Biological Chemistry & Chemical Biology

Cu^{II}-Tyrosinase Enzyme Catalyst-Mediated Synthesis of 2-Thioxopyrimidine Derivatives with Potential Mosquito Larvicidal Activity: Spectroscopic and Computational Investigation as well as Molecular Docking Interaction with OBPs of *Culex quinquefasciatus***

Chidambaram SathishKumar,[a] Selvaraj Keerthana,[a] Anis Ahamed,[b] Ibrahim A. Arif,[b] Radhakrishnan SurendraKumar,[a] and Akbar Idhayadhulla*[a]

A series of 2-thioxo pyrimidine derivatives **1**, (**1a-1e**) and **2**, (**2a-2e**) were synthesized via Biginelli reaction by using Cu^{II}-tyrosinase (Cu^{II}-Tyr) as an enzyme catalyst in up to 80–92% yield. The compounds **1**, (**1a-1e**) and **2**, (**2a-2e**) were characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analyses. The synthesized compounds **1**, (**1a-1e**) and **2**, (**2a-2e**) were screened for mosquito larvicidal activity against *Culex quinquefasciatus*. The compound **2a** was 80% mortality at 100 µg/mL with the LD_{50} value of 55.94 µg/mL than the control **Permethrin** 60.03 µg/mL respectively. Molecular docking studies of synthesized compounds were carried out and the results proposed that the compound **2a** as a potential candidate to mosquito odorant-binding protein 3OGN inhibitors. In addition, computational studies, the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies showed that the charge transfer occurs in the inside of the molecule and also gives the chemical reactivity descriptors, and molecular electrostatic potential (MESP) is also calculated. Therefore, experimental and theoretical studies were well supported for the compound **2a** as a potential larvicide activity aganist mosquito larvae of *Culex quinquefasciatus*.

1. Introduction

Mosquito-borne diseases, such as dengue fever, malaria, encephalitis, yellow fever, chikungunya, and filariasis are the most important cause for the defeat of human lifespan, around 700 million people affected by the above-mentioned diseases every year worldwide.[1]

The economic impact of the nation affected by mosquito-borne diseases, including a defeat in commercial and manpower; conversely, all part of world is affected by mosquito-borne diseases.[2]

Culex quinquefasciatus, is an important vector of lymphatic filariasis, is extensively circulated in tropical zones with over 120 million people diseased worldwide and 44 million people devising joint chronic manifestation.[3] Pyrimidines are an important class of heterocyclic skeleton widely distributed in nature. Pyrimidine analogues displays a broad range of biological activities for instance, antihistaminic,[4] antifungal,[5] antileishmanial,[6] calcium channel blockers,[7] anti-inflammatory,[8] analgesic,[9] antihypertensive,[10] antipyretic,[11] antiviral,[12] antidiabetic,[13] central nervous system (CNS) depressant properties,[14] antiallergic,[15] antibacterial,[16] anticonvulsant,[17] herbicidal,[18] anticancer,[19] and also act as antioxidants.[20] Some important bioactive thioxopyrimidine compounds were shown in Figure 1.[21] Biginelli reaction, is a classical method, for synthesis of 3,4-dihydropyridine-2(1*H*)-ones reported by Biginelli in 1893. It suffers from the harsh conditions, long reaction times and also produces low amount of yields, In order to overcome these issues we are developing Cu^{II}-Tyr enzyme as a novel eco-friendly catalyst. Thioxopyrimidine analogs have potent inhibition against mosquito larvae *Culex quinquefasciatus*.[22] Olfaction plays a major role in organisms and tangled in major activities such as food detection, host-seeking, reproduction, and also identification of predators.[23] OBPs (odorant-binding proteins) transport the odorants to olfactory receptors to induce signal transduction.[24,25] Keeping this in mind, the odorant-binding protein (OBP) of *Culex quinquefasciatus* (PDB ID: 3OGN) was chosen as a target protein for molecular docking studies. The present study, to synthesize the bioactive thioxopyrimidine derivatives via grindstone chemistry technique, and mosquito larvicidal screening, computational with molecular docking studies were investigated.

[a] C. SathishKumar, S. Keerthana, Dr. R. SurendraKumar, Dr. A. Idhayadhulla
Research Department of Chemistry, Nehru Memorial College (Affiliated to Bharathidasan University),Puthanampatti -621007, Tiruchirappalli District, Tamil Nadu, South India
E-mail: a.idhayadhulla@gmail.com
idhayadhulla@nmc.ac.in
[b] A. Ahamed, Prof. Dr. I. A. Arif
Prince Sultan Research Chair for Environment and Wildlife, Department of Botany & Microbiology, College of Sciences, King Saud University (KSU), Riyadh, Saudi Arabia.

[**] OBP= odorant-binding protein.

Supporting Information for this article is available on the WWW under https://doi.org/10.1002/slct.202000060