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Benzothiadiazine Dioxide Acyclonucleosides as Lead Compounds for the Development of New Agents Against Human Cytomegalovirus and Varicella-Zoster Virus Infections

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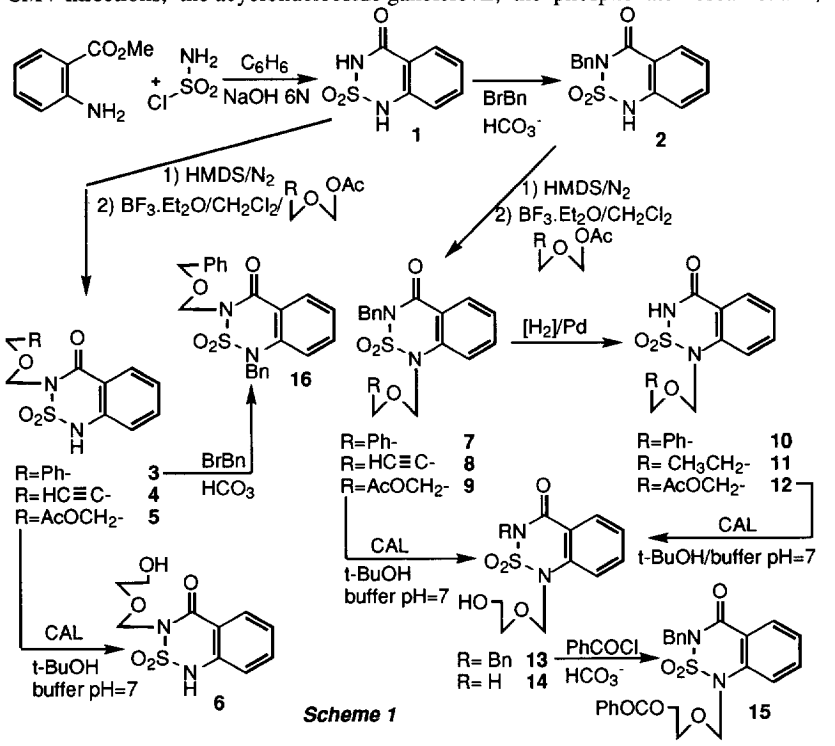
Abstract- The first acyclonucleosides derived from 2,1,3-benzothiadiazine dioxides were synthesized. From their antiviral activity evaluation results these compounds might be considered as new leads in the search for inhibitors of human cytomegalovirus (CMV) and varicella-zoster virus (VZV) infections.

Cytomegaloviruses (CMVs) are highly species-specific DNA viruses that are found universally throughout the world and that commonly infect many animals, including humans. In the vast majority of cases the initial infection is asymptomatic. However, HCMV can cause severe morbidity and mortality in congenitally infected newborns and immuno-compromised patients.[1] Individuals infected with HIV are nearly always HCMV seropositive and often develop symptomatic reactivation disease as immunocompromise progresses. Nucleoside analogues offer great potential for the treatment of herpes- and retrovirus infections.[2,3] For the treatment of CMV infections, the acyclonucleoside ganciclovir, the phosphonate foscarnet and, since a few months, the acyclonucleoside phosphonate cidofovir have been approved, although the use of ganciclovir and foscarnet has been compounded by their toxicity and the emergence of virus-drug resistances .[4]



Scheme 1

Continuing with our work on acyclic nucleosides,[5] here we report the first synthesis and antiviral evaluation of acyclonucleosides derived from the benzothiadiazine dioxide ring.[6]

The acyclonucleosides were obtained using

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the silylation procedure.[7] Several acyclic moieties have been introduced,[8] including acetoxyethoxymethyl, benzyloxymethyl and propargyloxymethyl fragments. In all conditions essayed, acycloglycosylation took place initially at N-3 (Scheme 1). The N-1 substituted acyclic nucleosides were prepared using a protection-deprotection strategy from 3-benzylbenzothiadiazine. A lipase-mediated deacylation was employed as deprotection procedure for the acyclic moiety. This previously described methodology[9] has been applied to the regioselective deacylation of a thiadiazine dioxide diacyclic nucleoside related to 6-methyluracil.[10]

The new benzothiadiazine acyclonucleosides prepared were evaluated for their activity against cytomegalovirus (CMV, strains AD-169 and Davis) and varicella-zoster virus (VZV, strains OKA, YS, 07/1 and YS/R) in human embryonic lung (HEL) cells[11] whilst their potential anti-HIV activity was evaluated (HIV-1, strain III_B and HIV-2, strain ROD) in MT-4 cells.[11] Compounds **7**, **8**, **15** and **16** showed activity against CMV and VZV at concentrations that were 5 to 10-fold below the cytotoxic concentrations for the host cells. Benzylacyclonucleoside **16** showed activity against CMV at a concentration that was >10-fold lower than the concentration that was toxic to the host cells. This activity may therefore qualify as a specific antiviral effect. Additionally, derivative **16** inhibits the replication of HIV-1 in MT-4 cells with a IC_{50}=3.7 μg/ml. All the compounds proved to be inactive against the replication of HIV-2 at subtoxic concentrations in MT-4 cells. The structure of these active compounds is quite unique not only for the nature of the heterocyclic base, but also because of the lack of the OH group in the acyclic counterpart specially regarding the anti-CMV activity. The HIV-1 specific nature found in this kind of acyclonucleosides probably implies binding at the NNRTI site.

Comp.	Antiviral Activity IC_{50}(μg/ml)		Cytotoxicity CC_{50}(μg/ml)
	CMV		
	AD-169	Davis	
7	11	12	>50
8	8.4	11	>50
15	12	12	24
16	3.6	3.6	>50
Ganciclovir	1.2	1.3	>50
	TK$^-$VZV		
	07/1	YS/R	
7	11	13	>50
8	>5	>5	>50
15	>12	>12	24
16	>5	3	>50
Aciclovir	24	26	200
	HIV-1 (IIIB)	HIV-2 (ROD)	
7	>8	>8	25
8	>8	>8	23
15	79.3	>86	>125
16	3.7	>99	>125

Benzothiadiazine dioxides acyclonucleosides might be considered as new lead compounds in the search for inhibitors of human cytomegalovirus and varicella-zoster virus infections, which are among the most common opportunistic infections in patients suffering from the acquired inmune deficiency syndrome (AIDS), taking profit of the anti-HIV-1 specific activity found.

Further efforts are directed at determining the structure-activity relationship of this new family of compounds and discovering new congeners with higher antiviral potency.

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