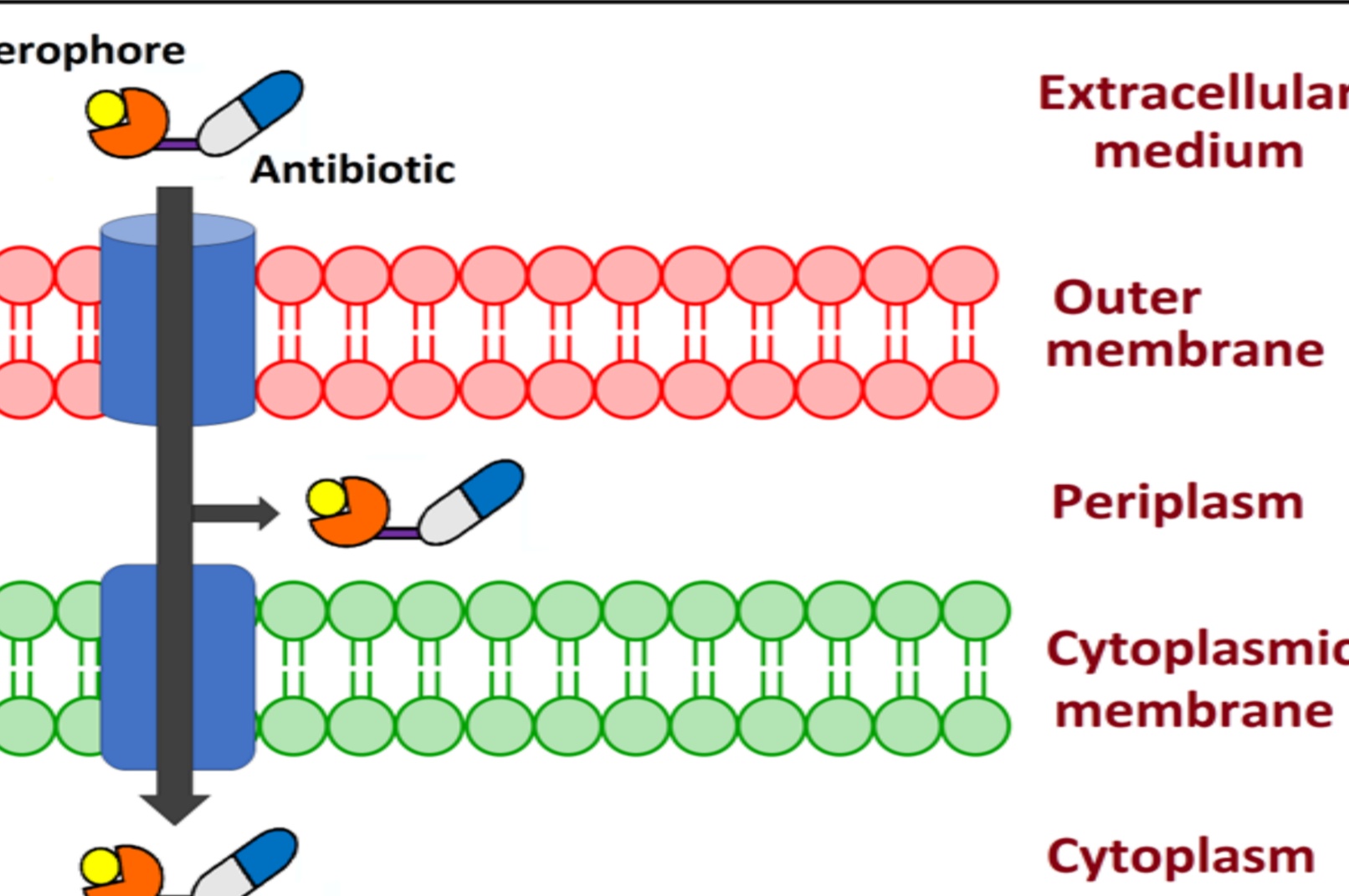
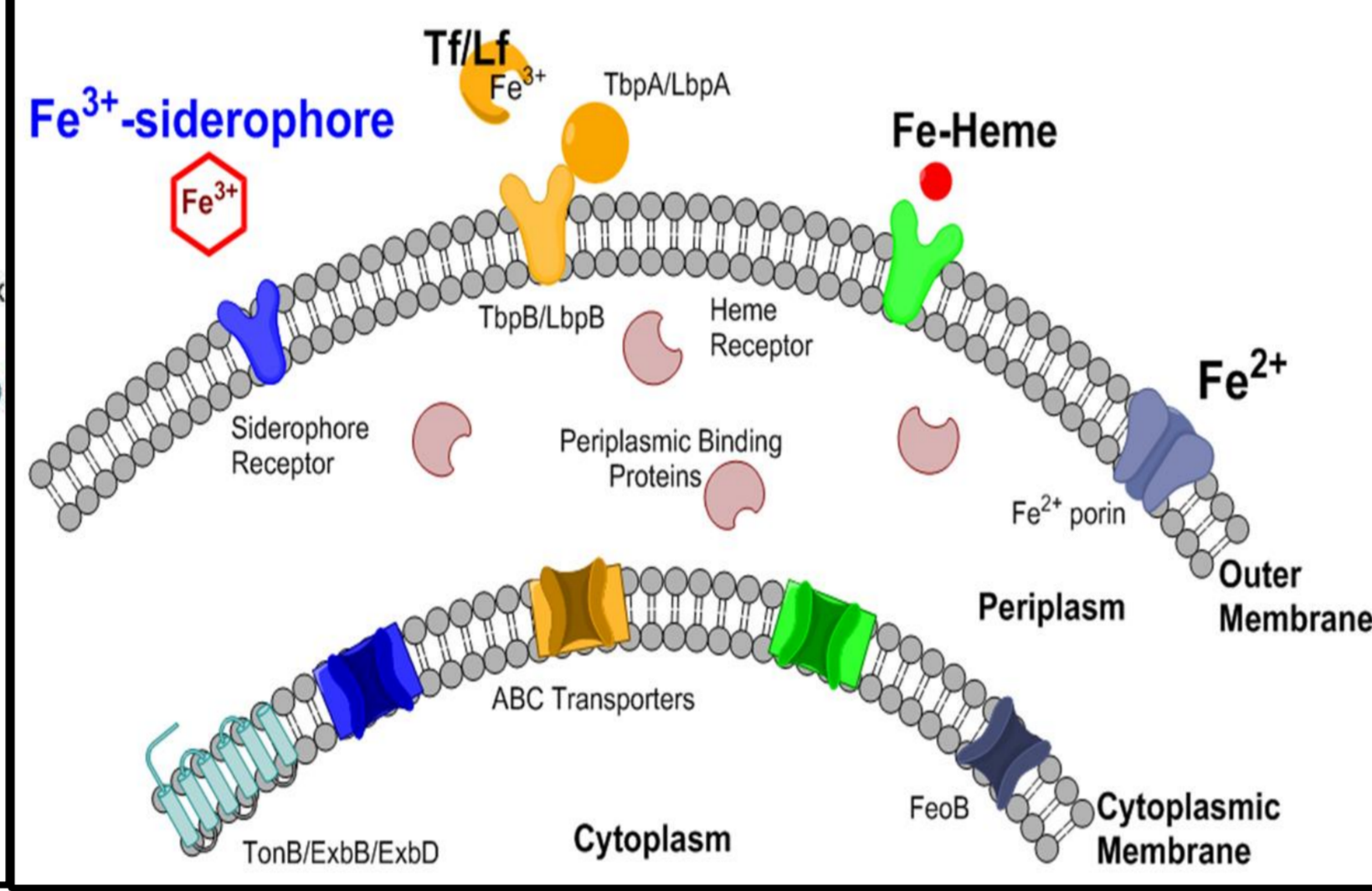
IMPACT ON GLOBAL HEALTH:



Mechanism

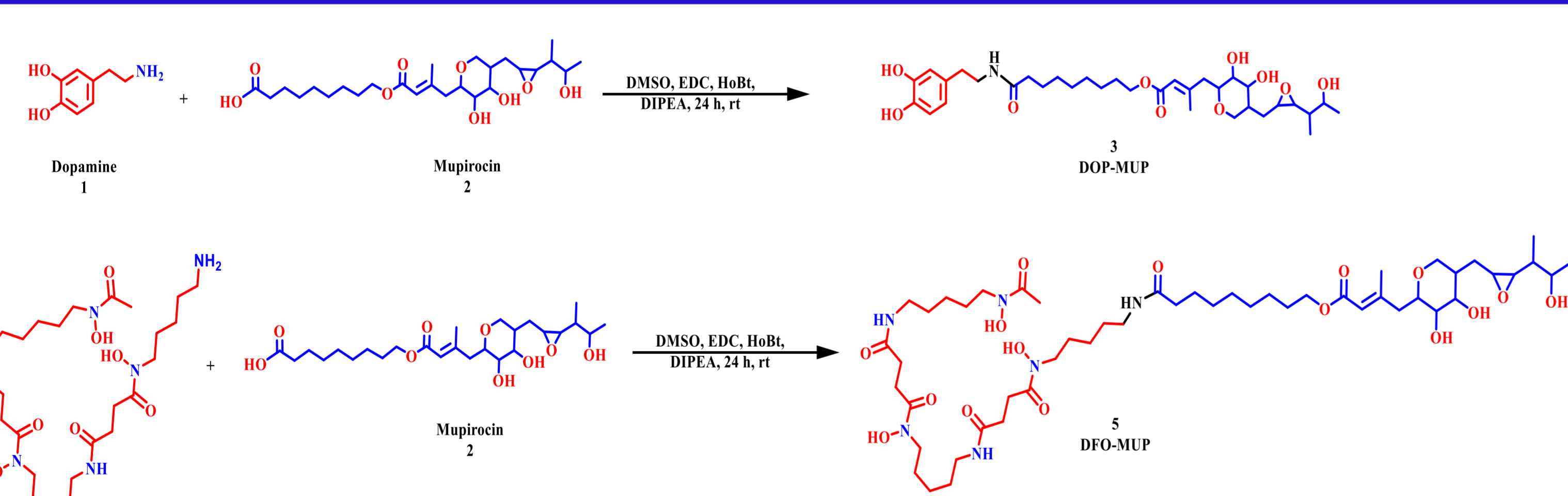
Iron Uptake Pathways in Gram-Negative Bacteria:

Siderophore, Transferrin/Lactoferrin, FeHeme, & Ferrous Ion

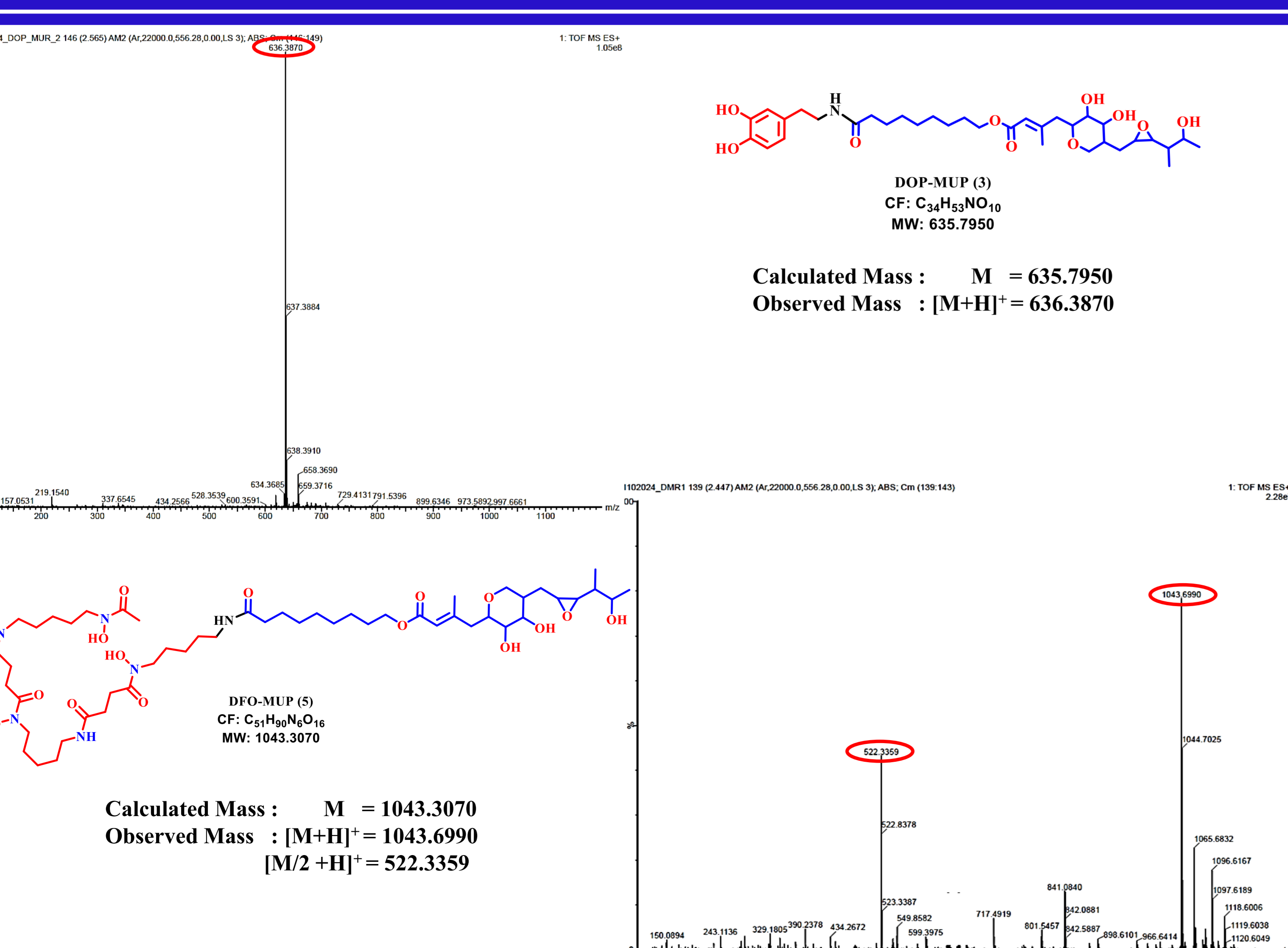


Siderophore-Antibiotic Conjugates efficiently deliver antibiotics into the bacterial periplasm and cytoplasm in a "Trojan horse" strategy

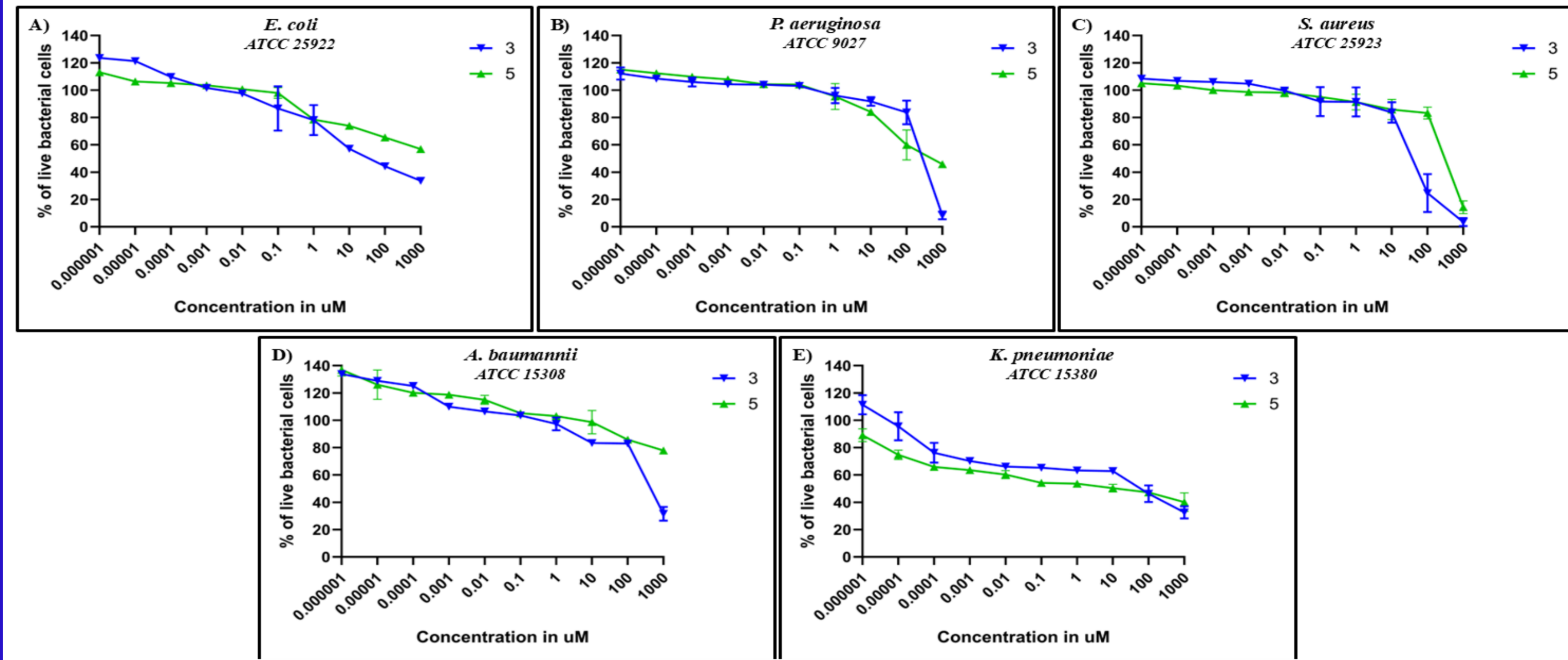
Synthesis Scheme



Mass Spectrum

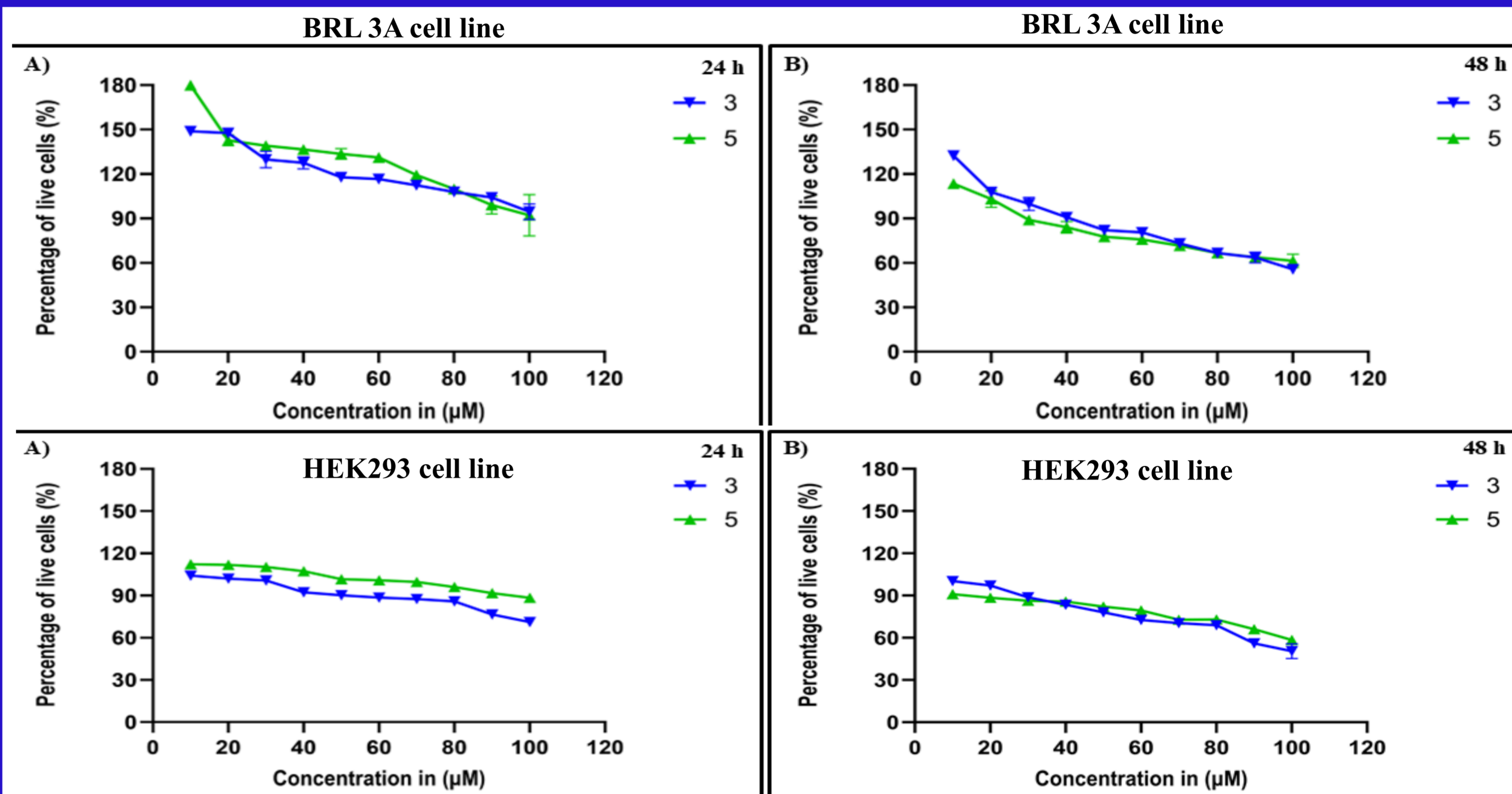


In vitro Cytotoxicity

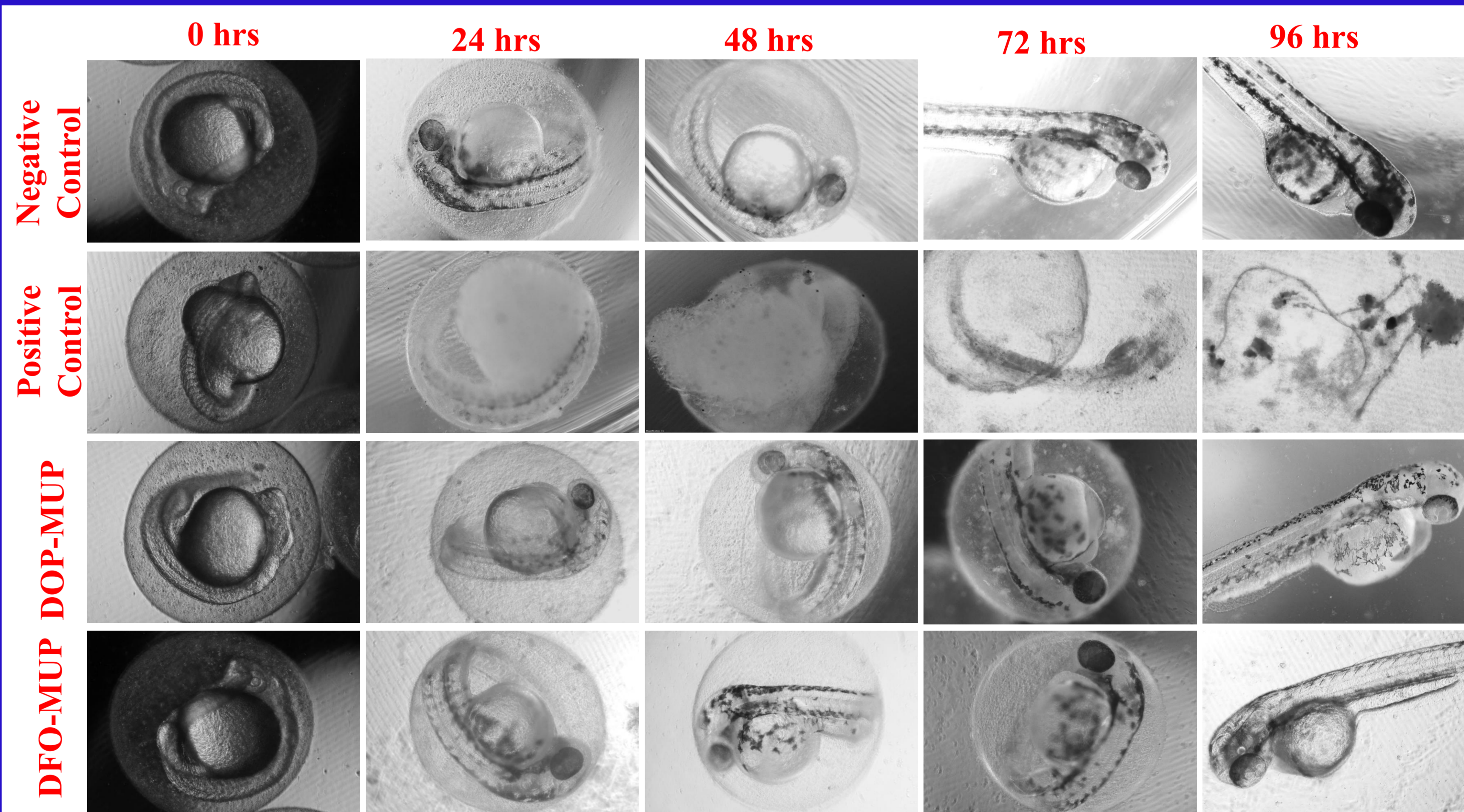


Compound	Minimum Inhibitory Concentration (MIC) in µM				
	<i>E. coli</i> ATCC 25922	<i>P. aeruginosa</i> ATCC 9027	<i>S. aureus</i> ATCC 25923	<i>A. baumannii</i> ATCC 15308	<i>K. pneumoniae</i> ATCC 15380
Mupirocin (2)	103 ± 0.07	> 1000	6.12 ± 0.18	> 1000	198.92 ± 3.43
DOP-MUP (3)	78.11 ± 0.23	401.28 ± 0.70	69.22 ± 1.02	657.67 ± 0.39	86.51 ± 0.47
DFO-MUP (5)	> 1000	812.12 ± 0.08	602 ± 0.98	> 1000	9.93 ± 0.29

In vitro Cytocompatibility



In vivo Cytocompatibility



Conclusion

- The SAC (3) DOP-MUP conjugate demonstrated enhanced antibacterial activity against *E. coli* (ATCC 25922), *P. aeruginosa* (ATCC 9027), *A. baumannii* (ATCC 15308), and *K. pneumoniae* (ATCC 15380), with MIC values of 78.11 µM, 401.28 µM, 657.67 µM, and 86.51 µM, corresponding to 1.3-, 2.5-, 1.5-, and 2.2-fold improvements over the parent antibiotic.
- The SAC (5) DFO-MUP conjugate displayed remarkable potency against *K. pneumoniae* (ATCC 15380), achieving a MIC of 9.93 µM, representing a 20-fold increase in activity compared to the parent antibiotic.
- In vitro* cytotoxicity assessments using BRL 3A and HEK293 cell lines confirmed that the SACs were non-toxic at concentrations exceeding 100 µM.
- Zebrafish embryo studies further validated the *in vivo* biocompatibility of SACs, with no observable developmental toxicity up to 300 µM during the 96 hours post-fertilization (hpf) period.
- Collectively, these findings establish SACs as promising candidates for antimicrobial resistance (AMR)-targeted therapy, offering enhanced antibacterial efficacy with minimal off-target effects and a favorable safety profile.

Acknowledgement

This research is supported by the Indian Council for Medical Research (ICMR) for the IIRP-2023-2387. Thanks for the International Travel Support from ANRF/ITS/2025/004716. Special thanks to the Drug Discovery Unit (DDU) team and the Centre for Biomaterials, Cellular and Molecular Theranostics (CBCMT), School of Advanced Sciences (SAS), Vellore Institute of Technology, Vellore, India.

References

[1] Rayner, B., Verderosa, A. D., Ferro, V., & Blaskovich, M. A. Siderophore conjugates to combat antibiotic-resistant bacteria, RSC Medicinal Chemistry, 2023, 14(5), 800-822.  
[2] L, Kalaiarasu; Rangasamy, Loganathan; A Siderophore-Antibiotic Conjugate for Targeted Antimicrobial Delivery to Pathogenic Bacteria. Application No: 202541036577; Field of Invention: Biochemistry; Published: 09/05/2025. (Patent)