This article was downloaded by:

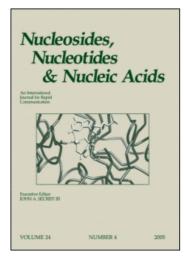
On: 26 January 2011

Access details: Access Details: Free Access

Publisher Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-

41 Mortimer Street, London W1T 3JH, UK



Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information: http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of AZA Analogues of TSAO

Albert Nguyen Van Nhien^a; Cyrille Tomassi^a; Christophe Len^a; José Luis Marco-Contelles^b; Denis Postel^{ac}

^a Laboratoire des Glucides, Université de Picardie-Jules Verne, Amiens, France ^b Laboratorio de Los Radicales Libres Instituto de Química Orgánica General, Juan de la Cierva, Madrid, Spain ^c Laboratoire des Glucides, Université de Picardie, 33, rue Saint Leu, Amiens, France

Online publication date: 09 August 2003

To cite this Article Van Nhien, Albert Nguyen , Tomassi, Cyrille , Len, Christophe , Marco-Contelles, José Luis and Postel, Denis(2003) 'Synthesis of AZA Analogues of TSAO', Nucleosides, Nucleotides and Nucleic Acids, 22:5,939-941

To link to this Article: DOI: 10.1081/NCN-120022690 URL: http://dx.doi.org/10.1081/NCN-120022690

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

www.dekker.com

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

Synthesis of AZA Analogues of TSAO

Albert Nguyen Van Nhien, Cyrille Tomassi, Christophe Len, José Luis Marco-Contelles,² and Denis Postel^{1,*}

¹Laboratoire des Glucides, Université de Picardie-Jules Verne, Amiens, France ²Laboratorio de Los Radicales Libres Instituto de Química Orgánica General, Juan de la Cierva, Madrid, Spain

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.

939

DOI: 10.1081/NCN-120022690 1525-7770 (Print); 1532-2335 (Online) Copyright © 2003 by Marcel Dekker, Inc.



^{*}Correspondence: Denis Postel, Laboratoire des Glucides, Université de Picardie, 33, rue Saint Leu, 80039 Amiens, France; Fax: +33 3 2282 7568; E-mail: denis.postel@ sc.u-picardie.fr.

Downloaded At: 11:08 26 January 2011

Reagents and conditions: (i) SO(Im)2, THF; (ii) silylated thymine, 130°C; (iii) TBDMSCl, imidazole, DMF; (iv) MeI, K₂CO₃, MeCN; (v) Cs₂CO₃, MeCN; (vi) C₆H₁₀- $Pd(OH)_2$, EtOH.

Starting from glyco-α-aminonitrile precursors which have been intensively studied in our laboratory and obtained in a stereospecific way, [3,4] 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)₂ in THF with about 85% yield as its exo/endo cyclic form. Finally, condensation of a silvlated 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 Cs₂CO₃ afforded 45% yield of the isothiazolic derivative 3. Deprotection of the benzyl group with C₆H₁₀-Pd(OH)₂ followed by silylation with TBDMSCl gave the A-TSAO-m³T (4) in 65% vield.

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)₂ 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.
- 2. 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.

- 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.