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DISCOVERY OF A NOVEL CLASS OF ORALLY BIOAVAILABLE HIV-1 FUSION INHIBITORS

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OBJECTIVES: Fusion inhibitors block conformational changes in HIV envelope glycoprotein (Env) critical for virus-cell fusion. Proof-of-concept for this therapeutic approach is provided by enfuvirtide, a peptide that is injected subcutaneously and is difficult to manufacture. The identification of non-peptide, orally bioavailable fusion inhibitors may provide valuable new therapeutic options for people living with HIV/AIDS. Reported here is the discovery of a novel class of small-molecule HIV-1 fusion inhibitors, with a mechanism of action distinct from enfuvirtide, which have the potential for oral delivery.

METHODS: Approximately 400,000 drug-like compounds were screened using a high-throughput, cell-based assay for inhibition of critical *Env* conformational changes. Screening hits were confirmed using viral inhibition assays. Compound mechanism of action was characterized using CD4-binding, time-of-addition, and resistance-selection experiments. Compound effects on *Env* conformational changes were studied using flow cytometry.

RESULTS: Three structurally distinct series of drug-like small molecules (median MW ~470; cLogP ~4.3) were identified, constituting a novel class of fusion inhibitors. Unlike enfuvirtide, these compounds bind to *Env* prior to CD4 binding. They specifically block receptor-induced conformational changes that occur after exposure of the gp120 coreceptor binding site, but before exposure of the gp41 intermediate to which enfuvirtide binds. Resistance determinants map to regions in both gp120 and gp41. The most potent compounds inhibited HIV-1 (but not HIV-2 or SIV) infection with an IC₅₀ of approximately 5 nM and retained activity against X4 or R5 primary isolates from clades A, B, C, D, F, G, H, and group O. At least one of these compounds exhibited 30% oral

bioavailability in rats.

CONCLUSIONS: We have discovered a novel class of potent, orally bioavailable HIV-1 fusion inhibitors with a mechanism of action and resistance profile distinct from enfuvirtide. These compounds are being optimized for pre-clinical drug development and may lead to attractive therapeutic alternatives to peptide-based fusion inhibitors.



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New Drug Targets and New Compounds

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