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## Nucleosides, Nucleotides and Nucleic Acids

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# Synthesis of AZA Analogues of TSAO

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## NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS Vol. 22, Nos. 5–8, pp. 939–941, 2003

## Synthesis of AZA Analogues of TSAO

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### ABSTRACT

TSAO derivatives which were first synthesized in 1992 have shown strong inhibitory effect and selectivity against HIV-1 (Camarasa, M.J.; Pérez-Pérez, M.J.; San-Félix, A.; Balzarini, J.; De Clercq, E. J. Med. Chem. **1992**, *35*, 2721–2727). The structure-activity relationship of these derivatives has shown strong binding between the amino acids constituting the reverse transcriptase and the different pharmacophore (tert-butyldimethylsilyl group, amino and sulfonate groups of the TSAO derivatives) (Camarasa, M.J.; San-Félix, A.; Pérez-Pérez, M.J.; Velázquez, S., Alvarez, R.; Chamorro, C.; Jimeno, M.L.; Pérez, C.; Gago, F.; De Clercq, E.; Balzarini, J. J. Carbohydr. Chem. **2000**, *19*, 6403–6406). We described the synthesis of an original TSAO analogue where, basically, the *O*-1" atom is replaced by a nitrogen atom.

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*Scheme 1.* Reagents and conditions: (i) SO(Im)<sub>2</sub>, THF; (ii) silylated thymine, 130°C; (iii) TBDMSCl, imidazole, DMF; (iv) MeI,  $K_2CO_3$ , MeCN; (v)  $C_{s_2}CO_3$ , MeCN; (vi)  $C_6H_{10}$ -Pd(OH)<sub>2</sub>, EtOH.

Starting from glyco- $\alpha$ -aminonitrile precursors which have been intensively studied in our laboratory and obtained in a stereospecific way,<sup>[3,4]</sup> successive mesylation and deprotection of a ribo derivative lead to the sulfonamido derivative **1** with an overall yield higher than 95%. Attempts to introduce a nucleic base such as thymine by a Vorbrüggen procedure did not lead to the corresponding nucleoside. This could be obtained, however, by the fusion method. The 1,2-*O*-sulfinyle derivative was prepared with SO(Im)<sub>2</sub> in THF with about 85% yield as its exo/endo cyclic form. Finally, condensation of a silylated thymine at 130°C with the 1,2-*O*-sulfinyle resulted in nucleoside **2** with 82% yield. Methylation on the *N*-positions created the precursor for the CSIC reaction. Cyclisation with Cs<sub>2</sub>CO<sub>3</sub> afforded 45% yield of the isothiazolic derivative **3**. Deprotection of the benzyl group with C<sub>6</sub>H<sub>10</sub>-Pd(OH)<sub>2</sub> followed by silylation with TBDMSCl gave the A-TSAO-m<sup>3</sup>T (**4**) in 65% yield.

In a similar way, A-TSAO-T analogue (non alkylated base) was obtained by selective protection of thymine with a BOC group. Then, the cyclisation followed by the one-pot deprotection of both the benzyl and BOC groups with  $C_6H_{10}$ -Pd(OH)<sub>2</sub> gave the leading compound, after silylation, with 55% yield.

Biological tests have shown selective inhibition on HIV-1 RT.

Investigations to obtain both non alkylated N-sulfonamide and substitution on the 5"-C are also in progress. In order to investigate SARs different substituents should be introduced on both the nucleic base and the sulfonamide cyclic moiety.

#### REFERENCES

- Camarasa, M.J.; Pérez-Pérez, M.J.; San-Félix, A.; Balzarini, J.; De Clercq, E. J. Med. Chem. 1992, 35, 2721–2727.
- Camarasa, M.J.; San-Félix, A.; Pérez-Pérez, M.J.; Velázquez, S.; Alvarez, R.; Chamorro, C.; Jimeno, M.L.; Pérez, C.; Gago, F.; De Clercq, E.; Balzarini, J. J. Carbohydr. Chem. 2000, 19, 451–469.

### Synthesis of AZA Analogues of TSAO

- 3. Postel, D.; Nguyen Van Nhien, A.; Pillon, M.; Villa, P.; Ronco, G. Tetrahedron Letters **2000**, *41*, 6403–6406.
- 4. Postel, D.; Nguyen Van Nhien, A.; Villa, P.; Ronco, G. Tetrahedron Letters 2001, 42, 593–595.



