Abstract

Although the currently approved NRTI's are highly potent, significant improvements in therapeutic utility are still required. The pyrimidinediones are small molecule HIV inhibitors with two distinct mechanisms of action, inhibiting HIV-1 RT at subnanomolar concentrations through interaction at the hydrophobic NNRTI binding pocket, and the entry of both HIV-1 and HIV-2 at low nanomolar concentrations by interaction with a novel conformational structure formed upon co-culture of virus and CD4+ target cells. From a SAR series of 68 compounds, two lead, therapeutic compounds have been identified with greater inhibitory potential and biochemical and metabolic stability for further evaluation and development. These pyrimidinediones remain highly active against multi-drug resistant (MDR) viruses with mutations in RT and/or protease, suggesting that the compounds may be highly useful as a potential salvage therapy in patients failing HAART, or as a primary therapy in those patients infected with drug-resistant strains. Finally, multiple additional changes in gp120, gp41 and gag proteins which allow the virus to escape entry or maturation RT, resulting in approximately 100-fold loss in sensitivity, followed by the accumulation of mutations in gpl20 and gpl41 and gag proteins which allow the virus to escape entry or maturation to induce drug resistant strains. Drug-sensitive virus selections have resulted in virus isolates which are completely resistant to the selecting pyrimidinediones. Genotypic and phenotypic evaluations of the strains which emerge during the selection process demonstrate the initial appearance of mutations in the RT, resulting in approximately 100-fold loss in sensitivity, followed by the accumulation of mutations in gpl20, gpl41 and gag proteins which allow the virus to escape entry or maturation to induce drug resistant strains. These pyrimidinediones remain highly active against multi-drug resistant (MDR) viruses with mutations in RT and/or protease, suggesting that the compounds may be highly useful as a potential salvage therapy in patients failing HAART, or as a primary therapy in those patients infected with drug-resistant strains.

Dose Escalation Drug Resistant HIV-1<sub>em</sub> Selections

Rapid Drug Resistant HIV-1<sub>em</sub> Selections at Fixed Concentrations

Antiviral Activity Versus Drug Resistant Viruses

Enzyme Kinetics of Pyrimidinedione Inhibitors

Combination Therapy Evaluations

Chemical Structure of Pyrimidinediones

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Summary

- Lead compounds were chosen based on their ability to reduce virus replication by inhibiting both virus entry (70 to 200 nM range) and RT (0.1 to 1.5 nM range).
- Drug resistant HIV-1 isolates were selected and compared for the relative rate of resistance and defined mutations. IQP-0232 and IQP-0349 demonstrated enhanced genetic barrier to resistance.
- Cross resistance evaluations determined IQP-0347 and IQP-0232 in the cyclopropane series demonstrated a higher genetic barrier to resistance active versus 5-8 drug resistant viruses.
- IQP-0243, IQP-0347 and IQP-0359 in the cyclopropane series were the most metabolically stable in the human microsome assay. IQP-0359 of the cyclopropane series was the least stable.
- Additional studies are in progress to synthesize analogs with increased bioavailability by increasing the thermodynamic solubility of the drug solid and improving the plasma half-life.