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Prodrugs of Eugenol as Antiplasmodial Agents and its Possible Mechanism of Action †

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Abstract: Considering the biological properties of eugenol and its derivatives and the urgency needed for effective drugs for neglected tropical diseases, we report the synthesis of a novel series of carbonates of eugenol using *N*,*N*-carbonyldiimidazole, and several aliphatic alcohols. The chemical structure of the resulting compounds was confirmed by ^{1}H-NMR, ^{13}C-NMR, FTIR, and GC/MS spectroscopy. *In vitro* studies, eugenol prodrugs were tested for their antiplasmodial activities and cytotoxicity. We found that eugenol was not active against P. falciparum with an EC_{50} of 665.6 μM (109.29 μg/mL); however, several prodrugs improved the EC_{50} dose-response against P. falciparum with respect to the parent drug eugenol. Molecular docking and dynamics simulations were used to determine eugenol's possible mode of action against *Plasmodium falciparum* dihydroorotate dehydrogenase (PfDHODH). Notably, the docking results showed that not only eugenol has binding energy similar to the natural substrate (-7.2 and -7.1, respectively), but it also has interactions with relevant biological residues of PfDHODH. In conclusion, results suggest that eugenol and their carbonate derivatives have promising therapeutic potential as antiplasmodial agents; nonetheless, further studies are needed to validate their efficacy as antiparasitic drugs *in vivo* assays.

Keywords: eugenol; prodrug; antiplasmodial activity; molecular docking; dynamic simulation.

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Conflicts of Interest

The authors declare no conflict of interest.