Evaluation of In Vitro/In Vivo Bioavailability of Saquinavir Dipeptide Prodrugs for Enhancing Intestinal Absorption
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Purpose
The objective of this study is to investigate the stereoselective disposition of dipeptide prodrugs of saquinavir, a HIV protease inhibitor, after oral administration to rats, and provide a prediction of oral bioavailability in humans.

Methods
A double-layered co-culture system of MDCK-MDR1-CYP3A4 (MMC) and HepG2 cells was applied in this study to evaluate in vitro oral bioavailabilities of SQV and various stereoisomeric valine-valine prodrugs (L-, D-, L-L-, L-D-, D-L-, and D-D-). Then single dose of SQV (25mg/kg) and its dipeptide prodrugs (30 mg/kg) were delivered to Sprague Dawley rats orally to delineate pharmacokinetic parameters.

Results
All prodrugs exhibited enhanced in vitro bioavailability over SQV by 2- to 5-fold across MMC/HepG2 co-cultured system, in which L-valine-D-valine-SQV (LDS) and D-valine-L-valine-SQV (DLS) displayed the most significant enhancement. Oral absorption studies conducted with rats indicate that in vivo bioavailability of SQV may be dramatically enhanced by conjugating with L-valine-D-valine- promoiety. The AUC and Cmax values for LDS were observed to be 1846.14±478.29 h*nmol/l and 366.3±89.1 nM, about 10-fold and 8-fold higher than those of SQV, respectively. DLS also showed enhanced oral bioavailability over SQV, but to less extent in comparison with LDS. Moreover, stereoselectivity was achieved in the present studies.

Conclusion
Prodrug L-valine-D-valine-SQV might be the most promising candidate for improving intestinal absorption and oral bioavailability of SQV.
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