HDP and ODE esters of (*S*)-HPMPA are potent inhibitors of HIV-1 replication in vitro ($EC_{50} = 0.4–7.0$ nM) whereas the unmodified phosphonic acid (*S*)-HPMPA and other unmodified HPMP series ANPs are generally inactive against HIV-1. To expand our approach to other HPMP nucleosides, we synthesized the ODE esters of (*S*)-HPMP-guanine (HPMPG), (*S*)-HPMP-thymine (HPMPT), (*S*)-HPMP-cytosine (HPMPC) and (*S*)-HPMP-2,6-diaminopurine (HPMPDAP) and evaluated these compounds against HIV-1 infection in MT-2 cells using a p24 reduction assay. ODE-(*S*)-HPMPA, ODE-(*S*)-HPMPDAP, and ODE-(*S*)-HPMPC were the most active compounds in this series with $EC_{50}$'s $\leq 1$ nM. ODE-(*S*)-HPMPG also suppressed HIV-1 replication with $EC_{50}$ value of 9 nM. However, ODE-(*S*)-HPMPT was inactive. Our results indicate that HDP-(*S*)-HPMPA, ODE-(*S*)-HPMPC, ODE-(*S*)-HPMPG and ODE-(*S*)-HPMPDAP should be evaluated further as potential therapies against HIV-1 infection. Alkoxyalkyl analogs of (*S*)-HPMPA and (*S*)-HPMPC are orally bioavailable and effective in animal models of various viral diseases such as vaccinia, ectromelia, HCMV and HBV infection. With the exception of ODE-(*S*)-HPMPT, ODE esters of HPMP-nucleosides are generally quite active and selective in MT-2 cells infected with HIV-1 and further studies of their possible utility in HIV infection are being pursued.

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## Dysregulation of the Antioxidant Enzyme Defense in Hispanic Women with HIV-associated Neurocognitive Disorder

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HIV-associated neurocognitive disorders (HAND) remains prevalent during HAART. Activated and HIV-infected monocytes are known to cross the blood brain barrier and contribute to the release of virus and inflammatory mediators including cytokines, chemokines, free radicals, and viral proteins. These neurotoxins and inflammatory mediators can induce oxidative stress and neuronal death. We hypothesize that monocyte innate immunity is defective therefore contributing to oxidative stress in the CNS in patients with HAND. Studies from our laboratories have demonstrated different protein profiles in blood monocyte-derived macrophages and CSF that are related to HAND. We confirmed differential expression and activity of Cu/Zn Superoxide Dismutase (SOD-1) in the CSF and monocytes in a cohort of Hispanic women with HAND using HAART. The present study investigates activity of glutathione peroxidase (GPx) in the CSF, monocytes, macrophages, and plasma of 36 Hispanic women with or at risk of developing HAND. GPx activity was measured indirectly by the change in absorbance at 340 nm upon oxidation of glutathione and NADPH. We found that CSF from women with cognitive impairment (CI, MSK $\geq 1$) had a significant decrease in GPx activity ($p = 0.001$). Monocytes showed a decreased Gpx activity although not significant ($p = 0.124$). Monocyte-derived macrophages showed a higher activity in the asymptomatic group of patients ($p = 0.056$) which decreased with HAND severity. Interestingly, we found a higher activity of GPx in plasma of patients with CI ($p < 0.05$). Our conclusion is that Hispanic women with CI have decreased protection from oxidative damage in the central nervous system. The reduction of GPx and SOD activity in monocytes may contribute to the significant low antioxidant activity found in the CSF of patients with CI. Our data supports the need for complementary therapy to antiretroviral drugs that increase the activity of the cellular antioxidant enzymatic complex. This combination will contribute to the prevention of development and or progression of HAND.

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## Characterization of Small Molecule Inhibitors of West Nile Virus NS3 Serine Protease

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Characterization of inhibitors of West Nile Virus NS3 Serine Protease. The members of Flaviviridae encode a serine protease (NS3-pro) that is essential for polyprotein processing and thus for virus replication, making it an attractive target for inhibitor design. This study details the biochemical characterization of inhibitors of WNV NS3-pro identified in a high throughput screen (HTS) followed by further analysis of selected compounds and their derivatives. Two of these compounds exhibited IC50 values of $3.74 \pm 0.17$ μM and $\sim 5.146 \pm 0.54$ μM and Ki values of $\sim 2.2 \pm 0.36$ μM and $\sim 5 \pm 0.46$ μM. Inhibitory values of structurally related compounds were also determined. The potency and selectivity of the compounds using cell-based and infectivity assays will be reported. The information derived from this study could be useful in designing potent inhibitors for therapeutic use.

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