Analogues of Oxamate, Pyruvate, and Lactate as Potential Inhibitors of Plasmodium knowlesi Lactate Dehydrogenase Identified Using Virtual Screening and Verified via Inhibition Assays

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Abstract

Malaria management remains a challenge, due to the resistance of malaria parasites to current antimalarial agents. This resistance consequently delays the global elimination of malaria throughout the world. Hence, the demand is increasing for new and effective antimalarial drugs. The identification of potential drugs that target Pk-LDH can be obtained through virtual screening analyses, as this has been previously applied to discover Pf-LDH inhibitors. In this study, the selected candidates from our virtual screening analyses were subsequently tested against purified Pk-LDH, and verified through an inhibition of Pk-LDH via enzymatic activity assays. Virtual screening analysis from this study showed that 3,3-Difluoropyrrolidine hydrochloride and 3-hydroxytetrahydrofuran exhibited binding affinity values of −3.25 kcal/mol and −3.74, respectively. These compounds were selected for evaluation towards inhibitory activity against Pk-LDH assays, including two compounds from a previous study which are oxalic acid and glycolamide. The earlier compounds were structurally similar to lactate and pyruvate, and the latter two compounds were structurally similar to a known LDH inhibitor, oxamate. Among all of the compounds tested, oxalic acid showed the highest inhibition activity at 54.12%; interestingly, this correlated well with the virtual screening analyses, which showed that this compound was the best among the oxamate analogues, with a binding affinity value of −2.59 kcal/mol. Hence, further exploration and development of this compound may result in a promising antimalarial drug for malaria treatment, especially for infection involving P. knowlesi. © 2022 by the authors.

Author keywords

inhibition assay; lactate dehydrogenase; malaria; Plasmodium knowlesi; virtual screening

Indexed keywords

Engineering controlled terms

Binding energy; Diseases

Engineering uncontrolled terms

Antimalarial drug; Binding affinities; Inhibition assays; Lactate dehydrogenase; Malaria; Oxamate; Plasmodium knowlesi; Pyruvates; Screening analysis; Virtual Screening

Engineering main heading

Oxalic acid

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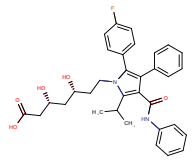
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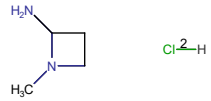
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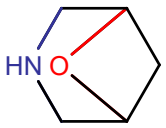
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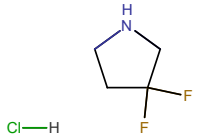
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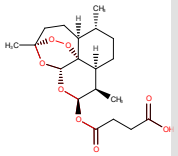
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