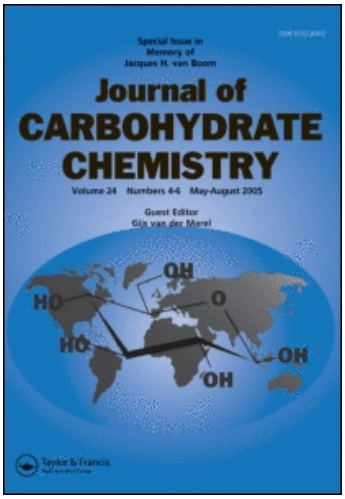

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COMMUNICATION

SYNTHESIS OF NOVEL 5'-SUBSTITUTED TSAO-T ANALOGUES WITH ANTI-HIV-1 ACTIVITY

A. San-Félix,[a]* C. Chamorro,[a] M. J. Pérez-Pérez,[a] S. Velázquez,[a] E. de Clercq,[b] J. Balzarini[b] and M. J. Camarasa[a]

[a]Instituto de Química Médica (C.S.I.C.), Juan de la Cierva 3, 28006 Madrid, Spain
[b]Rega Institute for Medical Research, Minderbroedersstraat 10, B-3000 Leuven, Belgium

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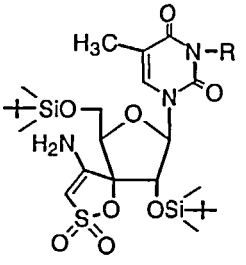
INTRODUCTION

TSAO derivatives are potent and selective HIV-1 reverse transcriptase (HIV-1 RT) inhibitors. Although, structurally, they can be considered as highly functionalized nucleosides, they inhibit their target enzyme (HIV-1 RT) similarly to the so-called Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI).[1-6] The different families of NNRTI, including TSAO, interact with the HIV-1 RT in a highly hydrophobic pocket, close but different from the active site, and several complexes of NNRTIs-HIV-1 RT have been resolved by X-ray crystallography.[7-15]

Among TSAO derivatives, the prototype compound is TSAO-T (**1**, Figure 1) [1-[2',5'-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]thymine]-3'-spiro-5"-(4"-amino-1",2"-oxathiole-2",2"-dioxide)]. However, the most selective compound is the 3-*N*-methyl substituted TSAO-T (TSAO-m^{3}T, **2**) (Figure 1). Structure-activity relationship studies carried out so far revealed that both *tert*-butyldimethylsilyl groups (TBDMS) at positions 2' and 5' of the sugar moiety play an important role in the potency of the compounds, the 2'-TBDMS being less critical than the 5'-TBDMS group.[16]

Our current working model of interaction of TSAO-T with HIV-1 RT suggests that the 5'-TBDMS group is located in a cavity delineated by three aromatic residues (Tyr181, Tyr188 and Tr229). These amino acids are involved in the binding of most of the NNRTIs.[7-15]



1 R= H (TSAO-T)
2 R= CH_3 (TSAO-m^3T)

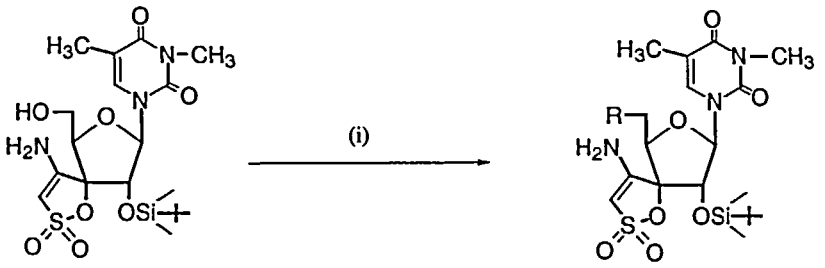
Figure 1. Structures of TSAO-T (**1**) and TSAO-m^3T (**2**)

In this paper we report on the synthesis of novel TSAO-m^3T analogues where the 5'-*tert*-butyldimethylsilyl group has been replaced by (thio)acyl groups, ethers and amines possessing different lipophilic and steric properties in order to assess the role of such substitutions in the antiviral activity/toxicity profile of the TSAO series. The selection of these substituents has been performed based on, among other factors, their presence in other NNRTIs whose coordinates inhibitor-HIV-1 RT are available and that locate such substituent in the cavity defined by the above mentioned aromatic residues.

RESULTS AND DISCUSSION

The 5'-*O*-acyl derivatives **4** and **5** were synthesised by treatment of the previously described 5'-OH-TSAO derivative **3**[16] with acetic anhydride or isobutyryl chloride in pyridine (65 % and 72 % yields, respectively) (Scheme 1). On the other hand, reaction of **3** with phenyl chloroformate[17] followed by treatment with a 33 % ethanolic solution of dimethylamine afforded the TSAO 5'-*O*-carbamate **6** (70 %). Similarly, reaction of **3** with *N,N'*-thiocarbonyldiimidazole, and then with dimethylamine yielded the corresponding 5'-*O*-thiocarbamate **7** (51 %).

The analytical and spectroscopic data from **4-7** were in agreement with the proposed structures. The ^{1}HNMR spectra showed a downfield shift ($\Delta\delta$ 0.59-0.9 ppm) of the signals corresponding to the H-5' protons, with respect to the same signals in **3** (δ 3.91 ppm).



3

4: R = $OCOCH_3$
5: R = $OCOCH(CH_3)_2$
6: R = $OCON(CH_3)_2$
7: R = $OCSN(CH_3)_2$

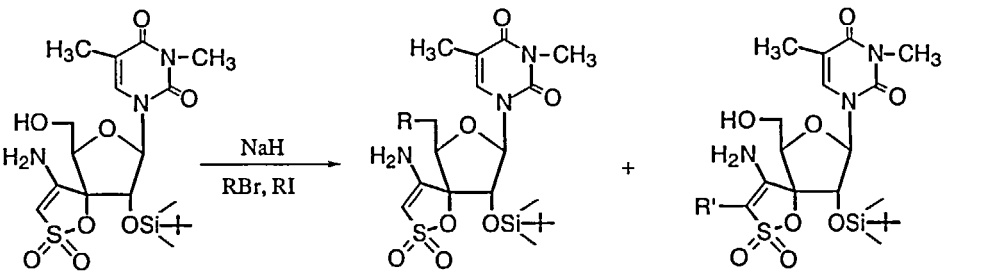
Reaction conditions: (i) $(CH_3CO)_2O$/ pyridine or $(CH_3)_2CHCOCl$/ pyridine or PhOCOCl/ $(CH_3)_2NH$ or Im_2CS/ $(CH_3)_2NH$

Scheme 1. Synthesis of 5'-*O*-(thio)acyl derivatives of TSAO-m^{3}T **4-7**

The synthesis of the 5'-*O*-ether protected TSAO derivatives **8-12** (Scheme 2) was performed by treatment of the 5'-OH TSAO-m^{3}T (**3**)[16] with equimolar amounts of NaH, and reaction *"in situ"* with the appropriate alkyl, alkenyl or benzyl halide. In this way, the corresponding *O*-allyl, *O*-dimethylallyl, *O*-isobutyl, *O*-methyl and *O*-benzyl TSAO-m^{3}T derivatives **8-12** were obtained. Yields were from moderate to poor (34-10 %). In some cases, the 3"-*C*-alkylated derivatives were also isolated as minor products [**13** (13 %), **14** (12 %), **15** (2 %)]. In general, we recovered varying amounts of starting material, as has been described in similar reactions.[18] Then, we tried addition of extra amounts of NaH (1 or 2 additional equivalents) in order to consume all the starting material, but this procedure resulted in the formation of complex reaction mixtures.

Structures of **8-15** were assigned on the basis of the corresponding analytical and spectroscopic data. The 5'-*O*-ether protected TSAO derivatives **8-12** showed in their ^{1}HNMR spectra the disappearance of the signal at 5.84 ppm assigned to the 5'-OH and the presence of a multiplet at δ 3.2-3.8 ppm corresponding to the *O*-CH_2 protons of the alkyl, alkenyl or benzyl moiety. No modification was observed at the signals of the protons of

the spirooxathiol moiety (NH_2-4" and H-3"), thus indicating that no alkylation had occurred at this part of the molecule. On the other hand, formation of the 3"-*C*-alkenyl and 3"-*C*-benzyl compounds **13-15** was established by the disappearance of the signal at 5.77 ppm assigned to the H-3" proton and by the presence of a multiplet at δ 3.2-3.8 ppm assigned to the *C*-CH_2 protons of the alkenyl or benzyl moiety. No modification was



3

8 R = O $CH_2CH{=}CH_2$
9 R = O $CH_2CH{=}C(CH_3)_2$
10 R = O $CH_2CH(CH_3)_2$
11 R = OCH_3
12 R = OCH_2Ph

13 R' = $CH_2CH{=}CH_2$
14 R' = $CH_2CH{=}C(CH_3)_2$
15 R' = CH_2Ph

Scheme 2. Synthesis of 5'-*O*-ethers of TSAO-m^3T **8-12**

observed at the signals corresponding to the 5'-OH and 4"-NH_2 with respect to those observed for the starting compound **3**.

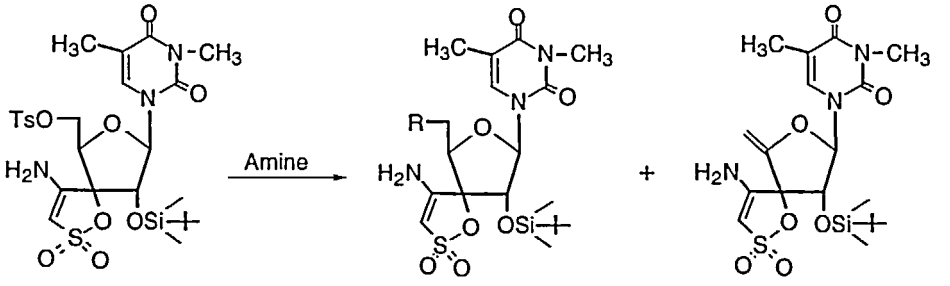
Finally, nucleophilic displacement of the 5'-*O*-tosyl protecting group of **16**[16] (Scheme 3) with excess of dimethylamine, diethylamine, pyrrolidine or piperidine, in refluxing acetonitrile, afforded the corresponding 5'-amino-5'-deoxy-TSAO derivatives **17** (23 %), **18** (30 %), **19** (34 %) and **20** (40 %) respectively, together with the 4',5'-didehydro nucleoside **21** (25 %).

Attachment of the amine to the 5'-position of TSAO-m^3T in compounds **17-20** was established from the ^{1}HNMR spectra by the disappearance of the signals corresponding to the tosyl group and by the strong upfield shift (Δδ 1.45-1.67 ppm) of the signals corresponding to the H-5' protons with respect to the same signals in the starting compound **16** (δ 4.44 ppm).

The ^{1}HNMR spectrum of the 4',5'-didehydro nucleoside **21** showed the disappearance of the signals corresponding to the H-4' and tosyl protons and the presence

of the characteristic 5'-olefin proton signals at 4.5 ppm as a set of doublets with J = 3.1 Hz.

Compounds **4-12** and **17-21** have been evaluated against HIV-1 and HIV-2 replication in human T lymphocyte MT-4 and CEM cells. According to the biological results, when the TBDMS group at the 5'-position was replaced by differently substituted (thio)acyl groups (**4-7**), dimethylamine (**17**) or diethylamine (**18**) antiviral activity was



16

17: R = $N(CH_3)_2$
18: R = $N(CH_2CH_3)_2$
19: R = $N(CH_2)_4$
20: R = $N(CH_2)_5$

21

Scheme 3. Synthesis of 5'-amino-5'-deoxy derivatives of TSAO-m^3T **17-20**

completely lost. However, moderate anti-HIV-1 activity was observed for the 5'-pyrrolidinyl, 5'-piperidinyl and the 4',5'-didehydro nucleosides **19-21**. Compounds **8-12** bearing ether groups at the 5'-position also showed moderate activity against HIV-1. Interestingly, compound **10** containing the isobutyl ether group at the 5'-position showed a marked anti-HIV-1 activity in CEM (EC_{50}: 0.6 μM) and MT-4 (EC_{50}: 4.5 μM) cells being the most active compound of this series.

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