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New Pseudonucleosides Containing Chiral Oxazolidin-2-Ones and Cyclosulfamides as Aglycones: Synthesis and Antiviral Evaluation

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NEW PSEUDONUCLEOSIDES CONTAINING CHIRAL OXAZOLIDIN-2-ONES AND CYCLOSULFAMIDES AS AGLYCONES: SYNTHESIS AND ANTIVIRAL EVALUATION

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□ *A series of chiral cyclosulfamides and oxazolidinon-2-ones have been synthesized starting from aminoacids. Regioselective substitution of these pseudopyrimidic heterocycles was carried out under Mitsunobu conditions. Best substitution results were obtained by preliminary deprotection of cyclosulfamides and their condensation with β -D-ribofuranose. Chiral oxazolidin-2-ones were coupled directly with D-ribofuranose. All compounds were tested against HSV-2, VV and SV viruses. Two compounds **6b** and **6e** showed significant activities against HSV-type 1.*

Keywords Aminoacids; cyclosulfamides; oxazolidin-2-ones; glycosylation; pseudonucleosides; Mitsunobu reaction

INTRODUCTION

Nucleosides analogues represent interest class of therapeutic agents in the treatment of cancers and virus infections.^[1,2] Most of them, natural or synthetic have been approved for the treatment of various viral diseases including Herpes Viruses, Human Immunodeficiency Virus (HIV) and

Dedicated to the loving memories of Pr. M. Abdessamad Guellati (1955–2006).

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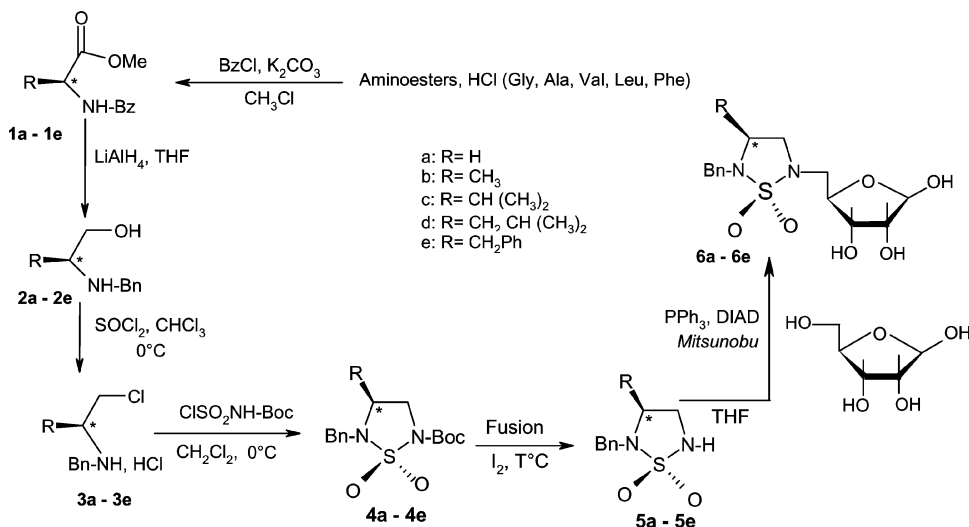
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hepatitis B virus infections. In order to discover new nucleotides derivatives with potent antiviral activity, the modification of heterocyclic aglycone of natural nucleosides is important for the synthesis of new nucleosides.

In our previous work, we reported the synthesis of new pseudonucleosides containing sulfamylated derivatives of natural amino acids as aglycone.^[3]

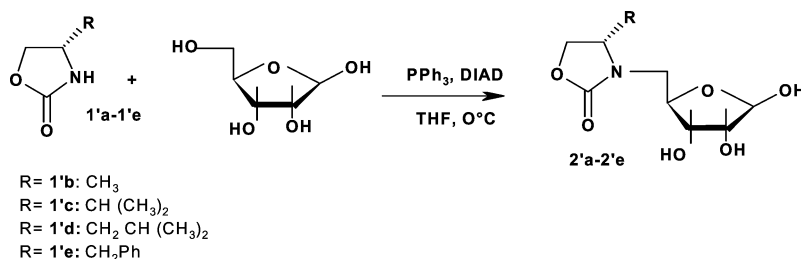
CHEMISTRY

The preparation of cyclosulfamides (**4a-4e**) was performed starting from *N*-substituted Gly, Ala, Val, Leu, Phe. Benzoylation of aminoacids, following by reduction using LiAlH_4 , and chlorination with thionyl chloride gave the 1-substituted *N*-benzyl 2-chloroethylamine hydrochlorides (substituted mustards) **3a-3d**. Under alkaline conditions the sulfonylation by *N*-Boc sulfamoyl chloride (using an excess of triethylamine in dichloromethane), spontaneously cyclised to give *N*⁵-Boc, *N*²-Bn thiadiazolidine 1,1-dioxides **4a-4e**.^[4] The *cyclosulfamides* **4a-4e** with orthogonal protecting group can independently be removed under the appropriate conditions. The fusion method^[5] was used for Boc cleavage to give the deprotected chiral *cyclosulfamides* **5a-5e** in 90–95% yield (Scheme 1).



SCHEME 1 Synthesis of pseudonucleosides containing cyclosulfamide as aglycone (5-deoxy-5-(5-2-benzyl-3(S)-alkylthiadiazolidinyl)-β-D-ribose).

The regioselective substitution of these pseudopyrimidic heterocycles was carried out using the Mitsunobu reaction. This reaction has found wide spread use in many fields because of its high reliability and extensive applicability. In heterocycle structures, the greater nucleophilicity of sulfonyl NH allowed its selective use by Mitsunobu reaction.^[6]



SCHEME 2 Synthesis of pseudonucleosides containing oxazolidin-2-one as aglycone: 5-deoxy-5-((4S)-4-alkyl-2-oxo-1,3-oxazolidin-3-yl)- β -D-ribose.

The 5'OH substitution of D ribofuranose by the NH of the cyclophosphamides using the tandem triphenylphosphine: diisopropylazodicarboxylate (DIAD) led to the **6a-6e** in 35% yield. In the same way, chiral oxazolidin-2-ones^[7] were condensed with a β -D-ribofuranose in tetrahydrofuran under Mitsunobu conditions. The nucleosides derivatives **2a'-2d'** were obtained in 32% overall yield (Scheme 2).

STRUCTURAL STUDY

The structure of all compounds was unambiguously confirmed by IR, 1H , and ^{13}C NMR, mass spectrometry and element analysis. *Cyclosulfamides* **3a-3d** were characterized by IR spectroscopy based on the presence of characteristic vibration at $1110\text{--}1170\text{ cm}^{-1}$ characteristic sulfonyl group and by intense absorption at $1700\text{--}1710\text{ cm}^{-1}$ characteristic of their carbamate group. As expected, this latter signal is not present in the spectrum after cleavage. Deprotection was also checked by 1H NMR based on the disappearance of signal corresponding to the *tert*-butyl protons. Regiospecific glycosylation in 5'-position was confirmed by disappearance of the signal NH proton and the diastereotopic ribose methylene protons. The β anomeric configuration of OH in 1'-position was confirmed by 1H NMR studies: 5.56 ppm (d, $J'_1J'_2 = 7.8\text{ Hz}$).

The fragmentation in mass spectrometry (FAB) showed the loss of a benzyl group of the pseudonucleosides containing *cyclosulfamide*.

The condensation (chiral oxazolidin-2-ones with ribose) was confirmed by usual spectroscopic methods. The structural study was completed by a Crystallographic analysis.

ANTIVIRAL EVALUATION

The antiviral activities of all described pseudonucleosides (**6a-6e**) and (**2a'-2d'**) were tested in vitro against the replication of a number of DNA viruses (Herpes Simplex Virus type 1 and type 2, Vaccinia virus) and RNA

virus (Parainfluenza Virus type III). Except **6a** and **6d**, none of them showed an antiviral activity at doses up to 1 mM. The virucide activities of **6a** and **6d** only affected only the virions produced by infected cells

CONCLUSION

We described here the synthesis of new pseudonucleosides containing chiral *cyclosulfamides* and oxazolidin-2-ones as aglycones. Regiospecific Mitsunobu reaction was used for the condensation (sugar-modified aglycone). The preliminary antiviral results were not encouraging. The antitumoral evaluation of the resulting compounds and their incorporation in biomolecules are currently in progress.

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