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

doi:10.1016/j.antiviral.2009.02.133

129

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

Marco Derudas[1,*], Christopher McGuigan[1], Andrea Brancale[1], Leonid Margolis[2], Jan Balzarini[3]

[1] *Welsh School of Pharmacy, Cardiff University, Cardiff, United Kingdom;* [2] *Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, USA;* [3] *Rega Institute for Medical Research, Leuven, Belgium*

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.

doi:10.1016/j.antiviral.2009.02.134

130

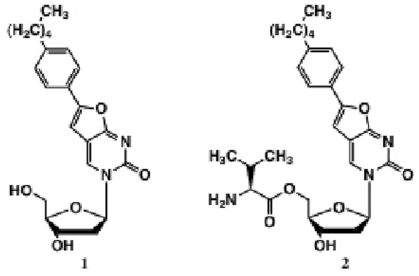
Design, Synthesis, and Biological Evaluation of Novel Fluoro Derivatives of BCNA

Marco Derudas[1,*], Maurizio Quintiliani[1], Christopher McGuigan[1], Andrea Brancale[1], Geoffrey Henson[2], Jan Balzarini[3]

[1] *Welsh School of Pharmacy, Cardiff University, Cardiff, United Kingdom;* [2] *Inibitex Inc., Alpharetta, USA;* [3] *Rega Institute for Medical Research, Leuven, Belgium*

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.



1 2

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.

doi:10.1016/j.antiviral.2009.02.135

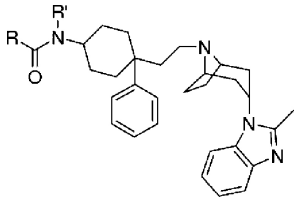
131

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

Maosheng Duan*, Wieslaw Kazmierski, Christopher Aquino, Rob Ferris, Terry Kenakin, Chris Watson, Pat Wheelan

Infectious Disease Center for Excellence in Drug Discovery, GlaxoSmithKline, Research triangle Park, USA

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.



doi:10.1016/j.antiviral.2009.02.136