length and the antiviral activity. Additionally, we will present the synthesis and the biological properties (pH- and cell extract stability, cytotoxicity) to give further insights into the behaviour of this novel series of BAB-d4TDPs.

Reference

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Synthesis, Antiviral and Cytotoxicactivities of 2-Phenyl, 3-Substituted Quinazolin-4(3H)-Ones

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Quinazolin-4-(3H)-one is a versatile lead molecule for the design of potential bioactive agents and its derivatives were reported to possess broad spectrum activities. 2-Phenyl-3-substituted quinazolin-4-(3H)-ones were reported to have anti-HIV activity and anti-cancer activity. Quinazolinones were screened for their wide spectrum anti-viral activity and they yield potential for further studies. A series of novel 2,3-disubstitutedquinazolin-4(3H)-ones have been synthesized by condensation of 2-substituted benzo[1,3]oxazine-4-ones and anthranilic acid. Their chemical structures were assigned by means of spectral analysis (FT-IR, ^{1}H NMR, MS). Synthesized compounds were evaluated for *in vitro* antiviral activity against HIV, HSV, vaccinia virus and other viruses. The compounds displayed cytotoxicity in MT-4 cells and were inactive against HIV-1 and -2 replication at non-cytotoxic concentrations. 2-(o-Phenyl carboxylic acid)-5,7-bromo-3-phenyl quinazolin-4(3H)-one and 2-(4-dibromo-2-phenyl carboxylic acid)-3-phenyl quinazolin-4(3H)-one showed activity against HSV and vaccinia virus. 2-(o-Phenyl carboxylic acid)-5,7-bromo-3-phenyl quinazolin-4(3H)-one inhibited the replication of HSV-1, -2 and vaccinia virus at an IC_{50} of 12 μg/ml. It was cytotoxic at 100 μg/ml. These compounds may be suitable as leads for designing newer derivatives and further molecular modification in this series may help optimizing antiviral activity.

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Synthesis of a Series of 2′-Modified Tricyclic Nucleosides as Potential HCV Agents

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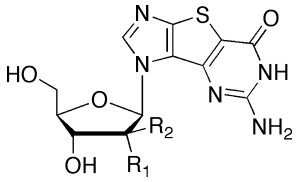
The hepatitis C virus (HCV) is a blood borne virus currently infecting 4 million people in the United States and over 170 million people worldwide. HCV is one of the leading causes of long term liver cirrhosis, which can result in liver failure and death. Compounding the impact of this disease is the rapid progression of liver degradation in patients that are co-infected with human immunodeficiency virus (HIV). Current therapies have exhibited low response rates and significant toxic side effects, thus there is an urgent need to develop more effective treatments.

HCV requires an RNA-dependent RNA-polymerase (RdRp) to replicate, more specifically the NS5B protein. NS5B has been shown to be essential in the HCV replication complex, thus is considered an ideal target. Multiple studies have shown that potent inhibitory activity against NS5B has resulted from structural modifications to the 2′-position including 2′-OMe, 2′-Me and 2′-F substitutions. Moreover, an analogue of 2′-C-methylguanosine has recently progressed to Phase I clinical trials. Related to this, a hetero-expanded purine tricyclic guanosine nucleoside synthesized in our laboratories exhibited moderate activity against HCV. Thus, combining these leads has focused our efforts on the development of 2′-modified analogues of the expanded tricyclic guanosine. The synthesis and preliminary studies are described herein.



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Acute Toxicity of Oral Octadecyloxyethyl Esters of 3-Hydroxy-2-(Phosphonomethoxy) Propyl Nucleosides in Balb/c Mice

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Octadecyloxyethyl esters of 3-hydroxy-2-(phosphonomethoxy) propyl adenine, guanine and diaminopurine (ODE-HPMPA, ODE-HPMPG, ODE-HPMP-DAP) have been synthesized and their antiviral activity evaluated against HCMV, vaccinia, and cowpox (Valiaeva, et al., 2009. Antiviral Res. 84, 254–259). These compounds have EC50 values ranging from 3 to 77 nM against these viruses in vitro. ODE-cidofovir (ODE-CDV) has previously been reported to have good oral bioavailability and in vivo antiviral activity in lethal poxvirus models of infection but shows significant oral toxicity at 30 mg/kg and above. To assess the acute toxicity of the new compounds, we gave 3, 10 and 30 mg/kg to mice daily for 7 days by oral gavage. Female Balb/c mice weighing approximately 18 g were dosed orally at the indicated doses for 7 days. Mice were observed and body weights were taken daily during dosing. After dosing was stopped, observations and body weight measurements were continued three times a week for one week. A control group received only the vehicle (0.9% saline). ODE-HPMPA at 30 mg/kg showed acute oral toxicity. Although there was no mortality in this group, dosing was stopped on day 4 because of a 20% loss of body weight from baseline. However, there were no signs of acute toxicity or weight loss in the 3 and 10 mg/kg groups. ODE-HPMPG at 30 mg/kg produced marked weight loss in all mice. Dosing was stopped in two mice at day 5 because of greater than 20% weight loss. Nevertheless 75% of the animals in this group died. Mice in the 10 mg/kg group showed moderate weight loss but tolerated dosing for the full 7 days. No mortality occurred in this group. In the 3 mg/kg group, no ill effects were noted. Mice treated orally with ODE-HPMP-DAP showed no signs of acute toxicity at all doses