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Computational Modeling and Molecular dynamics Simulations of Thiazolino 2-pyridone amide analog compounds as Chlamydia trachomatis inhibitor

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ABSTRACT

Computer-aided drug screening by 2D-QSAR, CoMFA, molecular docking, and molecular dynamics (MD) simulation may provide an effective approach to identifying promising drug repurposing candidates for Chlamydia trachomatis treatment. In this analysis, molecular descriptors were used to achieve a statistically momentous 2D-QSAR model (R^2 = 0.637; Q^2 = 0.5388). The 2D-QSAR model's robustness was considered by the internal leave-one-out cross-validated regression coefficient values (Q^2) and the training set values [(r^2-r0^2)/r^2]. Between the experimental and predicted pIC_{50} value, the overall standard deviation error of prediction (SDEP) was 0.2448, showing strong 2D-QSAR model predictability. The QSAR model was able to systematically predict anti-bacterial behavior with an R2pred value of 0.506 for the external data set 9 of the thiazolino 2-pyridone amide derivative. Comparative molecular field analysis (CoMFA (FFDSEL) Q^2_{LOO} = 0.238, R^2 = 0.943) and CoMFA (UVEPLS) (Q^2LOO = 0.553, R^2 = 0.943) were used. CoMFA (UVEPLS) had strong certification and prediction capabilities. We analyzed the binding effect of the derivatives, where compounds 29 and 31 have the least binding energy. Compounds 29 and 31 interact with main active site residues, including Glu154, Leu142, His87, Arg150, Phe151, Asn138, Gly141, His88, Ile137, Cys85 and 145, respectively, through the binding interaction modes of the molecular docking inhibitor sequence. Further molecular dynamics simulations (MD) were performed on both compounds, and their potential binding modes were explored. Glu154, Phe151, Arg150, Asn138, Gly141, Cys145, and Ile137 have been found to play a key role in stabilizing inhibitors. Besides, the prediction of a golden triangle for the series was carried out. The findings will provide useful guidance in the future for the design of new inhibitors of Chlamydia trachomatis.

1. Introduction

Chlamydia trachomatis is the most common sexually transmitted bacterial infection all around the world that can prompt barrenness and increased susceptibility to other sexually transmitted pathogens, such as HIV/AIDs [1], tumors and complications of pregnancy, as well as trachoma, a recurrent eye infection [2]. Without treatment with antibiotics, Chlamydia trachomatis infections of the female genital tract can prompt fruitlessness, a major public health concern [3]. 85 million people have received antibiotics for trachoma, a blinding eye infection that occurs in 42 countries [4], and there are more than 100 million yearly instances of sexually transmitted Chlamydia trachomatis overall [5]. There is no vaccine for Chlamydia trachomatis at present. Throughout the year's quantitative structural activity relationship (QSAR), 3D-QSAR procedures, for example, comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) assess key structural features and aid underlying alteration in structural modification of the compounds to improve their potency [6]. A 14-membered macrolide analog against mycobacterium tuberculosis was reported by Zitouni et al. Where the 2D-QSAR was established, the inhibitory activity of the investigated macrolide derivatives was predicted and near agreement was obtained between experimental and predicted values

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