Potential new drug targets for Trypanosomatid protozoan parasites from the pantothenate and coenzyme A biosynthesis pathway

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Trypanosomatid parasites, including *Leishmania mexicana*, *Trypanosoma brucei*, and *T. cruzi*, cause neglected tropical diseases such as leishmaniasis, African sleeping sickness, and Chagas disease. Current treatments suffer from toxicity, limited efficacy, and increasing drug resistance, necessitating new therapeutic approaches. The pantothenate and coenzyme A (CoA) biosynthesis pathway is essential for parasite viability and differs significantly from that of the human host, making it an attractive target for selective drug development. However, specific enzymatic targets within this pathway remain poorly characterized in relation to novel anti-leishmanial compounds.

This study aims to identify and validate potential drug targets within the CoA biosynthesis pathway, focusing on the enzyme dephospho-CoA kinase (DPCK), which catalyses the final phosphorylation step of dephospho-CoA to CoA. Two DPCK paralogues, *Lm*DPCK 1 and *Lm*DPCK 2, were identified in *L. mexicana*. Comparative genomic analysis revealed that salivarian trypanosomes such as *T. brucei* possess only the *Lm*DPCK 1 homologue. Based on prior metabolomic profiling, *Lm*DPCK 2 emerged as the likely molecular target of two novel compounds, SJ254 (Compound 5)[1] and VMS-7-25 (Compound 34)[2].

Computational docking using AutoDock Vina and AI-assisted methods (Protenix) revealed distinct binding affinities of SJ254 and VMS-7-25 for *Lm*DPCK 1 and *Lm*DPCK 2. Both compounds demonstrated strong, specific interactions with key catalytic and structural residues of *Lm*DPCK 2, notably within the lid domain controlling active site access.

Overall, these findings provide preliminary evidence that *Lm*DPCK 2 is a selective, essential drug target in *L. mexicana* with unique structural and phylogenetic features that differentiate it from human and related trypanosome enzymes. This work lays a foundation for further biochemical validation and structural studies to advance targeted drug development for leishmaniasis.

References

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