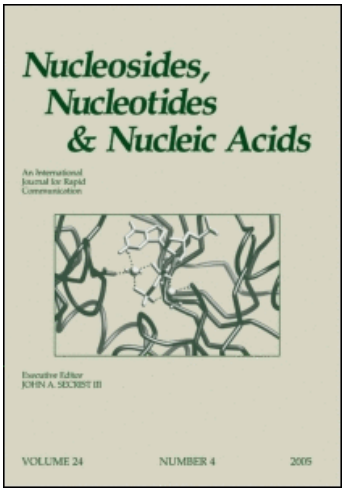

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N-3 Substituted TSAO Derivatives as a Probe to Explore the Dimeric Interface of HIV-1 Reverse Transcriptase†

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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-e^{3}T) 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.

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

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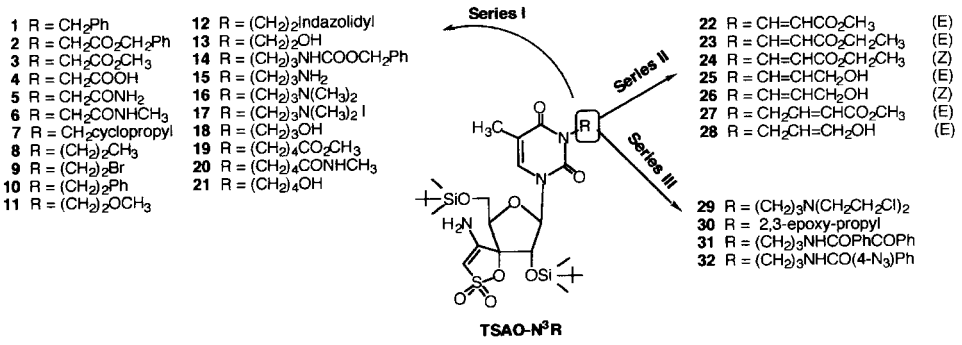
In order to explore new binding sites along the interface we have prepared novel series of N-3-substituted TSAO derivatives, with different functional groups, that may give additional interactions with one or more aminoacids at either the p66 or p51 subunit of the dimer interface, and thus may destabilize 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 lenght (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 ($EC_{50} = 0.03 - 0.76\,\mu M$) 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**.

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