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L-735,524: An Orally Bioavailable Human Immunodeficiency Virus Type 1 Protease Inhibitor. E.A. Emini, J.P. Vacca, B.D. Dorsey, W.A. Schleif, R.B. Levin, S.L. McDaniel, P.L. Darke, J.A. Zugay, J.C. Quintero, O.M. Blahy, E. Roth, V.V. Sardana, A.J. Schlabach, J.H. Condra, L. Gotlib, K. Holloway, J. Lin, J.-W. Chen, D. Ostovic, P.S. Anderson and J.R. Huff. Merck Research Laboratories, West Point, PA 19486 USA.

To date, numerous inhibitors of the human immunodeficiency virus type 1 (HIV-1) protease have been reported, but few have been studied extensively in humans, primarily as a consequence of poor oral bioavailability in animal models. L-735,524 represents a new class of HIV protease inhibitors, hydroxyaminopentane amides (HAPA), that incorporate a basic amine into the hydroxyethylene inhibitor backbone. L-735,524 is a potent inhibitor of virus replication in cell culture and inhibits the protease-mediated cleavage of the viral precursor polyproteins which results in the production of non-infectious progeny viral particles. The compound is effective against reverse transcriptase (RT) inhibitor-resistant virus and is synergistically active when used in combination with RT inhibitors. In addition, the compound is fully active against previously described viral variants that are resistant to structurally distinct HIV protease inhibitors. All attempts to derive L-735,524-resistant variants in cell culture or to molecularly construct such variants have failed. Most importantly, L-735,524 exhibits good oral bioavailability and plasma pharmacokinetic profiles in laboratory animals when administered in clinically acceptable formulations. The compound is presently being evaluated in humans for safety and oral bioavailability.

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Novel Aminoalcohol Inhibitors of HIV Protease. Design, Synthesis, and Characterization.

J. Barrish, S. Ahmad, M. Alam,† A. Ashfaq, G. Bisacchi, P. Chen, P. Cheng, R. Colonno, T. Dejneka, E. Gordon, J. Greytok, M. Hermsmeier, G. Humphreys, G. Jacobs, P. F. Lin,† K. Lis, M. Marella, Z. Merchant, R. Morrison, T. Mitt, M. Obermeier, J. Pluscec, D. Ryono, M. Skoog, W. Slusarchyk, S. Spergel, J. Stevenson, C. Q. Sun, P. Taunk, J. Tino, G. Vite, B. Warrack, R. White, R. Zahler.

Bristol Myers Squibb Pharmaceutical Research Institute
P.O. Box 4000, Princeton, New Jersey 08543 USA
†5 Research Parkway
Wallingford, Connecticut, 06492, USA

Among the various possible targets for inhibition of HIV replication, the virally encoded protease of the *pol* gene, HIV protease, has attracted considerable attention due to its critical role in the production of mature infectious virus. We have prepared a series of inhibitors of this aspartyl protease which contain a novel transition state mimic. Structure-activity studies have led to the identification of BMS 182,193 as a lead compound for further investigations. Biochemical, virological, and *in vivo* pharmacokinetic evaluation of BMS 182,193 will be presented and a proposed binding mode to the enzyme will be discussed.