

Synthesis of Enantiomeric Halolactones with Aromatic Ring, Their Anticancer Activity and Interactions with Biological Membranes [†]

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Studying the effect of chirality on the activity of tested compounds, we synthesized new series of the enantiomeric (ee = 98–100%) β -aryl- δ -halo- γ -lactones with defined configurations of stereogenic centers. The key step of the synthesis was the application of lipase B from *Candida antarctica* to the resolution of racemic (*E*)-4-(2',5'-dimethylphenyl)but-3-en-2-ol in the process of transesterification. The synthetic pathway included stereospecific Johnson-Claisen rearrangement of resolved alcohols to γ,δ -unsaturated esters followed by their hydrolysis to the corresponding acids and subsequent iodolactonization or bromolactonization. Due to the known configuration of starting allyl alcohols and transfer of chirality during Johnson-Claisen rearrangement, we were able to assign the configuration of all stereogenic centers in the molecules of final lactones.

Obtained halolactones showed high antiproliferative activity in vitro against a panel of canine cancer lines: D17, CLBL-1, CLB70, GL-1, and one human cancer line (Jurkat). Their activity was dependent on various structural features: configuration of stereogenic center, substituents at aromatic ring or a kind of lactone ring, and halogen atom.

In the first step of their biological action, anticancer drugs must penetrate the outer cell membrane to target the intracellular substructures. Therefore, our research was expanded by the studies on interactions of synthesized halolactones with red blood cell membranes. Tested compounds did not induce hemolysis of erythrocytes. The results of fluorescence spectroscopy suggest incorporation of these compounds into hydrophilic part of membrane and no influence on fluidity in the hydrophobic region.

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