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Computational Studies of gp41 6-Helix Bundle: Do Stabilized Energy of HIV Membrane Fusion Inhibitor C34 and Interaction Energy of gp41 6-Helix Bundle have Good Correlation with their Inhibitory Activity?

Norihito Kawashita[1,2,*], Yu-Shi Tian[1], Masashi Yasuda[1], U. Chandimal de Silva[2], Rie Kashiwada[3], Shota Nakamura[2], Naohisa Goto[3], Rika Nishikiori[4], Kousuke Okamoto[1], Masanori Kameoka[2], Teruo Yasunaga[2,3], Masaya Kawase[2,4], Kazuyoshi Ikuta[2,5], Tatsuya Takagi[1,2,3]

[1] Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka, Japan; [2] Research Collaboration Center on Emerging and Re-emerging Infections, established by Research Institute for Microbial Diseases, Osaka University, and National Institute of Health, Department of Medical Sciences, Nonthaburi, Thailand; [3] Genome Information Research Center, Research Institute for Microbial Diseases, Osaka University, Suita, Osaka, Japan; [4] Department of Pharmacy, Osaka Ohtani University, Tondabayashi, Osaka, Japan; [5] Research Institute for Microbial Diseases, Osaka University, Suita, Osaka, Japan

Membrane fusion inhibitor is the active ingredient in some anti-HIV drugs, and is designed to work before HIV enters the host cell. Envelope protein gp41 plays an essential role in membrane fusion by forming a 6-helix bundle between N-terminal heptad repeat (N-HR) and C-HR. Enfuvitide and C34 which are synthetic peptides based on C-HR inhibit the formation of the 6-helix bundle. Therefore, if we found a correlation between the intensity of membrane fusion and the amino acid sequence by computational studies, we could design more potent peptides in silico. Based on the above background, we have calculated stable conformation of the 6-helix bundle by molecular dynamics, and have investigated the relationship between the intensity of membrane fusion and the interaction energy of the 6-helix bundle model consisting of gp41 N-HR and a variety of C34 peptides (Isarangkura et al., 2005), and found a moderate correlation between the calculated interaction energy and reported inhibitory activity. Our calculation method would be applied for these interaction systems. Now we carry out another calculation in order to find potent peptides by using this methodology.

Reference

Isarangkura, P., Ikuta, K., et al., 2005. Microbes Infect. 7, 356–364.

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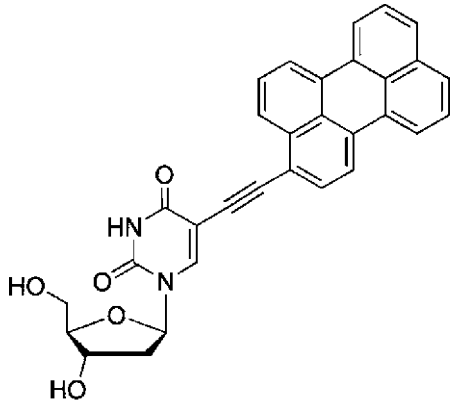
Synthesis of Structural Analogues of dUY11, A Potent Rigid Amphipathic Fusion Inhibitor Nucleoside

Stanislav Khramyshev*, Olga Valueva, Vladimir Korshun, Alexey Ustinov

Shamyakin-Ovchinnikov Institute of Bioorganic Chemistry RAS, Moscow, Russia

Recently, a unique non-nucleosidic mechanism of antiviral activity of certain 5-arylalkynylated deoxy- and arabino-uridines was suggested [Antiviral Res., 74 (2007), A87]. The preliminary SAR studies revealed that rigid ethynyl linkage and planar hydrophobic substituent at 5-position are essential for the fusion inhibitory antiviral activity. The most promising results were obtained for 5-(3-perylenylethynyl)deoxyuridine (dUY11). Thus, 3-perylenyl is the most appropriate aryl found until now.

Though some sites of the molecule appear critical, there is still potential for further structural analyses. Therefore, we have synthesized a series of compounds sharing some of the structural features of dUY11, in order to evaluate their antiviral activities, to therefore obtain an extended SAR profile.



dUY11

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Chemically Synthesized Tunicamycin Derivatives Effectively Inhibit the Propagation of Classical Swine Fever Virus—A Surrogate Model for Hepatitis C Virus

Ewelina Krol[1,*], Boguslaw Szewczyk[1], Ilona Wandzik[2], Grzegorz Grynkiewicz[3], Wieslaw Szeja[2]

[1] Department of Molecular Virology, University of Gdańsk, Gdańsk, Poland; [2] Silesian Technical University, Gliwice, Poland; [3] Pharmaceutical Institute, Warsaw, Poland

Classical Swine Fever Virus (CSFV) is often used as a surrogate model to study the role of envelope glycoproteins of closely related human Hepatitis C Virus (HCV). The need to work with surrogate models for HCV is due to the fact that, until today, only a single isolate of this virus can be grown in in vitro cultures. CSFV glycoproteins, E2, E0 (E^{rns}) and E1, are detected on the external part of viral particles and play a major role in