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ORIGINAL ARTICLE

Discovery and evaluation of inhibitory activity and mechanism of arylcoumarin derivatives on *Theileria annulata* enolase by in vitro and molecular docking studies

Sinem Yakarsonmez[1,2] · Ozkan Danis[3] · Ozal Mutlu[4] · Murat Topuzogullari[1] · Emrah Sariyer[5] · Basak Yuce-Dursun[3] · Dilek Turgut-Balik[1]

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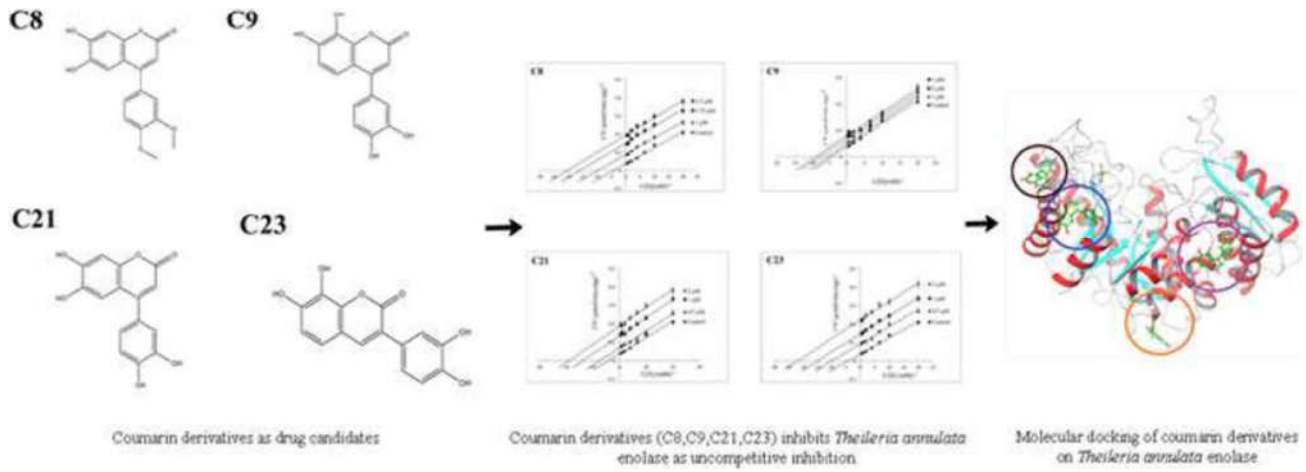
Abstract

In this study, the inhibition potential of 3- and 4-arylcoumarin derivatives on *Theileria annulata* enolase (*Ta*ENO) was assessed for the first time in the literature. Firstly, protein stabilization analyses of *Ta*ENO were performed and it was found that the enzyme remains stable with the addition of 6 M ethylene glycol at + 4 °C. Inhibitor screening analyses were carried out using 25 coumarin derivatives on highly purified *Ta*ENO (> 95%), and four coumarin derivatives [4-(3,4-dimethoxyphenyl)-6,7-dihydroxy-2H-chromen-2-one (C8); 4-(3,4-dihydroxyphenyl)-7,8 dihydroxy-2H-chromen-2-one (C9); 4-(3,4-dihydroxyphenyl)-6,7-dihydroxy-2H-chromen-2 one (C21); and 3-(3,4-dihydroxyphenyl)-7,8-dihydroxy-2H-chromen-2-one (C23)] showed the highest inhibitory effects with the IC_{50} values of 10.450, 13.170, 8.871 and 10.863 µM, respectively. The kinetic results indicated that these compounds inhibited the enzyme by uncompetitive inhibition. In addition, the successful binding of the most potent inhibitor (C21) into *Ta*ENO was confirmed by using MALDI-TOF mass spectrophotometry. Molecular docking analyses have predicted that C8 and C21 coumarin derivatives which showed high inhibitory effects on *Ta*ENO were interacted with high affinity to the potential regions out of the active site. Taken together, these coumarin derivatives (C8, C9, C21 and C23) are first known potent, nonsubstrate, uncompetitive inhibitors of *Ta*ENO and these results will facilitate further in vitro and in vivo analysis toward structure-based drug design studies.

Graphic abstract



Keywords Structure-based drug design · Theileriosis · Drug resistance · Coumarin · Enolase · Enzyme inhibition

✉ Dilek Turgut-Balik
dilekbalik@gmail.com

Extended author information available on the last page of the article

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