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SYNTHESIS AND BIOLOGICAL EVALUATION OF AN ALKENYLDIARYLMETHANE (ADAM) WHICH ACTS AS A NOVEL NON-NUCLEOSIDE HIV-1 REVERSE TRANSCRIPTASE INHIBITOR

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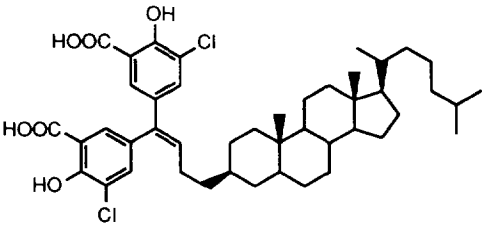
Abstract: ADAM, a novel non-nucleoside HIV-1 reverse transcriptase inhibitor, was synthesized and found to inhibit a variety of HIV-1 strains. In common with other known NNRTIs, ADAM is inactive against HIV-2, and it is much more active as an inhibitor of HIV-1 reverse transcriptase with poly(rC).oligo(dG) as the template/primer than it is with poly(rA).oligo(dT) as the template/primer.

The non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs) constitute a large and growing family of structurally diverse compounds.[1,2] Familiar examples include hydroxyethoxymethylphenylthiothymine (HEPT), tetrahydroimidazobenzodiazepinone (TIBO), dipyridodiazepinone (nevirapine), pyridinone, bis(heteroaryl)piperazine (BHAP), *tert*-butyldimethylsilylspiroaminooxathiole dioxide (TSAO), and α-anilinophenylacetamide (α-APA) derivatives. All of these compounds inhibit HIV-1 reverse transcriptase selectively by an allosteric mechanism involving binding to a location adjacent to the deoxyribonucleoside triphosphate binding site.[3] Several strategies are being investigated for overcoming the rapid emergence of resistant viral strains which seems to invariably accompany the administration of NNRTIs, including switching to another NNRTI, using NNRTI combinations which elicit mutations that counteract one another, and combining NNRTIs with nucleoside RTIs.[1] New NNRTIs which might cause unique patterns of resistance mutations will be useful in the exploration of the utility of these ideas.

We recently reported the synthesis and biological evaluation of cosalane (**1**), a compound which inhibits the cytopathic effect of HIV-1 and HIV-2 in cell cultures.[4] The mechanism of the anti-HIV effect of cosalane has been examined in some detail, and the available evidence indicates that it acts primarily by inhibition of gp120-CD4 binding as well as by inhibition of a postbinding event prior to reverse transcription. The promising anti-HIV activity displayed by cosalane has stimulated the synthesis of a number of cosalane (**1**) analogs, and the results have shown consistently that the antiviral activity requires the presence of the two phenolic hydroxyl

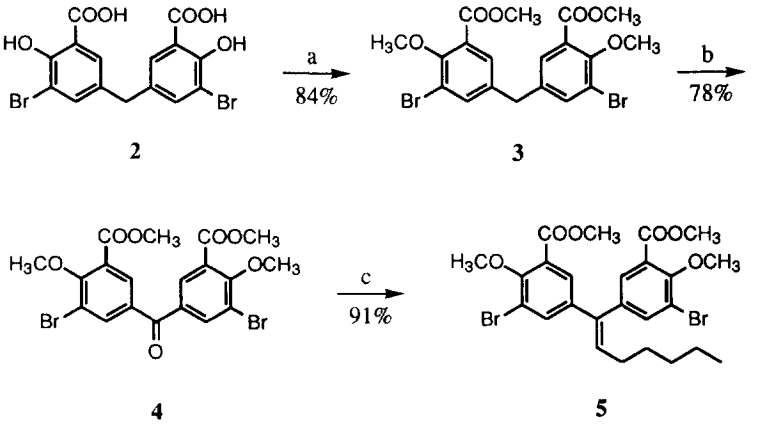
groups as well as the two carboxylic acid groups. The corresponding ether and ester derivatives have, in general, been inactive. However, an exception to this generalization was noted in compound **5** (Scheme 1), which consistently displayed the ability to inhibit the cytopathic effect of a variety of HIV-1 strains in cell cultures. The four-letter acronym ADAM has been applied to compound **5**, since it is an alkenyldiarylmethane derivative. The results presented herein indicate that the anti-HIV-1 activity of ADAM is due to inhibition of HIV-1 RT. ADAM (**5**) is therefore mechanistically distinct from cosalane (**1**).



1

The synthesis of ADAM (**5**) requires only three steps from readily available starting materials. Methylation of the substituted diarylmethane (**2**)[5] with dimethylsulfate in refluxing acetone, using potassium carbonate as the base, afforded intermediate **3**, which was oxidized to the benzophenone **4** with chromium trioxide in acetic anhydride. The Wittig reagent required for the conversion of **4** to ADAM (**5**) was prepared by deprotonation of *n*-hexyltriphenylphosphonium bromide in THF at 0 °C using sodium bis(trimethylsilylamide) as the base.

Scheme I



2 **3**

4 **5**

Reagents and conditions: [a]$(CH_3)_2SO_4$, K_2CO_3, $(CH_3)_2CO$, reflux (24 h). [b]CrO_3, Ac_2O, 23 °C, 3 h, reflux (5 min). [c](1)*n*-$C_6H_{13}PPh_3Br$, $NaN[Si(CH_3)_3]_2$, THF, 23 °C (20 min); (2) intermediate **4**, 60 °C (1 h), 23 °C (20 h).

The range of anti-HIV activity of ADAM (**5**) was investigated in cell culture-based assays and the results are listed in Table I. Activity was observed against a wide range of HIV-1 isolates, including HIV-1_{A17}, which is resistant to pyridinone non-nucleoside reverse transcriptase inhibitors. In common with the other known NNRTIs, ADAM (**5**) is inactive against HIV-2. It is much less active against HIV-1_{N119}, a strain that is resistant to nevirapine. These observations are consistent with the classification of ADAM (**5**) as an NNRTI.

Table I. Range of Activity of ADAM (5) against HIV-1 Isolates in Cell Culture-Based Assays.

Cells	Virus Strain	EC_{50} (μM)[a]	IC_{50} (μM)[b]	Mutation in RT Enzyme[c]
	Laboratory			
CEM-SS	HIV-1_{RF}	9.2 ± 2.8	138 ± 12	
MT-4	HIV-1_{IIIB}	16 ± 4.3	>200	
	Drug-resistant			
MT-4	HIV-1_{A17}[d]	14 ± 0.5	>200	Y181C, K103N
	HIV-1_{N119}[e]	151	>200	Y181C
	HIV-1_{6R}[f]	6.0 ± 3.4	>200	D67N, K70R, T215Y, K219Q
	HIV-1_{6S}	0.56 ± 0.39	>200	
	Clinical Isolates[g]			
PBL	HIV-1_{WEJO}	10.2	>100	
	HIV-1_{BAKI}	15.2	>100	
	HIV-1_{VIHU}	24.9	>100	
	Other			
MO/Mϕ	HIV-$1_{Ba\text{-}L}$[h]	5.5 ± 3.5	>200	
MO/Mϕ	HIV-1_{ADA}	1.85 ± 0.9	>200	
CEM-SS	HIV-2	Inactive		
MT-4	SIV	136	>200	

[a]EC_{50} values represent the concentration of compound that provides 50% protection in the XTT-based cytoprotection assay. [b]IC_{50} values represent the concentration of compound that results in 50% cell death, and >100 and >200 indicate that no toxicity was observed at that high test concentration. [c]Mutations found in the RT enzyme of the drug-resistant strain are indicated. [d]Pyridinone-resistant. [e]Nevirapine-resistant. [f]AZT-resistant. [g]EC_{50} values for the clinical strains represent the concentration of compound required to inhibit cell-free supernatant RT expression by 50%. [h]EC_{50} values for the monocytotropic HIV-$1_{Ba\text{-}L}$ and HIV-1_{ADA} strains represent the concentration of compound required to inhibit cell-free supernatant p24 expression by 50%.

ADAM (**5**) was an effective inhibitor of HIV-1 reverse transcriptase (IC_{50} = 0.38 ± 0.04 μM, mean ± 1 S.D., n = 3) with poly(rC).oligo(dG) as the template/primer. However, it was inactive with poly(rA).oligo(dT) as the template/primer. The greater sensitivity to inhibition of HIV-1 reverse transcriptase with poly(rC).oligo(dG) as the template/primer is characteristic of the NNRTIs.[2]

Although the NNRTIs are a structurally diverse family of compounds, many of them have two aromatic rings with heteroatoms or functional groups attached to them that can accept hydrogen bonds. Several NNRTIs, in common with ADAM (**5**), have two aromatic rings attached to the same atom.[6-11] In the HEPT and DABO derivatives, one of the aromatic rings is replaced by a pyrimidinedione ring.[12] The orientations of the two π-systems in these compounds fit a "butterfly-like" model proposed recently on the basis of comparison of the structures of several NNRTIs.[13] The hexenyl side chain of ADAM (**5**) projects into a "lipophilic site" proposed by the model.

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