A New Quinoline Family of HIV-1 Integrase Inhibitors Acting on HIV-1 Mutants Selected by Integrate Strand Transfer Inhibitors


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Abstract

Background: Integrate strand transfer inhibitors (INSTI) entered clinical use recently. Nevertheless, the development of new antiretroviral inhibitors with different mechanisms of action remains of particular interest. The recent selection of new INSTI-resistant viruses may have implications for the development of new antiretroviral agents.

Methods: Quinolines were synthesized and tested in vitro and in silico for their potential antiviral activity. A panel of either 3’ or 3’/5’ endogenous IN inhibitors was evaluated for their capacity to impair IN activity in cell culture models and on the basis of the NRTI and non-NRTI viral strain viability assay. To determine the efficiency of quinolines on RT-IN INSTI failures, viruses were co-exposed to the IN/INSTI nucleoside and their replication was assessed in presence of various concentrations of inhibitors.

Results: Quinoline family inhibitors showed activity on the IN processing step (WT and D67N INSTI-resistant) and, consequently, on the strand transfer step (after dNTP incorporation). Anti-HIV activity against INSTI-resistant viruses was demonstrated. Furthermore, full-length HIV-1 strain was used in an infection assay to assess the efficacy of quinolines. In all the tested cell lines (C8166, MT-4, and HeLa) full-length HIV-1 strain was shown to be resistant to quinolines. QNL111 inhibits the IN processing with an IC50 of 0.3 nM and IN and HIV-1 virus replication with an IC50 of 5.2 nM. QNL111 displays significant activity against dNRTI-resistant strains.

Conclusions: Quinolines are a new class of antiretroviral agents. In conclusion, the results suggest the potential use of quinolines as a new class of antiretroviral agents.

Antiviral activity methods

1. Ultrastructure of quinolines. A cell-free assay was performed on a panel of drug-resistant HIV-1 strains to determine the antiviral activity on the wild-type (WT) and INSTI-resistant (D67N) viral strain.

2. In vitro anti-HIV activity was performed on cell culture models and on the basis of the NRTI and non-NRTI viral strain viability assay. To determine the efficiency of quinolines on RT-IN INSTI failures, viruses were co-exposed to the IN/INSTI nucleoside and their replication was assessed in presence of various concentrations of inhibitors.

In vitro activity results

Quinolines characterization strategy:

1. To select and characterize quinolines as new specific inhibitors of the IN, the following tests were done:
   - Oligonucleotide-based IN assays to characterize the IN processing and strand transfer step, radioactive substrate and EMSA (Electrophoresis Mobility Shift Assay) migration.
   - Cellular Anti-Integrate Activity and cytotoxicity: and IC50, CC50s, SI were determined in HeLa-ECF cells and MT4.
   - Activity against multi-resistant viruses, with Quinolines antiviral activity on NRTIs & INSTIs viral strains.
   - Activity against INSTI-resistant viruses, with Quinolines antiviral activity on INSTI viral strains.

II. Activity of Quinolines on RTI’s mutants results

Table 1. Activity of Quinolines, including QNL111, on RTI’s mutants strains.

III. Activity of Quinolines on INSTI’s mutants results

Table 2. Activity of Quinolines, including QNL111, on INSTI’s mutants strains.

Conclusion

1. Quinolines family and, QNL111 as a lead, are new potent HIV integrase inhibitors.
2. In vitro assays demonstrate a specific activity of Quinolines during the IN processing step of integration and, consequently, an inhibition of the strand transfer step.
3. The data highlight that NRTI’s and INSTI’s mutations do not impact on Quinolines antiviral activity.
4. Furthermore, Quinolines remain still active against INSTI’s mutants suggesting a different mechanism of action.