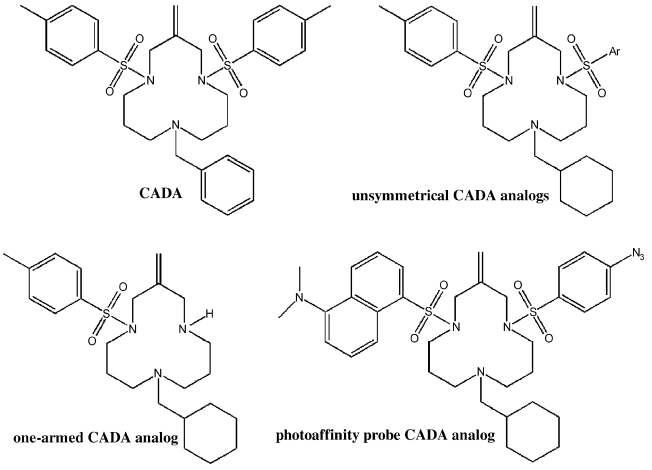
in preparing unsymmetrical analogs with two different arenesulfonyl side-arms is based on initial molecular modeling studies and on the potencies of the two unsymmetrical CADA analogs KKD015 and KKD016 (IC_{50} values for CD4 down-modulation are 1.72 ± 0.25 μM and 0.97 ± 0.13 μM, respectively). These results suggested that decreased symmetry may likely lead to sustained activity of the compounds. Using a new synthetic route, seven new unsymmetrical CADA analogs have been successfully prepared. All of these compounds exhibited CD4 down-modulating activity in the lower micromolar range. In fact, one of the new analogs showed a ca. 50-Fold increase in potency relative to CADA (IC_{50} values for CD4 down-modulation are 0.012 ± 0.010 μM for the new analog and 0.65 ± 0.21 μM for CADA). Thus, qualitative structure-activity relationships observed for these compounds suggest additional structures for unsymmetrical analogs that may be explored. New CADA compounds that are currently being prepared include a one-armed analog, and a photoaffinity probe bearing one side-arm consisting of a dansyl fluorophore and a second side-arm consisting of a photoactive aryl azide unit.



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The Discovery and Efficacy of a Small Molecule Inhibitor of Ebola Capsid Assembly in an Animal Model

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We have taken a novel approach for identifying viral capsid assembly inhibitors by targeting cellular host proteins rather than viral gene products. A cell free protein synthesis (CFPS)-based system was used to express and assemble the Ebola nucleocapsid (NP), VP35 and VP24 proteins. The system was adapted to an assay platform to screen this assembly pathway by an ELISA and the hits were identified from a small molecule library. When synthesized in the presence of the active compounds, the assembled structures show differential protease sensitivity compared to control, consistent with altered assembly architecture. Hits were validated by plaque reduction assay against live virus in cell culture. The impressive therapeutic profile of one of the early hits, justified moving the compound forward into preliminary *in vivo* efficacy studies. This compound provided complete protection of mice challenged with 1000 LD_{50} Ebola virus at a compound dose of 5 mg/kg (IP) daily for 5 days. Preliminary optimization of the potency and safety profiles for this pre-lead series resulted in a promising structure activity relationship (SAR) demonstrating very impressive improvements over the initial hits in this series. Together, the *in vitro* and *in vivo* experiments have demonstrated the potential of this approach for discovering anti-Ebola therapeutics.

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Structure–Activity Relationships of D- and L-analogs of Maribavir and 1-Beta-D-ribofuranosyl-2-bromo-5,6-dichlorobenzimidazole (bdcrb) Against Human Herpesvirus 6

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Human cytomegalovirus (HCMV) has been shown to be susceptible to a host of benzimidazole nucleoside analogs including, 1H-β-D-ribofuranosyl-2-bromo-5,6-dichlorobenzimidazole (BDCRB) and 1H-β-L-ribofuranosyl-2-isopropylamino-5,6-dichlorobenzimidazole (maribavir, MBV). Neither of these analogs exhibits good antiviral activity against either variant of human herpesvirus 6 (HHV-6A, HHV-6B), notwithstanding the relative conservation of their molecular targets. We evaluated nine analogs of both MBV and five analogs BDCRB against both variants of HHV-6. Neither the L- nor D-analogs of MBV exhibited detectable antiviral activity against these viruses. However, two L-analogs of BDCRB (L-ribosyl BDCRB and (−)-carbocyclic BDCRB) were identified that had good antiviral activity against HHV-6A (EC_{50} = 2.8 and 5.5 μM, respectively). Both molecules also exhibited more modest inhibition against HHV-6B (EC_{50} = 9.7 and 15 μM, respectively). Both molecules retained antiviral activity against HCMV (EC_{50} = 1.3–3.8 μM). This contrasts with results for D-ribosyl analogs of BDCRB, which were active against HCMV, but not either variant of HHV-6. These data taken together suggest that the substituent in the 2-position of the heterocycle, as well as the configuration of the ribose were essential for antiviral activity. The compounds that were active against HHV-6 did not appear to inhibit viral DNA synthesis, and failed to inhibit the enzymatic activity of the U69 protein kinase, suggesting that their mechanism of action was similar to that of BDCRB. Additional studies will be required to determine the effect of the analogs on the cleavage/packaging of the HHV-6 genome.

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Stereospecific Phosphorylation of Cyclopropavir by pUL97 and Inhibition by Maribavir

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Human cytomegalovirus (HCMV) is a widespread pathogen that can cause severe disease in immunologically immature and immunocompromised individuals. Cyclopropavir (CPV), a