INTERNATIONAL MASTER IN
SUSTAINABLE
DRUG DISCOVERY

UNLOCKING BACTERIAL FORTRESS BY ALTERING THE STRUCTURE of FOSMIDOMYCIN

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Summary

Since the discovery of fosmidomycin, many innovative attempts have been made to optimize its structure to promote its potency against its target: 1-Deoxy-D-xylulose 5-phosphate reductoisomerase (DXR). Although many fosmidomycin analogues exceeded its inhibitory activity on DXR, they still show poor accumulation inside bacteria.

Although many assumptions have been made to predict accumulation of small molecules inside bacteria, no ideal assumption has been developed until now. Recently, a set of rules called “eNTRy rules” were introduced to predict and increase accumulation of small molecules inside Gram-negative bacteria. This set of rules predicts that compounds are more prone to accumulate in *E.coli,* if they are relatively rigid (rotatable bonds ≤ 5), have low three-dimensionality (globularity ≤ 0.25), together with containing a non-sterically encumbered terminal ionizable nitrogen, and some non-polar moieties.

In this Master dissertation, we designed and synthesized six reverse β-aza fosmidomycin- analogues with a cyclicized hydroxamate inspired by the “eNTRy rules”.

Our synthetic pathway started with a linear synthesis of an amine used in a Kabashnik-Fields reaction with different aldehydes to obtain six targeted compounds after deprotection. Additionally, all synthetic steps were assessed for their greenness using green chemistry metrics.