ral drugs. Thorough investigation of the relationship between: (a) cytotoxic (HeLa cells CC_{50}, μg/ml), (b) antiviral activity against the pleconaril-resistant clinical CVB3 isolate Nancy (IC_{50}, μg/ml), and (c) selectivity index (ratio of CC_{50} to IC_{50}) and the structure of 2-amino-3-nitropyrazole[1,5-α]pyrimidine derivatives have been carried out.

Statistic characteristics for partial least squares (PLS) models are quite satisfactory ($R^2 = 0.96–0.99$, $Q^2 = 0.86–0.93$). The results are confirmed by experimental data. Structural fragments with positive or negative influence on antiviral activity as well as cytotoxicity and selectivity index have been determined on the base of these models. Additionally, obtained models provide the possibility to predict the antiviral activity and to design new well tolerated highly virus-specific drugs.

The analysis of competence regions for each QSAR model allows us to estimate additionally the quality of prognosis for all of designed compounds.

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55

The Design, Synthesis and Anti-HIV Activity of a Selected Group of 2′,3′-Didehydro-2′,3′-Dideoxyguanosine (d4G) and 2′,3′-Dideoxyguanosine (ddG) 'ProTide' Derivatives

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2′,3′-Dideoxyguanosine (ddG) is a nucleoside analogue that has been found to exert a relatively modest anti-HIV activity. This was attributed to the poor phosphorylation of ddG to its corresponding triphosphate form. Since the triphosphate of ddG was found to possess potent anti-HIV activity, we hypothesised that using a prodrug approach to deliver the monophosphate of ddG may improve the anti-HIV activity of this agent. As well as ddG, we decided to study the anti-HIV activity of 2′,3′-didehydro-2′,3′-dideoxyguanosine (d4G) and some of its pronucleotide derivatives, since 2′3′-dideydro-dideoxy nucleoside analogues, such as d4T, are useful therapeutics. The pronucleotide approach that we decided to apply for d4G and ddG is called the 'ProTide' approach. In this approach, the phosphate group is masked to improve the poor membrane permeability seen when the free nucleotides are used. Upon entering the cell, the group masking the phosphate moiety may undergo enzymatic metabolism to release the nucleoside monophosphate, which may be subsequently phosphorylated by cellular kinases into the di- and triphosphates of d4G or ddG. Hence, we synthesised d4G, ddG and a selected group of their 'ProTide' derivatives, general structure given below, and tested them against HIV-1 and HIV-2 (Fig. 1). The synthesis of these agents as well as the biological data will be presented at the meeting.

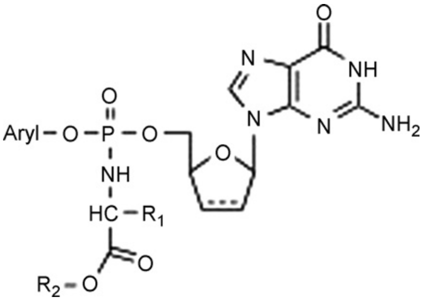

Fig. 1.

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56

Novel Diketo Phosphonic Acids Constructed on Nucleobase Scaffolds: Design, Synthesis, Molecular Modeling and Anti-HIV Activity

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Research efforts on drug discovery pertaining to one of the viral enzymes of the HIV *pol* gene, HIV integrase, have not resulted in a single FDA-approved drug for which the mechanism of action is inhibition of HIV integrase. Recently, we have been exploring a novel class of diketo acids that are constructed on nucleobase scaffolds and that have a specific arrangement of the functional and hydrophobic groups on the scaffold. These compounds are inhibitors of both the 3′-processing and strand transfer steps of HIV integrase. One lead compound from this group has been found to have remarkable in vitro anti-HIV activity (Nair et al., 2006. J. Med. Chem. 49, 445–447). As phosphonic acids have been viewed commonly as mimics of carboxylic acids, particularly with reference to biological activity, we utilized this concept to design a phosphorus-based isostere of our lead diketo carboxylic acid. Design of this target compound will be explained and illustrated with molecular modeling data. The presentation will also describe the development of a general methodology for the synthesis of this class of compounds, which, in spite of their multifunctional nature, are very stable. Structural, functional and conformational data obtained from extensive spectroscopic studies will be discussed. Biological data, including antiviral data, and comparisons of activity with other active diketo acids, will be presented. These isosteric compounds represent the first examples of b-diketo phosphonic acids of structural, synthetic and antiviral interest.

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