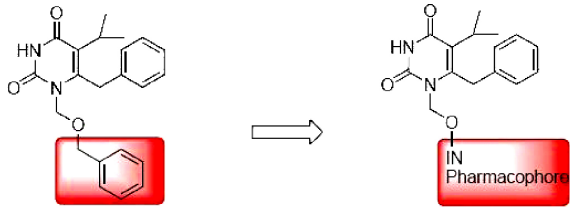
89

From RT Inhibitor to RT/IN Dual Inhibitor: An Rational Design

Zhengqiang Wang *, Robert Vince

Center for Drug Design, University of Minnesota, Minneapolis, USA

As the standard HIV chemotherapy, highly active antiretroviral therapy (HAART) is compromised by high cost and toxicity. These problems could be alleviated by using designed multiple ligands (DMLs) which are compounds with a single structure that engages multiple biological targets. In this study, HIV RT/IN dual inhibitors featuring two distinct pharmacophores were rationally designed and synthesized. The design was based on TNK-651, a potent RT inhibitor of the HEPT family. A tolerant region of HEPT type RT inhibitors was identified and a pharmacophore responsible for IN activity was introduced to generate dual inhibitory activities. The detailed design and chemical synthesis are described, and results of enzymatic assays against RT and IN, as well as cell-based assay against HIV are presented.



TNK-651, RT inhibitor RT/ IN dual inhibitor

doi:10.1016/j.antiviral.2008.01.103

90

Withdrawn.

doi:10.1016/j.antiviral.2008.01.104

91

Check of Antiviral Activity of Nanocomposites with Active Ligand Based on Model of Cattle's Diarrhea Virus (Model of Hepatitis C Virus)

Viktor Zinoviev [1,*], Aleksey Evdokimov [1], Evgeniy Belanov [1], Ernst Malygin [1], Sergey Balachnin [1], Olga Serova [1], Dmitriy Pletnev [1], Valentina Zarytova [2], Asya Levina [2], Marina Repkova [2], Zinfer Ismagilov [3], Nadegda Shikina [3], Stanislav Zagrebelnyi [4], Sergey Baiborodin [5]

[1] FSRI SRC VB "Vector", Novosibirsk, Russia; [2] Institute of Biochemistry and Fundamentel Medicine SB RAS, Novosibirsk, Russia; [3] Institute of Catalysis SB RAN, Novosibirsk, Russia; [4] Novosibirsk State University, Novosibirsk, Russia; [5] Institute of Citology SB RAN, Novosibirsk, Russia

Hepatite C is one of the infection of interest for public health. It causes by virus with (+)RNA genome. Search of methods of efficient influence on this dangerous viral infection still go on [Locarnini, S.A., Bartholomeusz, A., 2002. J. Gastroenterol. Hepatol. 17, 442–447]. Progress reached in bionanotecnology recently give researchers new technological possibilities which give new way to solve the tasks. One way is to use nanoparticles as delivery agents for reactive derivative of oligonucleotides to target-gene. Objective of present work is to research possible use conjugants reactive derivative of oligonucleotides with TiO_2-nanoparticles for selective inactivation viral nucleic acid in affected cells. Tests for TiO_2-nanoparticles' and their conjugants' cytotoxic effect on cells culture Vero and MDCK are passed. This effect on Vero appear when TiO_2-nanoparticles' concentration was higher than 100 mkg/ml. On MDCK max non toxic value was 30–60 mkg/ml. Penetration of TiO_2-nanoparticles and nanocomposites into eucariotic different lines cells were shown. Ability of inhibition viral activity BVDV in KCT cell culture was researched. Shown that conjugants based on amorphous nanoparticles TiO_2-polylysine-oligo and TiO_2-PL-DA-Oligo have antiviral activity which have the most expression with UV illumination in two to three after infection, in period of forming replicative complexes when drugs without direct oligonucleotides shown no activity.

Acknowledgement: The work is supported by Programme FCSTP 2007-2-1.2-05-02 (lot no. 3).

doi:10.1016/j.antiviral.2008.01.105

92

MIV-170, a Novel NNRTI With Potent Activity Against HIV and HIV Mutants

Bo Öberg *, Britt Louise Sahlberg, Christer Sahlberg, Bertil Samuelsson, Kristina Wikström, Lotta Vrang, Hong Zhang

Medivir AB, Huddinge, Sweden

MIV-170 is an NNRTI designed to have potent activity both against wtHIV-1 and HIV-1 mutants resistant to the NNRTIs on the market. In MT-2 cells MIV-170 showed EC50 values of 0.2nM against wtHIV and 0.3 nM against the K103N mutant while efavirenz showed EC50 values of 1.4 nM and 39 nM, respectively. The rate of resistance development to MIV-170 in MT-4 cells, even when starting with the NNRTI resistant mutant K103N, was slower than with efavirenz. A panel of HIV strains with typical NNRTI resistance mutations were all resistant to efavirenz while 85% were sensitive to <20 nM MIV-170. In a large panel of 185 multiple drug resistant HIV patient isolates, 65% showed a change in sensitivity to MIV-170, as compared to wt virus, of less than 4 (FC < 4) while 41% showed a less than 4 fold (FC < 4) change in sensitivity to efavirenz. MIV-170 has a free fraction of 2.1% in human serum as compared to 0.4% for efavirenz. MIV-170 has a very high oral bioavailability and a long plasma half-life in dogs, and was well tolerated in a 10 days tox study in rats.

doi:10.1016/j.antiviral.2008.01.106