27

Systematic SAR Studies of BMS-182,193, A Novel Inhibitor of HIV Protease

G. Bisacchi*, P. Chen*, S. Ahmad, M. Alam,† A. Ashfaq, J. Barrish, P. Cheng, R. Colonno, T. Dejneka, B. DeLange, E. Gordon, J. Greytok, G. Jacobs, M. Hermsmeier, P.-F. Lin,† K. Lis, M. Marella, Z. Merchant, T. Mitt, D. Ryono, M. Skoog, S. Spergel, J. Tino, G. Vite, R. Zahler

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

Following the identification of the lead compound BMS-182,193, a novel aminoalcohol inhibitor of HIV protease, our effort was focused on the improvement of its intrinsic potency and other *in vitro* properties including therapeutic index. The above goals have been achieved by the modification of the P_1' and P_2' side chains of BMS-182,193 through the introduction of various polar groups. In general, substitution at the P_1' side chain of BMS-182,193 resulted in improvements in the therapeutic index as well as in intrinsic potency. Certain modifications at the P_2' side chain lead to significant increases in intrinsic potency which could be explained by the binding mode to HIV protease developed from molecular modeling studies. This poster will disclose our SAR results in those respects.

28

Potent Inhibitors of HIV Protease: P_2 and P_3 Extended Analogs of BMS-182,193

S. Ahmad*, P. Cheng*, M. Alam,† A. Ashfaq, J. Barrish, G. Bisacchi, P. Chen, R. Colonno, T. Dejneka, J. Greytok, M. Hermsmeier, G. Jacobs, P.-F. Lin,† M. Marella, Z. Merchant, T. Mitt, D. Ryono, M. Skoog, S. Spergel, J. Stevenson, C.-Q. Sun, J. Tino, G.Vite, R. Zahler

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

As part of a program to design potent inhibitors of HIV protease, we have synthesized and evaluated a number of analogs of an aminoalcohol-derived lead compound BMS-182,193 (HIV-Pr IC_{50} = 150 nm; HIV-1 ED_{50} = 80 nm). Extension of the core of BMS-182,193 *via* an amide linkage into the S_2 and S_3 binding sites of HIV protease resulted in compounds with up to 50-fold enhancement in potency against the enzyme, as well as substantial improvement in the antiviral activity in cell culture. A proposed binding mode for the various P_2 and P_3 extended analogs based on structure-activity relationships and molecular modeling will be presented.