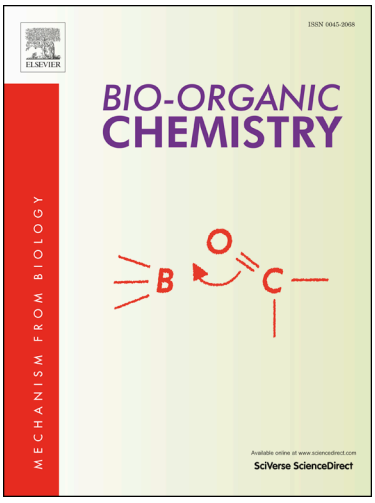

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Dicoumarol derivatives: green synthesis and molecular modelling studies of their anti-LOX activity

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Abstract

Dicoumarol derivatives were synthesized in the $InCl_3$ catalyzed pseudo three-component reactions of 4-hydroxycoumarin with aromatic aldehydes in excellent yields. The reactions were performed in water under microwave irradiation. All synthesized compounds were characterized using NMR, IR, and UV-Vis spectroscopy, as well as with TD-DFT. Obtained dicoumarols were subjected to evaluation of their *in vitro* lipid peroxidation and soybean lipoxygenase inhibition activities. It was shown that five of ten examined compounds (**3e**, **3h**, **3b**, **3d**, **3f)** possess significant potential of antilipid peroxidation (84 to 97%), and that compounds **3b**, **3e**, **3h** provided the highest soybean lipoxygenase (LOX-Ib) inhibition (IC_{50} = 52.5 μM) and **3i** somewhat lower activity (IC_{50} = 55.5 μM). The bioactive conformations of the best LOX-Ib inhibitors were obtained by means of molecular docking and molecular dynamics. It was shown that, within the bioactive conformations interior to LOX-Ib active site, the most active compounds form the pyramidal structure made of two 4-hydroxycoumarin cores and a central phenyl substituent. This form serves as a spatial barrier which prevents LOX-Ib Fe^{2+}/Fe^{3+} ion activity to generate the coordinative bond with the C13 hydroxyl group of the α-linoleate. It is worth pointing out that the most active compounds **3b**, **3e**, **3h** and **3i** can be candidates for further examination of their *in vitro* and *in vivo* anti-inflammatory activity and that molecular modeling study results provide possibility to screen bioactive conformations and elucidate the mechanism of dicoumarols anti-LOX activity.

Keywords: Dicoumarol derivatives, $InCl_3$ catalyzed synthesis, microwave irradiation, anti-inflammatory activity, molecular docking, molecular dynamics

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