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# CF3-pyridinyl substitution on anti-malarial therapeutics: Probing differential ligand binding and dynamical inhibitory effects of a novel triazolopyrimidine-based inhibitor on Plasmodium falciparum Dihydroorotate dehydrogenase

The quest for reliable Dihydroorotate dehydrogenase (DHODH) inhibitors has engendered the discovery of potential therapeutic compounds at different stages of clinical trials. Although promising, high attrition rates and unfavorable bioactivities have limited their drug developmental progress. A recent structural modification of DSM265, a triazolopyrimidine-based inhibitor, yielded DSM421, derived by the substitution of the SF5-aniline group on DSM265 with a CF3-pyridinyl moiety. Consequently, DSM421 exhibited improved pharmacological and pharmacokinetics attributes relative to DSM265. The improved bioactivity mediated by the CF3-pyridinyl group leaves us with a curiosity to investigate underlying ligand-binding mechanisms and dynamics using computational methods. Presented in this study are insights that clearly explain the effects of structural SF5-aniline → CF3-pyridinyl modifications on pfDHODH inhibition. Findings showed that the CF3-pyridinyl group induced an optimal and stabilized positioning of DSM421 within the binding pocket, allowing for steady and strong intermolecular interactions which favored its stronger binding affinity as estimated and correlated with bioactivity data. These interactions consequently induced a pronounced stabilization of the structural conformation of pfDHODH by restricting residue motions, which possibly underpinned its enhanced inhibitory activity relative to DSM265. Active site interactions of the CF3-pyrinidyl group with residues Ser236, Ile237, and Phe188 characterized by strong π-π stacking and halogen interactions also stabilized its positioning which altogether accounted for its enhanced inhibitory prowess towards pfDHODH. On the contrary, fewer and weaker interactions characterized DSM265 binding which could explain its relatively lower binding affinity. Findings will facilitate the design of novel pfDHODH inhibitors with enhanced properties.

## Supported Student

**Primary authors:** Mr AGONI, Clement (University of KwaZulu-Natal, Westville, Durban 4000, South Africa.); Mr SALISU, Elliasu Y (University of KwaZulu-Natal, Westville, Durban 4000, South Africa.); Dr OLOTU, Fisayo A. (, University of KwaZulu-Natal, Westville, Durban 4000, South Africa.); Ms MUNSAMY, Geraldene (University of KwaZulu-Natal, Westville, Durban 4000, South Africa.); Ms OMOLABI, Kehinde Foluke (University of KwaZulu Natal, Durban); Prof. SOLIMAN, Mahmoud (University of KwaZulu-Natal, Westville, Durban 4000, South Africa.)

**Presenter:** Ms OMOLABI, Kehinde Foluke (University of KwaZulu Natal, Durban)

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