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Antiviral Activity of Tetrahydro-2(1H)-Pyrimidinones and Related Compounds: Classification SAR Study

V. Kuz'min

As was established in the end of last millennium, tetrahydro-2(1H)-pyrimidinones are promising compounds from the point of view of theirs antiviral action. The main target of the given work is solution of classification SAR (Structure–Activity Relationship) task for antiviral activity of tetrahydro-2(1H)-pyrimidinones and molecular design of novel potent antivirals. The objects of investigation are 23 derivatives of tetrahydro-2(1H)-pyrimidinone and tetrahydro-2(1H)-pyrimidinethione including several of their structural analogs. Antiviral activity against following viruses has been investigated: (i) Semliki Forest Virus (SFV), (ii) Fowl Plague Virus (FPV), and (iii) Vaccinia Virus (VV). The testing procedure followed the agar-diffusion plaque-inhibition method, the antiviral effects been expressed as diameter (mm) of the plaque inhibition zone. The compounds has been divided into five activity classes from inactive to very active depending on the difference between the diameters of plaque inhibition zone and zone of cytotoxicity. 2D (topological) level of representation of molecular structure has been used for generation of simplex structural descriptors, i.e. information has been extracted only from structural formulas. More complicated models are inexpedient for this task because 2D level is enough for errorless classification of investigated molecules from the point of view of their activity. Successful classification SAR models for each of investigated activities have been obtained by Answer Trees statistical approach. The structural parameters which allow ones to classify investigated tetrahydro-2(1H)-pyrimidinones and related compounds according to their activity levels were determined. Thus, e.g. the presence and variation of the number of butane- and amino-propane linkers plays the crucial role for the level of FPV and VV inhibition. Obtained classification trees were used for the prediction of activity classes for new compounds of investigated row. Three new designed compounds DD-37, DD-40 and DD-45 hopefully will be effective agents against SFV, FPV, and VV and are under the consideration now.

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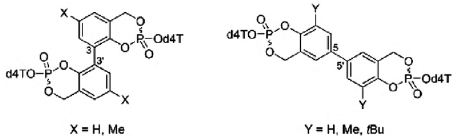
*Cyclo*Saligenyl-di-d4TMP: Highly Loaded CycloSal-pronucleotides that Release Two Equivalents of Nucleotides and Leaving One Masking Unit

Chris Meier[a,*], Nicolas Gisch[a], Ducho Christian[a], Balzarini Jan[b]

[a] *Organic Chemistry, Department of Chemistry, Faculty of Sciences, University of Hamburg, Hamburg, Germany;* [b] *Rega Institute for Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium*

Latest cycloSal-pronucleotides are efficient drug delivery systems that release therapeutically active nucleotide in human cells by chemical hydrolysis combined with enzymatic triggering. The cycloSal-approach is the only pronucleotide concept in which the ratio of the masking unit to nucleotide is 1:1. Others used approaches having a ratio of up to 4:1 (masking units to nucleotide). The reason for that is the complex releasing process which is always enzyme-based. Due to the chemical releasing process our system works with only one masking unit and a coupled cleavage mechanism. Here, we report on a further increase of the ratio of nucleotide per masking unit to 2:1. Therefore, di-salicyl alcohols were prepared using metal-catalyzed cross-coupling chemistry that were "loaded" with 2 equivalents of d4TMP as the antivirally active nucleotide analogue. This approach represents a novelty in the field of pronucleotides. The two saligenyl units of these cycloSaligenyl-di-d4TMPs are connected either via the 3-positions or the 5-positions of the aromatic rings. The compounds were studied for their chemical stability in aqueous buffers and biological media to prove the delivery of the cargo and the antiviral activity in wild-type CEM/0- and in mutant TK-deficient cells. Furthermore, the hydrolysis pathway of these cycloSaligenyl-di-d4TMPs has been investigated via ^{31}P NMR spectroscopy combined with analytical HPLC studies. All compounds showed an entirely selective and consecutive release of 2 equivalents of d4TMP by chemical means and showed good activities against HIV-1 and HIV-2 in wild-type CEM cells in vitro. Moreover, these compounds achieve a thymidine kinase-bypass, partially with complete retention of anti-HIV-2 activity in TK-deficient CEM cells although they are not fulfilling all the Lipinski rules (molecular weight too high).



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Computer-aided Drug Design of Novel Anti-coxsackievirus B3 Nancy Agents by Means of Hit QSAR

E. Muratov*, E. Varlamova, V. Kuz'min

Coxsackieviruses (CVB) are very common and can cause severe diseases of the heart, liver, eyes and pancreas, as well as acute infections of the central nervous system. Etiological therapy for diseases caused by CVB remains elusive. Thus, battling CVB remains important health care task that requires design and development of new drugs. Application of modern computer technologies shortens the development time and reduces costs of antiviral drug research. The goal of the present study is design of novel selective antiviral agents by the means of QSAR analysis of antiviral activity of various chemicals against pleconaril-resistant CVB3 Nancy strain. The dataset comprised 93 structurally diverse compounds mainly represented by N,N′-(bis-5-nitropyrimidyl)dispirotripiperazine, [(biphenyloxy)propyl]isoxazole and 4H-pyrazolo[1,5-a]pyrimidin-7-one derivatives and several well-known antivirals including pleconaril, spirobromine, etc. Thorough investigation of the relationship between antiviral activity against the pleconaril-resistant clinical CVB3 isolate Nancy (IC_{50}, μM), selectivity index (ratio of CC_{50} to IC_{50}) and the structure of investigated compounds was carried out using HiT QSAR. Cytotoxicity on HeLa cells (CC_{50}, μM) was predicted by HiT QSAR HeLa Virtual Screening Tool represented on ICAR21. Statistically significant PLS (Partial Least Squares) models with $R^2 > 0.81$ and $Q^2 > 0.6$ were used for consensus prediction. 5-fold external cross-validation was used for the predictivity estimation. $R^2_{test} > 0.6$ was observed for each external fold. Structural fragments with positive or negative contributions to antiviral activity as well as cytotoxicity and selectivity index were determined by examination of the successful models. New selective anti-CVB3 Nancy agents were computationally designed and synthesized. High level of their activity was validated by experimental testing. Key words: drug design, CVB3 Nancy, selectivity index.

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