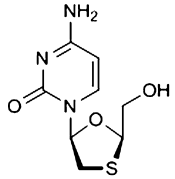
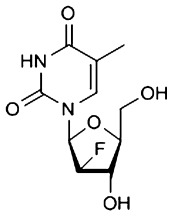
The aim of our work is to prepare new antivirally active carbocyclic L-nucleoside analogues with the help of an efficient and stereoselective synthesis. Starting from enantiomerically pure 2-benzyloxymethylcyclopent-3-enol it was possible to synthesize numerous analogues. Using the Mitsunobu coupling reaction for a convergent synthetic strategy modified nucleobases or functionalized carbocyclic moieties could be introduced. By this means a comprehensive library of carbocyclic compounds was synthesized (Jessel et al., 2007) as well as the corresponding *cyclo*Sal-pronucleotides to improve the activity of the carbocyclic nucleosides (Meier, 2006). Furthermore, different nucleotides were prepared using nucleoside triesters as starting material (Warnecke and Meier, 2008). For antiviral evaluation carbocyclic nucleosides and *cyclo*Sal-nucleoside triesters were used.



3TC, Lamivudine **1**



L-FMAU, Clevudine **2**

Reference

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A Novel Fullerene-Based Antiviral Active Against *Herpes Simplex* Virus *In Vitro* and *In Vivo*

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Background: Herpesviruses represent a group of human pathogens causing diseases ranging from *herpes labialis* to fatal encephalitis with immunocompromized persons as the main target. Infections transmitted by these viruses take the second place (15.8%) after influenza as a reason of death due to viral infection. Herpesviruses are therefore a serious challenge for medicinal science and health care. The purpose of the present study was to evaluate anti-viral activity of newly synthesized water-soluble derivative of fullerene, fullerene-polyaminocaproic acid (FPAC), against *Herpes simplex* virus type I.

Materials and methods: Toxicity of FPAC was determined by MTT. *Herpes simplex* virus type I (HSV-I) was propagated in Vero cells. FPAC was serially diluted in medium and added to cells 1 h before the virus inoculation. Virus titer was determined for each concentration of FPAC based on the study of virus-induced cell destruction after 72 h of cultivation by MTT. Virus titer was then plotted against FPAC concentration, and EC_{50} was calculated. For *in vivo* experiments mice were inoculated intracranially with HSV-1 and treated with FPAC intraperitoneally once a day. Animals were then monitored for 14 days for mortality. On days 3 and 7 post-inoculation brains of five mice from each group were studied for virus titer and virus-induced lesions. Acyclovir was used as reference compound.

Results: Based on the data of *in vitro* experiments, CTD_{50} and EC_{50} of FPAC were estimated as >1000 and 2 μg/mL, respectively, that gives a selectivity index >500. Application of FPAC to infected mice resulted in decreasing of mortality (68 and 90% in the group of treated and non-treated mice, respectively) and increasing of mean day of death (8.3 and 5.7 days). Virus titer in brain tissue of treated animals was slightly lower (4.1 against 5.1 $\log_{10}$ $TCID_{50}$/20 mg tissue in control). These values, nevertheless, were lower that those for acyclovir (mortality 50%, MDD 10.9 days, virus titer 3.0 $\log_{10}$ $TCID_{50}$/20 mg tissue). Morphological signs of infection in the brain, such as neuronal death, gliosis and cell infiltration were less manifested than in control animals.

Conclusion: Taken together, these data suggest that a novel fullerene derivative might be prospective anti-herpetic drug and should be further developed.

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Overview on Clinical Trials and Resistance Breaking Activity of the Anti-Cytomegalovirus Compound AIC246

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Background: CMV remains an important pathogen in immunocompromised individuals including transplant recipients. To date, all available drugs for HCMV infection/disease target the viral DNA-polymerase. Disadvantages of current therapies include toxicity and emergence of drug resistance. Hence, safe and improved antivirals with different molecular targets are urgently needed. Here we report on the results of clinical trials with AIC246, which belongs to a novel class of anti-CMV agents with a different mode of action compared to available drugs.

Methods: Anti-CMV activity of AIC246 was evaluated in vitro using laboratory strains and clinical isolates incl. drug resistant viruses. AIC246 was tested in phase I trials in over 200 healthy subjects and in a phase IIa trial, which enrolled 27 transplant recipients under a 14 days pre-emptive treatment strategy in comparison to observational treatment. DNA PCR was used as biomarker for HCMV.

Results: In vitro AIC246 exhibited excellent inhibitory activity against CMV including Ganciclovir resistant virus strains. In all clinical trials AIC246 was generally well tolerated. Within the limits of the small sample size of the phase II trial, reduction in viral markers were similar in all treatment groups. AIC246 reduced DNA PCR in a transplant patient who had developed a multiresistant CMV to the limit of detection.

Conclusion: AIC246 represents a novel CMV inhibitor with potent antiviral activity and which acts via a different mode of action compared to Ganciclovir. AIC246 was generally well tolerated in over 200 healthy subjects and in transplant patients with CMV viremia and also showed activity against a multidrug-resistant CMV strain.

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