Target fishing docking studies of novel aryldiketo acids with promising antibacterial activity toward MDR strains

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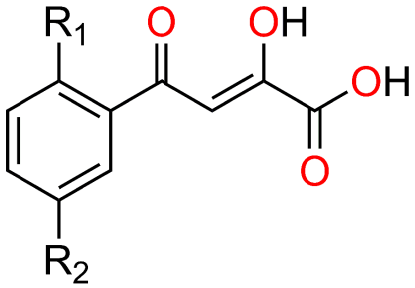
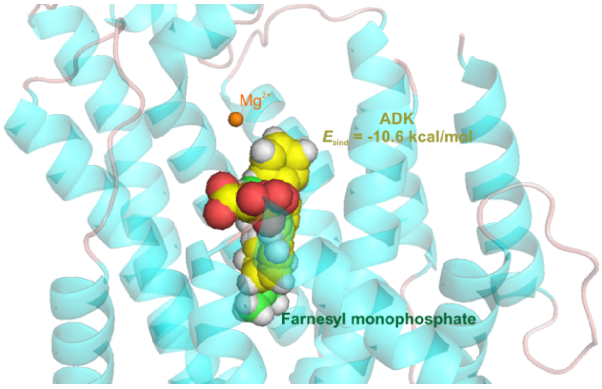
Antimicrobial resistance (AMR) is a major health problem worldwide, because of ability of bacteria, fungi and viruses to evade known therapeutic agents used in treatment of infections. Aryldiketo acids (ADK) exerted antimicrobial activity against several resistant strains of Gram-positive *S. aureus* bacteria. Our previous studies revealed that ADK analogues having bulky alkyl group in ortho position on a phenyl ring have up to ten times better activity than norfloxacin against the same strains [1].

In order to elucidate a mechanism of action for these potentially novel classes of antimicrobials, several bacterial enzymes were identified as possible targets according to literature data and pharmacophoric similarity searches for potent ADK analogues. Among the seven bacterial targets chosen, the strongest favorable binding interactions were observed between most active analogue and *S. aureus* dehydrosqualene synthase (CrtM; PDB entry: 4F6V), in the binding site of natural substrate farnesyl monophosphate.





Protein structures were prepared for docking by adding hydrogen atoms and removing steric clashes using the constrained MD simulation with the protein backbone and metal ions fixed in order to preserve the key features of experimental structures. The 10 ps molecular dynamics simulation at 300 K followed by conjugate gradient minimization was performed using NAMD 2.12 program [2] and CHARMM force field. The .sdf database consisting of 26 ADKs and five structural analogs lacking the diketo moiety was prepared using the best-ranking conformation generated with OMEGA 2.5.1.4. software [3], and further optimized using semiempirical PM7 method implemented in MOPAC 2016 [4]. AutoDock Vina software [5] was used for docking by setting exhaustiveness to 15, and only the most favorable binding mode was calculated for each molecule. Vega ZZ software was used as a GUI for majority of calculations [6].

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