Abstract

Synthesis of new Apoptosis-Inducing Nucleoside Analogues Bearing a Butadiene-$Fe(CO)_3$-Substructure for Exploration of the Mechanism of Action and Improvement of Biological Properties

Iron-containing nucleoside analogues with $Fe(CO)_3$-complexed 3´-Vinyl-2´,3´-dideoxy-2´,3´-dehydronucleosides show high apoptosis-inducing activity, even in highly resistant cell lines (Caspase 3 and CD 95 inactive). Therefore a new mechanism of action is proposed, perhaps even a new molecular target.

The synthesis of conjugates with nucleosides of this type and fluorescent-labels or biotin as biochemical tools to learn more about this mechanism of action is described. In addition a new Tryptanthrin conjugate, which shows strong apoptosis inducing activity, is introduced.

Ring contraction of methyl-α-D-glucopyranosid leads to an enantiomerically pure 2,5-dihydrofuran-carbaldehyd, which is transformed into the corresponding dienes by a *Wittig*-olefination with different halogenoaceticacid-6-phthalimidohexylesters. Those dienes can be complexed with $Fe_2(CO)_9$ diastereoselectively and converted by a *Vorbrüggen* glycosidation. After hydrazinolysis of the phtalicamide the conjugates were synthesized using standard methods of peptide chemistry and a nucleophilic addition. It appeared that the length of the akyl-linker is crucial for the activity of the fluorescence label conjugates (7-dimethylaminocoumarin). Therefore Halogenoaceticacid-18-phthalimidooctadecylesters were synthesized from dec-9-enol by using cross-metathesis. Those were then applied for the synthesis.

Additional experiments concern the introduction of a diol-sidechain to improve the water solubility of these substances, as well as the attempt to use carbamate protecting groups on the cytosin-NH_2 to enhance tumor selectivity.