NLM AIDSLINE

Structure-based design of novel HIV protease inhibitors: sulfonamide-containing 4-hydroxycoumarins and 4-hydroxy-2-pyrones as potent non-peptidic inhibitors.

Thaisrivongs S; Janakiraman MN; Chong KT; Tomich PK; Dolak LA; Turner

October 30, 1996

J Med Chem. 1996 Jun 7;39(12):2400-10. Unique Identifier : AIDSLINE

The low oral bioavailability and rapid biliary excretion of peptide-derived HIV protease inhibitors have limited their utility as potential therapeutic agents. Our broad screening program to discover non-peptidic HIV protease inhibitors previously identified compound I (phenprocoumon, Ki = 1 microM) as a lead template. Structure-based design of potent non-peptidic inhibitors, utilizing crystal structures of HIV protease/inhibitor complexes, provided a rational basis for the previously reported carboxamide-containing 4-hydroxycoumarins and 4-hydroxy-2-pyrones. The amino acid containing compound V (Ki = 4 nM) provided an example of a promising new series of HIV protease inhibitors with significantly improved enzymatic binding affinity. In this report, further structure-activity relationship studies, in which the carboxamide is replaced by a sulfonamide functionality, led to the identification of another series of nonamino acid containing promising inhibitors with significantly enhanced enzyme binding affinity and in vitro antiviral activity. The most active diastereomer of the sulfonamide-containing pyrone XVIII (Ki = 0.5 nM) shows improved antiviral activity (IC50 = 0.6 nM) and represents an example of a new design direction for the discovery of more potent non-peptidic HIV protease inhibitors as potential therapeutic agents for the treatment of HIV infection.

Chromatography, High Pressure Liquid Comparative Study Crystallography, X-Ray Drug Design HIV Protease Inhibitors/*CHEMISTRY/CHEMICAL SYNTHESIS/ PHARMACOLOGY HIV-1/DRUG EFFECTS/*ENZYMOLOGY HIV-2/DRUG EFFECTS/*ENZYMOLOGY Models, Molecular Molecular Structure Phenprocoumon/ANALOGS & DERIVATIVES/CHEMISTRY Pyrones/*CHEMISTRY/CHEMICAL SYNTHESIS/PHARMACOLOGY Stereoisomers Structure-Activity Relationship Sulfonamides/*CHEMISTRY/CHEMICAL SYNTHESIS/PHARMACOLOGY 4-Hydroxycoumarins/*CHEMISTRY/PHARMACOLOGY JOURNAL ARTICLE

See the topic on aegis.org