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HiT QSAR Study of Antivirals' Bioavailability

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The therapeutic action of a drug is usually correlated with the delivery of the active substance to the site or more accurately, sites, of pharmacological action. Thus, the bioavailability (F) is typically defined as the degree to which or rate at which a drug or other substance is absorbed or becomes available at the site of physiological activity after administration. The F of a drug is an important attribute that is investigated early in drug development and used throughout development. In many cases, it is the deciding factor as to whether or not a drug candidate is selected for further development. Thus, the aim of the present work is QSAR analysis of bioavailability of various antivirals and some other drugs and development of adequate and predictive tool for virtual bioavailability screening for new candidate antiviral agents. The dataset included 362 structurally diverse drugs mainly represented by antivirals, e.g. ozeltamivir, valacyclovir, amprenavir, etc. Hierarchical QSAR technology based on simplex representation of molecular structure and PLS (partial least squares) was used for data modeling. 5-fold external cross-validation was used. $R^2_{test} > 0.6$ was observed for each external fold. Structural fragments with positive or negative contributions to bioavailability variation were determined by examination of the successful models. Statistically significant models with $R^2_{test} > 0.8$ and $Q^2 > 0.7$ were used for consensus prediction. The predictivity of consensus HiT QSAR model has been additionally validated by applying it to an additional external test set of antiviral compounds, and the results were satisfactory ($R^2_{test} > 0.6$). In summary, we have succeeded in developing novel and externally predictive computational model applicable for virtual screening of drug candidates for their bioavailability.

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Synthesis and Evaluation of Novel Acyclovir Phosphoramidates as Anti-HIV Agents

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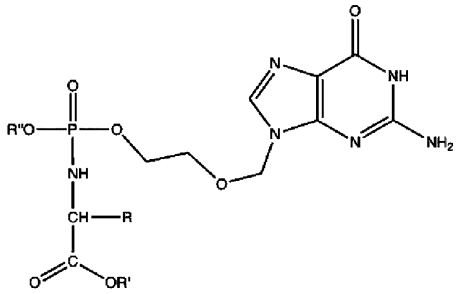
Acyclovir (ACV) is a guanine antiviral drug used in the treatment of HSV and VZV infection. The mechanism of action involves a phosphorylation, which is mediated by a herpes virus-specified thymidine kinase (TK), to give the monophosphate, which is converted to the di- and tri-phosphate by cellular kinase (Elion et al., 1977). The triphosphate is the bio-active form. The ProTide approach, affording directly the monophosphate, allows a by-pass of the thymidine kinase phosphorylation. Here we have evaluated the capacity of acyclovir-phosphoramidates to inhibit the replication of HIV and have found them to be active in vitro (Lisco et al., 2008). Varying the ester and aryl unit of alaninyl phosphoramidates of ACV it has been demonstrated that the overall lipophilicity may be an important feature for activity. The amino acid moiety is also important for activity (McGuigan et al., 2008). In this work, we report the synthesis of novel acyclovir ProTide, varying the aryl, amino acid and ester moieties, as well as SARS for anti-HIV activity for these compounds (.1).



References

Elion, G.B., Furman, P.A., et al., 1977. Selectivity of action of an antiherpetic agent: 9-(2-hydroxy-ethoxymethyl)guanine. Proc. Natl. Acad. Sci. U.S.A. 74, 5716–5720.

Lisco, A., Vanpouille, C., et al., 2008. Acyclovir Is Activated into a HIV-1 Reverse Transcriptase Inhibitor in Herpesvirus-Infected Human Tissues. Cell Host Microbe 4 (3), 260–270.

McGuigan, C., Derudas, M., et al., 2008. Successful kinase bypass with new acyclovir phosphoramidate prodrugs. Bioorg. Med. Chem. Lett. 18 (15), 4364–4367.

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Design, Synthesis and SAR of New Potent HIV-1 RT Inhibitors

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Studies in HIV biology have provided important information about the main steps of virus life cycle which consists of viral entry, reverse transcription, integration, gene expression, virion assembly, budding and maturation. The officially approved drugs belong to the class of reverse transcription and protease inhibitors and, recently, viral entry and integrase inhibitors. Despite the successes with such treatments as HAART combination regimens, the permanent use of anti-AIDS drugs induces drug-resistant viral variants and emergence of unwanted metabolic side effects. Therefore, there is a need for the development of new drugs able of suppressing drug-resistant HIV strains and/or targeting different stages in the virus life cycle. In recent papers, aimed at the discovery of new NNRTIs, we reported a 3D-pharmacophore model for NNRTIs which led to the discovery of N1-substituted 1,3-dihydro-2*H*-benzimidazol-2-ones and their sulfones [J. Med. Chem. 2005, 48, 3433; Biorg. Med. Chem. Lett. 2007, 17, 1956; Biorg. Med. Chem. 2008, 16, 7429]. In particular SAR studies highlighted that compounds containing a sulfonyl moiety were more potent than the analogues with a methylene linker and that the 3,5-phenylsubstituted derivatives with a chlorine atom at 6 position of the benzimidazolone system proved to be potent HIV-1 RTIs which were less toxic and more active than nevirapine and, in same cases, than efavirenz against both wild-type and mutant strains of HIV-1. Supported from these promising results, we planned the synthesis of new benzimidazolone ana-

logues with the aim to establish further SAR on this class of NNRTIs. Molecular modelling studies have also been performed.

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The Application of Phosphoramidate Protide Technology to Acyclovir confers Novel Anti-HIV Inhibition

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The antiviral drug acyclovir is a guanosine nucleoside analogue which shows inhibitory activity against human herpesviruses (HHV) and in particular against herpes simplex virus (HSV) and varicella-zoster virus (VZV) showing low cytotoxicity. To show this activity, acyclovir needs to be phosphorylated to its active triphosphate form to inhibit the viral DNA polymerase (Elion et al., 1977).

Recently it has been reported that acyclovir inhibits HIV-1 in HHV coinfected tissues (Lisco et al., 2008). This activity is due to the phosphorylation to the monophosphate form mediated by HHV encoded kinase followed by further phosphorylation to di- and triphoshate form and consequent inhibition of the HIV-1 reverse transcriptase.

The phosphoramidate ProTide approach has been applied to acyclovir as a means to bypass the first phosphorylation. These compounds showed inhibitory effect against HIV-1 and 2, while acyclovir does not show any significant activity.

In the present work, we reported a series of acyclovir ProTides considering alanine as amino acid moiety and varying the aryl and the ester moiety to study the anti-HIV activity for these compounds.

References

Elion, G.B., Furman, P.A., Fyfe, J.A., De Miranda, P., Beauchamp, L., Schaeffer, H.L., 1977. Selectivity of action of an antiherpetic agent: 9-(2-hydroxy-ethoxymethyl)guanine. Proc. Natl. Acad. Sci. U.S.A. 74, 5716–5720.

Lisco, A., Vanpouille, C., Tchesnokov, E.P., Grivel, J.-C., Biancotto, A., Brichacek, B., Elliott, J., Fromentin, E., Shattock, R., Anton, P., Gorelick, R., Balzarini, J., McGuigan, C., Derudas, M., Gotte, M., Schinazi, R.F., Margolis, L., 2008. Acyclovir is activated into a HIV-1 reverse transcriptase inhibitor in herpesvirus-infected human tissues. Cell Host Microbe 4, 260–270.

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Design, Synthesis, and Biological Evaluation of Novel Fluoro Derivatives of BCNA

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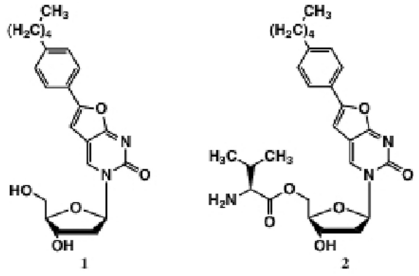
Bicyclic nucleoside analogues (BCNAs), which are characterised by a fused bicyclic pyrimidine ring, showed potent and extremely selective activity against varicella-zoster virus (VZV). The 6-pentylphenyl-substituted BCNA, Cf1743, has been found to be the most potent inhibitor of VZV being inhibitory in the sub-nanomolar range (McGuigan et al., 2000). Its valyl ester prodrug, FV-100, has concluded successfully Phase I clinical trials (McGuigan et al., 2007).

In the present work, a new series of BCNA derivatives has been designed considering fluorine as bioisostere for its chemical and biological properties. The synthesis, the affinity studies for VZV-TK and the biological evaluation of a series of novel BCNA fluoro derivatives will be reported.



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References

McGuigan, C., Barucki, H., Blewett, S., Carangio, A., Erichsen, J.T., Andrei, G., Snoeck, R., De Clercq, E., Balzarini, J., 2000. J. Med. Chem. 43, 4993–4997.

McGuigan, C., Pathirana, R.N., Migliore, M., Adak, R., Luoni, G., Jones, A.T., Diez-Torrubia, A., Camarasa, M.-J., Velazquez, S., Henson, G., Verbeken, E., Sienaert, R., Naesens, L., Snoeck, R., Andrei, G., Balzarini, J., 2007. Preclinical development of bicyclic nucleoside analogues as potent and selective inhibitors of varicella zoster virus. J. Antimicrob. Chemother. 60, 1316–1330.

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4,4-Disubstituted Cyclohexylamine based CCR5 Chemokine Receptor Antagonists as Anti-HIV-1 agents

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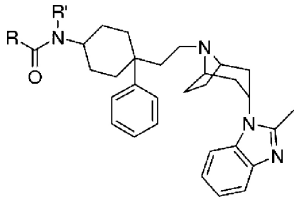
HIV/AIDS continues to be a threat to global public health care. While current anti-HIV therapies resulted in dramatic increase of life expectancy of AIDS patients, issues arising from these treatments such as the emergence of the resistant HIV-1 strains and long-term treatment side effects have brought significant challenges to drug discovery research. Need for drugs with novel treatment mechanism becomes increasingly urgent. Discovery of chemokine receptors 5 (CCR5) as a co-receptor for HIV-1 infection opened a new avenue to anti HIV-1 treatment and prevention. Over years, successful research and development in the pharmaceutical industry resulted in several small molecule clinic candidates and the launch of one FDA approved drug. This poster will present our efforts in identification and optimization of 4,4-disubstituted cyclohexylamine based CCR5 antagonists as anti-HIV-1 agents.



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