Investigation of structural concepts for rational design of potent compounds against *Mycobacterium tuberculosis* type II dehydroquinase

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**Abstract:** *Mycobacterium tuberculosis* type II dehydroquinase (mtDHQ) is an attractive target because it is essential for *M. tuberculosis*, but absent from humans. MD simulations combined with energy decomposition have been applied to investigate structural concepts for designing 2,3-anhydroquininate derivatives that can target mtDHQ. The quantitative contribution of mtDHQ residues responsible for inhibitor binding was visualized using energy decomposition. His101 has the greatest contribution for binding of 2,3-anhydroquininate derivatives in the mtDHQ pocket. The carboxylate moiety is crucial for binding of 2,3-anhydroquininate derivatives, whereas the R-substituent has a small contribution. A small linker attached to the C3 atom of the 2,3-anhydroquininate core is preferable for the R-substituent because the positions of Pro11, Asn12, Leu13 and Asp88a located near the C3 atom are not rearranged to accommodate a different sized R-substituent. The structural concepts provided here can be applied to assist in the rational design of potent compounds against mtDHQ.

**Keywords:** *Mycobacterium tuberculosis*; Type II dehydroquinase; Shikimate pathway; MD simulation