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Synthesis, Anti-HIV and CD4 Down-Modulation Activities of Novel CADA Compounds

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Cyclotriazadisulfonamide (CADA) specifically down-modulates the CD4 receptor expression on the surface of lymphocytes and monocytes/macrophages, the primary receptors utilized by HIV for infection of its target cells. CADA thus inhibits the entry of HIV and HHV-7. The CD4 down-modulating and antiviral potencies of more than 25 CADA analogs have been described. Structural modifications of CADA were made to increase potency, reduce cytotoxicity and improve physical properties. Several head group analogs were synthesized with polar groups and good leaving groups. The anti-HIV and CD4 down modulation activities of these compounds are being studied. Some of these head groups may regenerate the double bond of CADA by elimination reactions, potentially producing water-soluble pro-drugs. IsoCADA (SA05), an isomer of CADA, was synthesized by cyclization of 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD). This structural modification may reveal a relationship between the symmetry of the molecule and its biological activity. An alternate method for the macrocyclization of disulfonamide using a palladium catalyst is being investigated. This new method avoids the high dilution, slow addition of the reagent and formation of polymer side products, which have limited the synthetic utility of the classical Richman-Atkins macrocyclization method. Two new fluorine containing analogs were also synthesized by modifying the toluenesulfonamide side arms. The anti-HIV and CD4 down modulation activities of these new CADA analogs are summarized (Fig. 1).

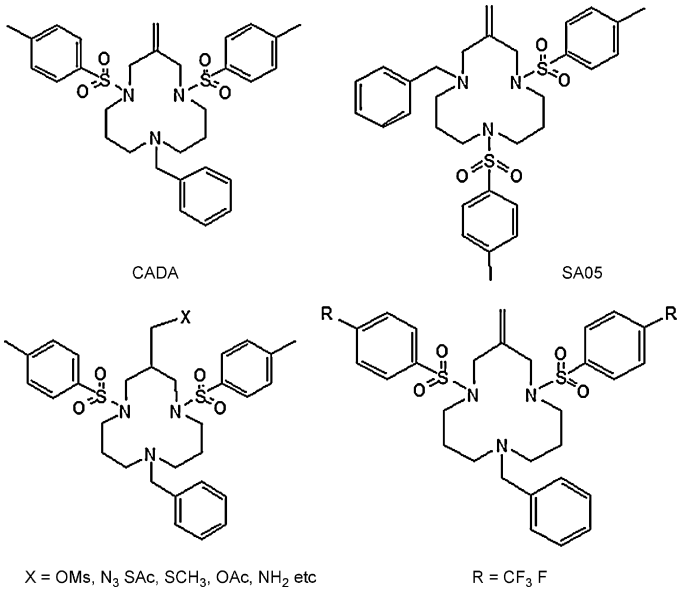

Fig. 1.

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Synthesis and Antiviral Evaluation of Iso-methyl-alkoxyalkyl (S)-HPMPA Esters

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Acyclic nucleoside phosphonates (ANPs) are an important group of clinically useful antiviral agents. To be orally active, ANPs are converted to prodrugs such as the dipivoxil or disoproxil esters. We have developed an alternative technology where one of the phosphonate negative charges is masked with a long-chain alkoxyalkyl group, such as the hexadecyloxypropyl ester. These phospholipid-like prodrugs are readily absorbed from the GI tract into the plasma. They are taken up in tissues and metabolized intracellularly, mainly by cleavage of the phosphonoester bond. The released ANP is then phosphorylated twice to give the active metabolite, ANP diphosphate. In the small intestine and liver, the alkoxyalkyl group is also susceptible to omega oxidation which leads to an inactive short chain carboxylic acid metabolite which is excreted in the urine. To slow this process, we prepared a series of iso-methyl-alkoxyalkyl esters of (S)-HPMPA. The iso-methyl and corresponding straight chain esters possessed similar antiviral activity against cowpox, vaccinia and ectromelia, in vitro. Hexadecyloxypropyl (S)-HPMPA and 15-methyl-hexadecyloxypropyl (S)-HPMPA had EC_{50} values of 0.01–0.04 μM and selectivity indexes of 140–285 against cowpox and vaccinia viruses, in vitro. Oral treatment of ectromelia-infected mice with 15-methyl-hexadecyloxypropyl (S)-HPMPA at a dose of 2.5 mg/kg daily for 14 days, led to 87.5% survival compared to 0% survival in the untreated controls. The iso-methyl branched compounds should be explored further to determine if this modification significantly improves the pharmacokinetic and therapeutic properties of ANP alkoxyalkyl esters.

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