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Inhibition of Wild Type and Mutant HIV Reverse Transcriptases by a New Class of Non-Nucleoside Reverse Transcriptase Inhibitors. H. Zhang[1], L, Vrang[1], K. Backro[2], T. Unge[2], P. Engelhardt[1], M. Hogberg[2], J. Kangasmetsa[1], P. Lind[1], R. Noreen[1], C. Sahlberg[1], X.-X. Zhou[1], N. G. Johansson[1], A. S. Cantrell[3], S. R. Jaskunas[3], J. M. Morin, Jr.[3], R. J. Ternansky[3], F. W. Bell[3], C. L. Jordan[3], M. D. Kinnick[3], J. A. Palkowitz[3], C. A. Parrish[3], P. Pranc[3], R. T. Vasileff[3], S. J. West[3], and B. Oberg[1].
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A new class of non-nucleoside inhibitors of HIV reverse transcriptase (RT) has been recently identified. The prototype compound LY300082 and its analogs have been studied with respect to inhibition of HIV RTs of wild type and with various mutations. The mechanism of inhibition of the wild type enzyme was found to be noncompetitive or uncompetitive with respect to substrate and primer-template. With RT mutants Ile100 and Cys181 the inhibition was mixed with respect to substrate. The relative inhibition of RTIle100 and RT Cys181 differed between this new class of non-nucleoside inhibitors and other non-nucleoside inhibitors, such as 9-Cl-TIBO and L697,661. The results indicate that inhibitors from this new series act at a binding site overlapping with that of 9-Cl-TIBO and L697,661, but that the interactions of these inhibitors with the HIV RTs are not identical.

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Comparative Rates of *In Vitro* Resistance Development of HIV-1 to New Non-Nucleoside Analog RT Inhibitors. L. Vrang[1], C. Rydergard[1], C. Ahgren[1], P. Engelhardt[1], M. Hogberg[1], N. G. Johansson[1], J. Kangasmetsa[1], P. Lind[1], R. Noreen[1], C. Sahlberg[1], X.-X. Zhou[1], A. Karlsson[2], C. Lopez[3], J. M. Morin, Jr.[3], R. J. Ternansky[3], F. W. Bell[3], C. L. Jordan[3], M. D. Kinnick[3], J. A. Palkowitz[3], C. A. Parrish[3], P. Pranc[3], R. T. Vasileff[3], S. J. West[3], and B. Oberg[1].
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One of the aspects to be considered in the selection of antiviral compounds for further evaluation is the development of resistance. This is especially important for a rapidly changing virus such as HIV. We have used a new *in vitro* model to compare the rates of resistance development of compounds in a new series of non-nucleoside RT inhibitors. In this model, HIV-1 is grown in MT-4 cells at stepwise increasing concentrations and the rate of development of resistance to each drug is determined. Resistant HIV-1 mutants are then analyzed for aa-sequence changes in the RT. For LY300082 and related compounds the rates of resistance development were similar, but the time to reach resistance at the highest non-cytotoxic concentrations depended on the efficacy of the compound against the wild type virus. Amino acids acid changes in HIV-RT at several positions, e.g., 100, 103, 181, 230 and 241 were observed in various mutants.