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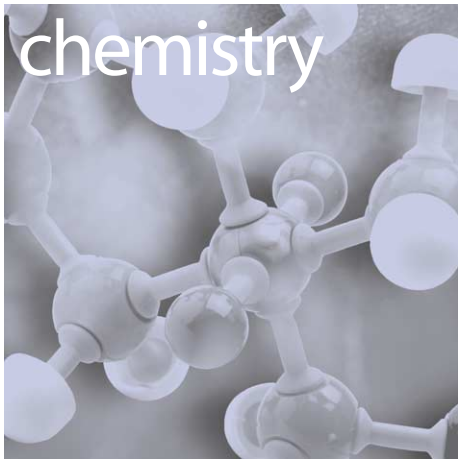


ANTIRETROVIRALS

The first [Foscarnet]–[TSAO-T] conjugates

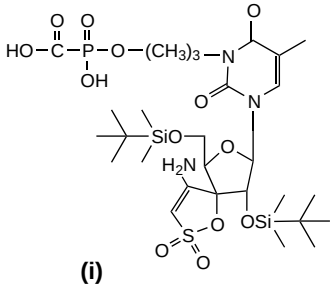
Emergence of HIV drug resistance and the need for long-term antiretroviral treatment are currently the major milestones and the main causes for the failure of antiretroviral therapy. It is now a general concept that HIV-infected individuals should be treated by drug combination therapy to keep the viral load at undetectable levels and to prevent emergence of virus that are resistant to drugs. This can be afforded by mixing individual drugs in one cocktail or, alternatively, by administering conjugates of drugs that are split into the individual drugs once taken up by the target cells.

TSAO-T is the prototype compound of a unique (from a structural and a mechanistic point of view) family of non-nucleoside reverse transcriptase inhibitors (NNRTIs) that are able to destabilize the p66–p51 RT heterodimer. HIV-1 resistance to TSAO compounds is associated with the selection of a single mutation (Glu-138->Lys) in the p51 subunit of HIV-1 RT.

Phosphonoformate (PFA, foscarnet) is an effective antiviral agent approved for treatment of AIDS-related cytomegalovirus retinitis. PFA is also effective against HIV replication. PFA inhibits HIV reverse transcriptase (RT) by blocking the pyrophosphate site. Although PFA is a potent inhibitor of HIV RT, its highly ionic nature at physiological pH is an impediment to its cellular uptake.

Prodrug approaches or PFA-amino acid conjugates have been used to overcome many problems associated with oral bioavailability and cellular permeability of PFA. To date, no PFA–NNRTI conjugates have been reported. However, numerous combination experiments have been performed between different classes of RT inhibitors, although combinations of PFA with NRTIs other than AZT, or with NNRTIs were not reported. Interestingly, in preliminary experiments it was found that PFA was a potent inhibitor of TSAO-characteristic HIV-1 RT/138 Lys mutant strain. The activity against the 138K mutant was one order of magnitude higher than that against virus wild type [IC_{50} (μg/mL)= 0.34 vs 2.59, respectively]. This observation prompted the combination of both inhibitors in a single molecule, leading to [PFA]–[TSAO-T] conjugates, through a labile covalent ester bond to permit hydrolytic cleavage at physiological pH, or enzyme-mediated catalysis. The essential criteria in the design of these conjugates was to explore whether the conjugation of foscarnet with the highly lipophilic TSAO derivative could facilitate the penetration of the conjugates through the cell membrane and if the hybrids would escape extracellular hydrolysis and regenerate the parent inhibitors intracellulary.

Several [TSAO-T]–[PFA] conjugates proved markedly inhibitory to HIV-1. In particular, the deprotected PFA–TSAO conjugate **(i)**, exhibited an EC_{50} value of 0.47–0.82 μM. Some of them also showed potent activity against PFA-resistant HIV-1 strains (EC_{50}: 0.027–0.63 μM), but fewer had detectable inhibitory activity against TSAO resistant HIV-1 strains (EC_{50}: 20–50 μM) [1]. These results indicated a pivotal role of the TSAO component of the hybrid but not the PFA component in the activity of the conjugates. Moreover, stability studies of the [TSAO-T]–[PFA] conjugates demonstrated that the compounds were stable in phosphate-buffered saline, whereas some of the conjugates regenerated the parent inhibitors, (TSAO and PFA) at equimolecular concentrations, in extracts from CEM cells [1].



(i)

These [TSAO-T]–[PFA] conjugates constitute the first examples of molecules in which two known different types of DNA polymerase inhibitors that are active in their own right and do not need metabolic conversion to interact with their target are conjugated through a labile covalent ester bond. Although it has been shown that the antiviral activity displayed by the conjugate was merely due to the action of the NNRTI, it is important to stress these findings to allow scientists in this field to further explore new therapeutic modalities and concepts in a rational way.

1 Velázquez, S. *et al.* (2004). Hybrids of [TSAO-T]-[Foscarnet]: The first conjugate of foscarnet with a non-nucleoside reverse transcriptase inhibitor through a labile covalent ester bond. *J. Med. Chem.* 47, 3418–3426

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