Research & Reviews: Journal of Medicinal Chemistry

Extended Abstract
Vol. 6, Iss. 3
2019

Organic Chemistry- 2018: Practical asymmetric synthesis of a chronic hepatitis C virus nucleoside cyclic prodrug - Yong-Li Zhong

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Chronic hepatitis C virus (HCV) is a liver disease that has infected an estimated 130 to 150 million people worldwide as of 2016 and killed an estimated 500,000 people around the world annually. In spite of several medicine therapies for the treatment of HCV being available, treatment failure and resistance still remain a clinical challenge. For these reasons, the search for effective antiviral agents to combat HCV is an ongoing endeavor within the global medical/pharmaceutical community. As part of an ongoing drug discovery program in our laboratories, the title compound has been identified as one such selective and potent inhibitor of HCV NS5B nucleoside polymerase. This nucleoside cyclic prodrug is a complex, densely functionalized small molecule, which represents numerous challenges for chemical synthesis. Herein, we report a new asymmetric, practical synthetic route, which features several remarkably diastereoselective and high yielding transformations for the synthesis of the target starting from readily available starting materials.

his long-lasting liver infection is caused by the hepatitis C virus. It begins as an acute hepatitis that starts within the primary 6 months of exposure to the virus. for many people that catch on -- up to 85% -- the illness moves into a long-lasting stage. this is often called a chronic hepatitis C infection.

Hepatitis C treatments are changing quickly. Until recently, the foremost common method was a mix of shots and pills. It most frequently combined an attempt of interferon or peginterferon with the pills ribavirin and one among several other drugs. This caused some unpleasant side effects.

Treatment now centers around direct acting antiviral drugs (DAAs). These medicines are highly effective for many people with hepatitis C and are interferon-free and sometimes ribavirin-free. this suggests they typically have fewer side effects. The treatments are often simpler -- consisting of fewer pills for a shorter amount of your time. DAAs are available as either single drugs or combined with other medicines in one pill.

Other treatment options include: daclatasvir (Daklinza); ombitasvir-paritaprevir-ritonavir plus dasabuvir (Viekira Pak); ombitasvir-paritaprevir-ritonavir (Technivie); or some combinations of simeprevir (Olysio); sofosbuvir (Sovaldi); peginterferon or ribavirin. Ask your doctor what's best for you, supported your medical needs. All of those drugs are quite expensive, so ask your insurance firm or ask your doctor about any pharmaceutical company assistance programs.

Phosphate monoesters are charged at physiological pH, as are the corresponding phosphonates, and people with small and/or hydrophilic substituents may have difficulty in diffusion across biological membranes and sometimes require endocytosis for cell entry. While this limitation could also be ameliorated within the case of compounds with larger, more lipophilic substituents, it's always a priority that has got to be considered in drug design. Thus efforts to organize biologically active organophosphorus compounds often are followed by studies to delineate strategies that temporarily mask any negative charges at physiological pH. Potential drugs based upon this approach may offer variety of benefits over their non-protected counterparts. especially, addition of cell-cleavable protecting/masking groups (i.e. the prodrug approach) can: 1) increase oral bioavailability; 2) enhance cell penetration; 3) improve the specificity of tissue delivery; and avoid or minimize degradation in serum via cellular sequestration. additionally, once the prodrug moieties are cleaved within the cell, an equivalent factor that might normally limit entry of the non-protected drug into the cell now can restrict the free drug from leaving the cell. Thus, prodrugs can effectively allow the drug to realize elevated concentrations within cells, further enhancing efficacy.

Study of phosphonate prodrugs may have an extended history, but pro-drug strategies to guard and deliver

This work is partly presented at International Conference on ANALYTICAL CHEMISTRY
held from November 21-22, 2018 in Madrid, Spain.

phosphate monoesters even have been of great interest. Efficient delivery of a phosphate monoester into the cell can afford important metabolic advantages. for instance, nucleoside analogues like arabinofuranosyl cytidine (AraC) and gemcitabine (GemC) undergo activation after cell entry by conversion to the corresponding mono-, di- and ultimately triphosphates, and use of a protected phosphate may allow intersection with natural metabolic processes at a later stage. This strategy could also be particularly important with nucleotide prodrugs where it can allow the agent to bypass the rate-limiting initial phosphorylation. Furthermore, phosphate prodrugs may confer stability to serum phosphatases, and thus support simpler dosing.

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