68

Structural and Conformational Studies on a New Class of Non-Nucleoside Reverse Transcriptase Inhibitors. R. F. Abdulla, J. M. Morin, Jr., R. J. Ternansky, M. D. Kinnick, and J. B. Deeter. Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA.

X-ray coordinates of TIBO (A and B isomer), Nevirapine, and representatives of a new class of non-nucleoside HIV reverse transcriptase inhibitor were available in the literature and at the x-ray crystallography laboratory of the Lilly Research Laboratories. Initial calculations were done for the purpose of establishing calibration in the subsequent development of the model and for introducing a level of rigor in the work. After the initial calibration, subsequent molecules were not all treated in this way, especially if x-ray data were available. Molecular modeling, whose details will be shown in the poster, indicated that a preliminary analysis of the fitted molecules of R and S TIBO (TIBOA and B respectively), Nevirapine, and two representatives of the new class of RT inhibitors, based on their x-ray crystal coordinates, resulted in a consistent model relating structural and electronic requirements with HIV-RT inhibitory activity. Additionally, the model shows that there are specific regions of importance in obtaining significant levels of biological activity. These appear to be a hydrophobic region that exists in the area of the TIBOA side chain. The steric requirements of this region at this state of the model should be considered as spanning a region of space 7A across, 4A deep and 6A high approximately and located above the polar region of the pharmacophore. Considerable flexibility of lipophilic substituents appears to be tolerated in this region within the constraints of the above dimensions. A third region of significance appears to be the heterocyclic ring (absent in TIBO, but present in the new compounds), its substituents and the nature of whether or not the heterocycle is pi-excess or pi-deficient in nature.

69

Conformationally Restricted Analogs of a New Class of Potent Non-Nucleoside Reverse Transcriptase Inhibitors. R. Noreen[1], P. Engelhardt[1], J. Kangametsa[1], C. Sahlberg[1], L. Vrang[1], J. M. Morin, Jr.[2], R. J. Ternansky[2], and H. Zhang[1].

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LY73497 is a lead compound for a new class of non-nucleoside HIV-1 RT inhibitors, with a high degree of rotational freedom. To obtain more information on conformational parameters important for potency, several conformationally restricted analogs of LY73497 have been synthesized and studied. The design was aided by molecular modeling using the MMX force field. A strong correlation between *in vitro* potency and calculated 3D-geometry was found. This approach resulted in a number of potent compounds inhibiting HIV-1 RT in the subnanomolar range.