21

Thiocarboxanilide Derivatives Synergistically Suppress the Breakthrough of Human Immunodeficiency Virus Type 1 (HIV-1) in CEM Cell Cultures When Used in Combination with TSAO Derivatives

J. Balzarini[1], M.-J. Pérez-Pérez[2], S. Velázquez[2], A. San-Félix[2], M.-J. Camarasa[2], E. De Clercq[1] and A. Karlsson[3]

[1]Rega Institute for Medical Research, K.U.Leuven, B-3000 Leuven, Belgium; [2]Instituto de Química Médica, C.S.I.C., 28006 Madrid, Spain; [3]Karolinska Institute, S-171 77 Stockholm, Sweden

The oxathiin carboxanilide derivatives NSC 615985 (UC84) and NSC 629243 (UC38) are potent and selective inhibitors of HIV-1 replication in CEM cell cultures. They are specific for HIV-1 in that they do not inhibit HIV-2 (or other retroviruses). Five structurally related thiophene and furane analogues of the oxathiin carboxanilide derivatives UC10, UC68, UC81, UC42 and UC16 were identified as even more potent inhibitors of HIV-1 and showed 50% effective concentration (EC_{50}) values for HIV-1 replication in the range of 4 to 8 nanogram/ml, and for HIV-1 reverse transcriptase (RT) in the range of 20 to 80 nanogram/ml. Moreover, these compounds were also markedly active against a series of mutant HIV-1 strains, containing the 106 Val → Ala, 138 Glu → Lys or 181 Tyr → Cys mutations in their reverse transcriptase (RT). The thiocarboxanilide derivatives selected for mutations at amino acid positions 100 (Leu → Ile), 101 (Lys → Glu/Ile), 103 (Lys → Asn/Thr) and 141 (Gly → Glu) in the HIV-1 RT. The thiocarboxanilide UC42 completely suppressed HIV-1 replication when used at a concentration of 0.5 μg/ml. If UC42 was combined with TSAO-m^3T, another HIV-1-specific RT inhibitor that lead to different resistance mutations in the HIV-1 RT, virus breakthrough could be synergistically prevented for a much longer time, and at much lower concentrations, than if the compounds were used individually. Virus breakthrough could be suppressed for even longer, and at even lower drug concentrations, if another HIV-1-specific RT inhibitor such as BHAP U-90152 was added to the combination of UC42 with TSAO-m^3T.

22

DMP450, A New Cyclic Urea Inhibitor of HIV Protease With Potent In Vitro Antiviral Activity

D.L. Winslow, C.D. Reid, S. Garber, P. Aldrich, H. Scarnati, E. Anton, M.J. Otto,
The DuPont Merck Pharmaceutical Company, Glenolden, PA, USA

Objective: Previously we reported on the antiviral activity of a new class of non-peptidyl inhibitors of HIV protease referred to as cyclic ureas. Our objective in this study was to identify inhibitors of HIV-1 protease with increased potency and bioavailability as potential candidates for further development.

Method: The antiviral activity of test compounds was determined by yield reduction assays in MT-2, H9 and peripheral blood mononuclear cells. The yield of virus was measured by p24 and by plaque assays and the 90% inhibitory concentrations, IC90s, were calculated from dose response curves.

Results: DMP450, a representative of the cyclic urea class of non-peptidyl inhibitors, was identified as a potent inhibitor of HIV-1 and HIV-2 replication in vitro. The compound was equally effective against laboratory strains of HIV-1 and HIV-2 and against AZT sensitive and resistant clinical isolates of HIV-1 with a mean IC90 against all viruses tested of 0.15 +/- 0.07 uM. Serial passage of a clinical isolate of HIV-1 in culture in the presence of gradually increasing concentrations of DMP450 resulted in the selection of a variant virus containing I84V substitution in protease which demonstrated an approximately 10-fold reduction in susceptibility. DMP 450 was well tolerated by MT-2 and PBM cells in culture with an in vitro therapeutic index of > 500.

Conclusion: DMP450 is a potent inhibitor of HIV replication in vitro with the potential of being significantly better than previously described compounds.