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

N-3 Substituted TSAO Derivatives as a Probe to Explore the Dimeric Interface of HIV-1 Reverse Transcriptase

María-Cruz Bonache^a; Cristina Chamorro^a; Sonsoles Velázquez^a; Erik De Clercq^b; Jan Balzarini^b; María-José Camarasa^a; Ana San-Félix^a

^a Instituto de Química Médica (C.S.I.C.), Madrid, Spain ^b Rega Institute for Medical Research, Leuven, Belgium

Online publication date: 09 August 2003

 $\label{eq:continuous} \textbf{To cite this Article} \ Bonache, \ María-Cruz \ , \ Chamorro, \ Cristina \ , \ Velázquez, \ Sonsoles \ , \ De \ Clercq, \ Erik \ , \ Balzarini, \ Jan \ , \ Camarasa, \ María-José \ and \ San-Félix, \ Ana(2003) \ 'N-3 \ Substituted \ TSAO \ Derivatives \ as \ a \ Probe \ to \ Explore \ the \ Dimeric \ Interface \ of \ HIV-1 \ Reverse \ Transcriptase', \ Nucleosides, \ Nucleotides \ and \ Nucleic \ Acids, \ 22:5,947-949$

To link to this Article: DOI: 10.1081/NCN-120022692 URL: http://dx.doi.org/10.1081/NCN-120022692

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.

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS Vol. 22, Nos. 5–8, pp. 947–949, 2003

N-3 Substituted TSAO Derivatives as a Probe to Explore the Dimeric Interface of HIV-1 Reverse Transcriptase[†]

María-Cruz Bonache, ¹ Cristina Chamorro, ¹ Sonsoles Velázquez, ¹ Erik De Clercq, ² Jan Balzarini, ² María-José Camarasa, ¹ and Ana San-Félix ^{1,*}

¹Instituto de Química Médica (C.S.I.C.), Madrid, Spain ²Rega Institute for Medical Research, K. U. Leuven, Leuven, Belgium

Reverse transcriptases (RTs) from both human immunodeficiency viruses type 1 (HIV-1) and 2 (HIV-2) are obligatory dimers and only dimeric forms of this enzyme are actives.^[1] It has been suggested that the dimerization of RT might be a good target for therapeutic intervention in AIDS.^[1,2]

TSAO-T bearing at N-3 an ethyl moiety (TSAO-e³T) belongs to a unique family of HIV-1-specific non-nucleoside RT inhibitors (NNRTIs).^[3] It is the only small molecule that has been shown to interfere with the HIV-1 RT dimerization process by destabilizing the p66/p51 and p66/p66 dimeric forms of HIV-1 RT.^[4] Recently, we have reported a model of interaction of TSAO derivatives with the HIV-1 RT.^[5] In this model, TSAO straddles between the subunits at the p66/p51 interface. The N-3 substituents of the thymine base of the TSAO compounds are positioned parallel to the subunit interface.

947

DOI: 10.1081/NCN-120022692 Copyright © 2003 by Marcel Dekker, Inc. 1525-7770 (Print); 1532-2335 (Online) www.dekker.com

270 Madison Avenue, New York, New York 10016



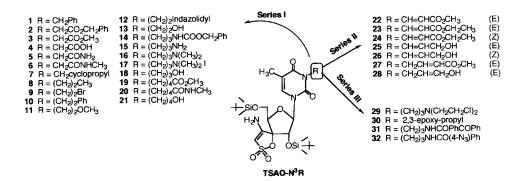
[†]This paper is dedicated to the memory of Dr. Manfred Stud.

^{*}Correspondence: Ana San-Félix, Instituto de Química Médica (C.S.I.C.), C/Juan de la Cierva 2, E-28006 Madrid, Spain; Fax: +34 1564 4853; E-mail: anarosa@iqm.csic.es.

Downloaded At: 11:08 26 January 2011

948 Bonache et al.

In order to explore new binding sites along the interface we have prepared novel series of N-3-substituted TSAO derivatives, with different functional groups, that may give additional interactions with one or more aminoacids at either the p66 or p51 subunit of the dimer interface, and thus may destabilize the RT dimer by disrupting crucial interface interactions. A first series of compounds having at N-3 position functional groups of different nature (alkyl, aryl, acid, ester, amido, ether, halogen, alcohol, amino), linked to this position through flexible polymethylene linkers of different length (n = 1-4), were prepared (1-21). A second series of compounds with restricted conformational flexibility in the linker was also prepared by introduction of cis or trans double bonds (22–28). We also prepared a third series of compounds that may form covalent bonds with aminoacids of the dimer interface. These compounds may, in addition, help to identify the aminoacids at the interface that are involved in the interaction of TSAO derivatives with HIV-1 RT. Thus, we prepared irreversible inhibitors bearing at the N-3 position alkylating groups that may bind covalently to different aminoacids (29 and 30) or compounds bearing at the N-3 position photoreactive cross-linking groups that, upon irradiation with UV light generate reactive intermediates that may form strong covalent bonds with neighbouring aminoacids (31 and 32).



All the compounds synthesized showed pronounced activity against HIV-1 replication (EC $_{50} = 0.03 - 0.76\,\mu\text{M}$) while being inactive against HIV-2. The N-3 methylcarboxamide TSAO compound (6) proved two-fold more active than the prototype TSAO-T and did not show toxicity, thus being the most selective TSAO derivative prepared so far. Photoaffinity labeling experiments are now under progress with compounds 31 and 32.

ACKNOWLEDGMENTS

The Spanish CICYT, the Comunidad de Madrid (CAM) and the European Commission are acknowledged for financial support. The European Commission is also acknowledged for the René Descartes-2001 Prize.

N-3 Substituted TSAO 949

REFERENCES

1. Restle, T.; Müller, B.; Godoy, R.S. J. Biol. Chem. 1990, 265, 8986–8988.

- 2. Restle, T.; Müller, B.; Godoy, R.S. FEBS Lett. 1992, 300, 97–100.
- 3. a) Camarasa, M.J.; Pérez-Pérez, M.J.; San-Félix, A.; Balzarini, J.; De Clercq, E. J. Med. Chem. 1992, 35, 2721–2727; b) Balzarini, J.; Pérez-Pérez, M.J.; San-Félix, A.; Schols, D.; Perno, C.F.; Vandamme, A.M.; Camarasa, M.J.; De Clercq, E. Proc. Natl. Acad. Sci. USA 1992, 89, 4392–4396; c) 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.
- 4. Sluis-Cremer, N.; Dmitrienko, G.I.; Balzarini, J.; Camarasa, M.J.; Parniak, M.A. Biochemistry **2000**, *39*, 1427–1433.
- 5. Rodríguez-Barrios, F.; Pérez, C.; Lobatón, E.; Velázquez, S.; Chamorro, C.; San-Félix, A.; Camarasa, M.J.; Pelemans, H.; Balzarini, J.; Gago, F. J. Med. Chem. **2001**, *44*, 1853–1865.