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In silico docking studies of bioactive natural plant products as putative DHFR antagonists

Anuj Sharma, Manoj Kumar, Anuradha and V. K. Gupta
Indian Institute of Technology Roorkee, India

The genesis and spread of resistant forms against malaria have seriously compromise the effectiveness of current chemotherapies. To address this issue, testing/screening of diverse small molecule database against malarial targets can be a frontline strategy.

Consistent with this theme, we have initiated a receptor-guided exploration of small molecular scaffolds/ligands.This type of *in silico* studies is particularly suited for academic laboratories to access a large chemical space in limited time and resource. Our expedition commenced with a computational investigation of an in-house library of plant based natural products against Plasmodial DHFR (1J3I) active site. Lamarckian genetic algorithm (LGA) was employed for conformational searching. Out of 185 candidates, 11 have displayed higher binding affinity (-8.52 to -12.07 kcal/mol) than 3rd generation cycloguanil derivative WR99210 (-8.35 kcal/mol), a benchmark of the study. Interestingly, almost all the xanthenes inspected were among the top scorer, pinpointing them as promising candidates for further inquisition.

Encouraged by these primary findings, we decided to virtually examine the biological spectrum of xanthene (from natural source and wet lab synthesis) against *pf*-DHFR. Surprisingly, we were able to distinguish the two face of DHFR binding pocket with opposite polarity. Furthermore, there is a significant increase in the hit rate (41.33%) also suggesting general xanthene template can be envisioned as a potential pharmacophore in the quest of novel antimalarial (published results).

In next stage, we aimed at small focused library of xanthene and related substructure from easily available starting materials such as dimedone, 1,3-cyclohexandione,Naphthol, aldehyde, glyoxal and glyoxalic acid. In order to elevate diversity, some novel multi-component reactions are highly warranted and in this direction work is currently underway in our laboratory. Since the size of such library would be a critical factor for further efficacy evaluation, so the evaluation of other parallel oxygen and nitrogen heterocyclic compounds(such as acridines) can be a fruitful endeavor (unpublished results).