



# Molecular dynamics simulations of T-2410 and T-2429 HIV fusion inhibitors interacting with model membranes: Insight into peptide behavior, structure and dynamics



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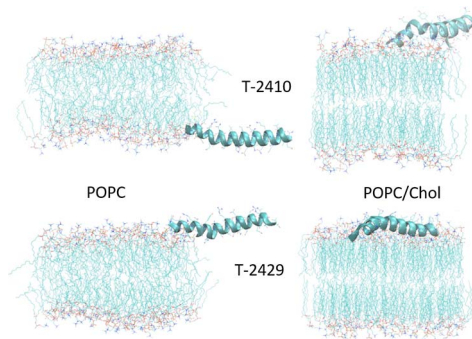
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## HIGHLIGHTS

- Both T-2410 and T-2429 interact with model membranes.
- T-2410 and T-2429 interaction with membranes is stronger which correlates to their lower IC50.
- FI interaction with rigid bilayers has a low dependence on FI-Chol interaction.

## GRAPHICAL ABSTRACT



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## ABSTRACT

T-2410 and T-2429 are HIV fusion inhibitor peptides (FI) designed to present a higher efficiency even against HIV strains that developed resistance against other FIs. Similar peptides were shown to interact with model membranes both in the liquid disordered phase and in the liquid ordered state. Those results indicated that such interaction is important to function and could be correlated with their effectiveness. Extensive molecular dynamics simulations were carried out to investigate the interactions between both T-2410 and T-2429 with bilayers of pure 1-palmitoyl-2-oleoyl-phosphatidylcholine (POPC) and a mixture of POPC/cholesterol (Chol) (1:1). It was observed that both peptides interact strongly with both membrane systems, especially with the POPC/Chol systems, where these peptides show the highest number of H-bonds observed so far. T-2410 and T-2429 showed higher extent of interaction with bilayers when compared to T-20 or T-1249 in previous studies. This is most notable in POPC/Chol membranes where, although able to form H-bonds with Chol, they do so to a lesser extent than T-1249 does, the latter being the only FI peptide so far that was observed to form H-bonds with Chol. This behavior suggests that interaction of FI peptides with rigid Chol rich membranes may not be as dependent from peptide/Chol H-bond formation as previous results of T-1249 behavior led to believe. As in other similar peptides, the higher ability to interact with membranes shown by T-2410 and T-2429 is probably correlated with its higher inhibitory efficiency.

**Abbreviations:** FI-HIV, fusion inhibitor peptides; Chol, cholesterol; POPC, 1-palmitoyl-2-oleoyl-phosphatidylcholine

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