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Conformational Studies on a New Class of Potent Non-Nucleoside Reverse Transcriptase Inhibitors. P. Lind[1], R. Noreen[1], and J. B. Deeter[2].

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The conformational properties of 25 selected members of a new class of non-nucleoside RT inhibitors was studied using MMX-force field methods. A strong correlation was found between the RT inhibitory activity and the preferred conformation. A derivative of LY73497 was found to crystallize in the computed lowest energy conformation. It was found that stability of a conformation close to the lead conformation was a necessary, but not sufficient criterion for potency. As a consequence, many compounds calculated to prefer other conformations could be excluded from the synthetic plans.

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SAR Studies Optimizing HIV-1 Inhibiting Activities of LY73497, A New Series of Non-Nucleoside Inhibitors of Reverse Transcriptase. P. Engelhardt[1], M. Hoberg[1], J. Kangametsa[1], P. Lind[1], R. Noreen[1], C. Sahlberg[1], X.-X. Zhou[1], L. Vrang[1], H. Zhang[1], B. Oberg[1], N. G. Johansson[1], F. W. Bell[2], A. S. Cantrell[2], J. A. Palkowitz[2], S. R. Jaskunas[2], C. L. Jordan[2], M. D. Kinnick[2], J. M. Morin, Jr.[2], C. A. Parrish[2], P. Pranc[2], R. J. Ternansky[2], R. T. Vasileff[2], and S. J. West[2].

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The lead compound in the series, LY73497, inhibits HIV-1 in MT4 cells with an ED_{50} of 0.35 μg/ml. The 50% cytotoxic dose in MT-4 cells is >100 μg/ml. This poster describes the SAR studies combining the optimal substituents from independent variation of the four quadrants of the lead compound (described separately in the previous poster) resulting in even more active compounds. Through an integrated effort involving synthesis and molecular modeling, compounds have been developed with a 50-1000 times increase in potency versus HIV-1 RT when compared to LY73497. In addition, some of these derivatives also inhibit HIV-1 RT with mutations Leu100 to Ile and Tyr188 to Cys at IC_{50s} ranging from 1-10 ng/ml. Furthermore, some derivatives showed activity against HIV-2 RT.