Structure-Guided Optimization of INSTIs to Increase Antiviral Potencies Against HIV-1 Integrase Mutants

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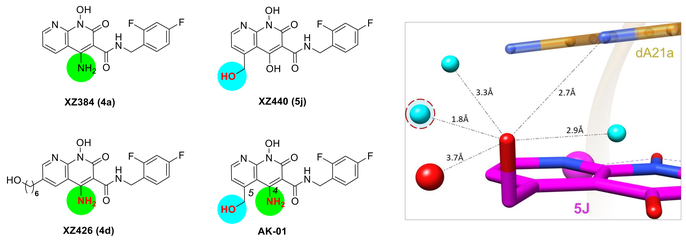
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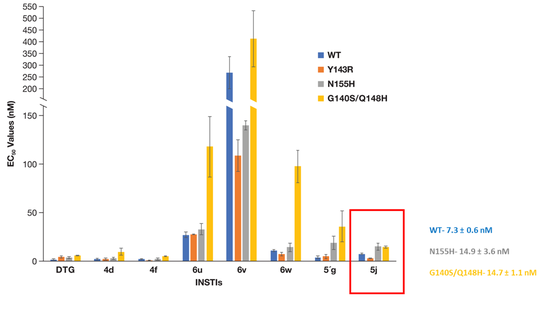
BACKGROUND

There are at least four distinct resistance pathways that emerge against second-generation INSTIs: G118R, G140A/S + Q148H/K/R, N155H, and R263K. Although it is critical to develop INSTIs that retain potency against all four resistance pathways, an important aspect of our research has been directed at overcoming resistance associated with G140S/Q148H mutants, a pathway common in people living with HIV-1 (PLWH) who have undergone virological failure. We are using combinations of our most promising compounds to develop new INSTIs with improved antiviral potencies against the IN G140S/Q148H mutants.

METHODS and Design

AK-01 was generated by combining some of the best structural features of our previous compounds **4d** and **5j** to produce a naphthyridine scaffold with modifications at the 4' and 5' positions.

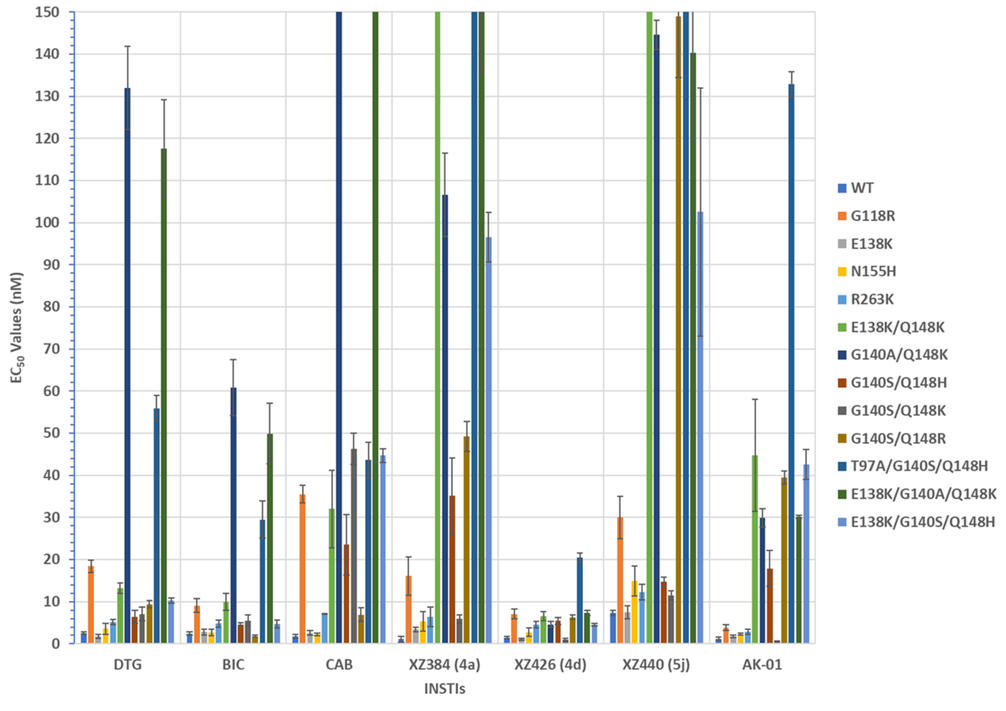




Single round infectivity assays were used to measure EC_{50} values against a panel of clinically relevant IN mutants. We compared the antiviral potencies of **AK-01** with the potencies of parent compounds, **4d**, **5j**, and FDA-approved second-generation INSTIs **DTG**, **BIC**, and **CAB**.

AK-01 exhibited high antiviral potencies against WT HIV-1 (1.2 ± 0.4 nM) and several well-characterized IN mutants (G118R = 3.8 ± 0.7, N155H = 2.3 ± 0.2 nM, and R263K = 2.8 ± 0.6 nM). Importantly, **AK-01** showed only a modest loss in potency against the key IN mutant G140S/Q148H (17.9 ± 4.2 nM). However, there was a more pronounced loss of antiviral potency when **AK-01** was challenged with some other well-known IN double and triple mutants.

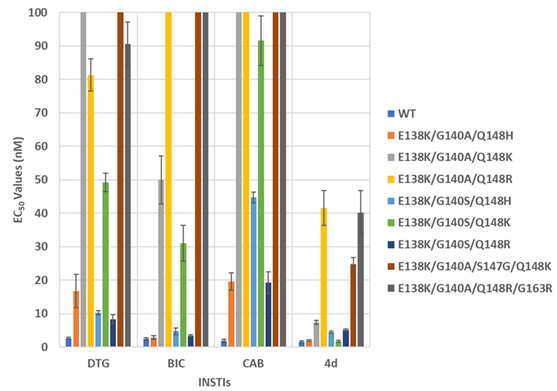
RESULTS



Antiviral profile of INSTIs

AK-01 contains 4'-amino and 5'-hydroxymethyl groups. **AK-01** is a potent inhibitor of WT HIV-1 and several of the well-characterized IN mutants. **AK-01** exhibits an improved potency against the IN mutants G140A/Q148K and E138K/G140A/Q148K when compared to second-generation INSTIs **CAB** and XZ compounds **384** and **440**.

Antiviral activities of 4d and FDA-approved INSTIs against a panel of IN triple and quadruple mutants



4d and the FDA-approved INSTIs were tested against several IN mutants that featured mutations at IN positions E138, G140, and Q148. **4d** exhibited the strongest potencies when compared to the FDA-approved INSTIs.

CONCLUSIONS

- Although **AK-01** is not a fully optimized compound, our results show that combining structural modifications of promising naphthyridine-based INSTIs can be used to produce new compounds that are effective against some of the known drug-resistant mutants.
- Importantly, **AK-01** had an improved antiviral profile when compared to **CAB**.
- We are currently using the available structural and virological data to design and evaluate additional INSTIs.

Future Work

We will add previously studied modifications to optimize this new INSTI platform.

ADDITIONAL KEY INFORMATION

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