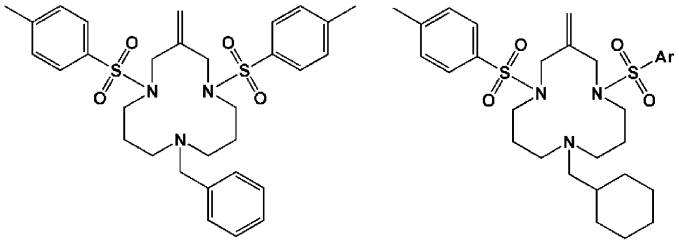
ies and on the potencies of two known unsymmetrical CADA analogs, decreased symmetry may likely lead to improved activity of the compounds. To fully explore the potential of the unsymmetrical analogs as antiviral agents, a new synthetic route was developed towards their production. One of the synthetic modifications involves a new macrocyclization method using palladium as a catalyst. This technique avoids large solvent volumes, long reaction times, and polymer side products associated with the conventional, Richman–Atkins macrocyclization method. The anti-HIV and CD4 down-modulation activities of the novel CADA compounds will be presented.



CADA Target CADA analogs

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91

Pradimicin-S is a Highly Soluble Non-peptidic Small-size Carbohydrate-binding Antibiotic that may Qualify as a Potential Drug Lead for HIV Treatment

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Pradimicin-S (PRM-S) is a highly water-soluble negatively charged derivative of the antifungal antibiotic PRM-A in which the terminal xylose moiety has been replaced by 3-sulfated glucose. PRM-S does not prevent HIV adsorption, but inhibits virus entry into its target cells. It inhibits a wide variety of HIV-1 laboratory strains, HIV-1 clade isolates, HIV-2 and SIV in various cell cultures (50% effective concentration ranges in the lower micromolar range; 50% cytostatic concentration higher than 100 μM). It blocks syncytium formation between persistently HIV-1- and SIV-infected cells and uninfected T-lymphocytes, and prevents DC-SIGN-mediated HIV-1 and SIV capture and subsequent virus transmission to T-cells. Alike PRM-A, PRM-S strongly binds to gp120 in a Ca^{++}-dependent manner at a K_D in the lower micromolar range. Dose-escalating exposure of PRM-S to HIV-1-infected cells led to the isolation of mutant virus strains that had multiple deleted N-glycosylation sites in the envelope gp120. There was a strong preference for the deletion of high-mannose-type glycans. Genotypic resistance occurred slowly, and significant phenotypic resistance occurred only after the sequential appearance of more than 3–5 mutations in gp120, pointing to a relatively high genetic barrier of PRM-S. A variety of virus strains that are resistant to other anti-HIV drugs kept sensitivity to the inhibitory effects of PRM-S. The antibiotic is non-toxic against a variety of tumor cell lines, not mitogenic, not (anti)-angiogenic, and does not markedly trigger cytokines and chemokines in drug-exposed peripheral blood mononuclear cells. Therefore, PRM-S may qualify as a potential anti-HIV drug candidate for extended (pre)clinical studies.

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92

Highly Potent and Dual-acting Pyrimidinedione Inhibitors of HIV-1 Possess a High Genetic Barrier to Resistance

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With the increasing incidence of HIV drug-resistant viruses in the HIV-infected population, it is critical that a new generation of highly safe and potent drugs be developed to address this issue. Among a SAR series of 68 dual-acting pyrimidinedione compounds, a number were found to potently inhibit viruses with typical NNRT-resistance engendering mutations (Y181C, L100I, and K103N), suggesting that the molecules may interact with the RT in a manner resulting in a higher genetic barrier to resistance. The series of compounds are also highly active against multidrug-resistant viruses obtained from patients failing prolonged courses of RT and PI therapies. In order to further evaluate this hypothesis, viruses resistant to the antiviral effects of the lead compounds were selected in cell culture using both serial dose escalation and fixed dose resistance selection methods, as well as through the evaluation of the activity of the pyrimidinediones against biologically selected and site-directed viruses with defined NNRTI-resistance mutations. These studies confirmed that the pyrimidinediones required the complex accumulation of multiple mutations in the RT and Env in order to develop high level NNRTI resistance. Antiviral assays with drug resistant and multidrug-resistant viruses indicated that the compounds were able to effectively inhibit viruses with NNRTI-resistance mutations and exhibited enhanced sensitivity to multidrug-resistant viruses obtained from patients failing long courses of PI therapy as well as RT/PI therapy. Additional studies were performed with NNRTI-resistant viruses with the entire SAR series of molecules in an effort to define molecules with specific capability of inhibiting highly resistant viruses such as those with the Y181C, L100I, and K103N (alone and in combination) as well as with MDRs with resistance phenotypes/genotypes to RT inhibitors, PI inhibitors and both RT and PI inhibitors. These results would indicate that the pyrimidinediones possess a high genetic barrier to resistance based on both their dual mechanism of action as well as their low intrinsic level of resistance to individual RT amino changes.

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93

Design, Synthesis and Anti-HIV-1 Evaluation of Novel Arylazolylthioacetanilides as Potent NNRTIS

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Despite the demonstrated clinical efficacy of combination antiviral regimens using HIV-1 NNRTIs, the emergence of clinical resistance has become a key issue for this class of compounds and has become a major cause of treatment failure. Therefore, to search for the novel NNRTIs with potent and broad spectrum antiviral activity, as well as with safe and good pharmacokinetics profiles is urgently needed. Recently, from high-throughput screening (HTS) of compound libraries, several interesting sulfanyltriazole- and sulfanyltetrazole-type leads (A and B) were identified as novel HIV-1 NNRTIs, which have a simple, yet distinctively different chemical