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Successful Combination Therapy in a Novel Animal Model of Concomitant Retroviral/Lethal Opportunistic Fungal Infection by John W. Blasecki and Nanci M. Mayer-Mikalski, Du Pont Merck Pharmaceutical Company, Glenolden, PA 19036 and Wilmington, DE 19880, USA

HIV-induced depletion of CD-4-positive T-lymphocytes leads to concomitant opportunistic infections (OI's) in AIDs patients. These underlying OI's are the ultimate cause of death in this patient population. Successful treatment of AIDS, therefore, depends strongly upon effective combination therapy with anti-retroviral agents and other anti-infectives targeted toward control of the concomitant OI's. Lack of valid models, in which animals exhibit mixed pathogenesis induced by concomitant inoculation of multiple infectious agents, has significantly hampered assessment of the potential clinical utility of such combination treatment regimens in vivo. To this end, we have developed what may be the first small animal model of concomitant retroviral/lethal opportunistic fungal infection validated for use with combination chemotherapeutic agents. Mice singly infected with Friend leukemia virus (FLV), a murine retrovirus which induces viremia, splenomegaly and immunosuppression, were successfully treated with DUP 925, a polyoxoanion active against retro- and lentiviruses, or with Zidovudine. Mice singly infected with Candida albicans, at levels which induced fatal renal dysfunction in 90 percent of the recipients, were successfully treated with the alpha-styrylcarbinol antifungal agent, DUP 860. Mixed pathogenesis in mice concomitantly inoculated with both infectious agents was successfully treated with combinations of these anti-retroviral and anti-fungal agents. Details of treatment regimens and correlations between efficacy and levels of infectious agents in various treatment groups will be presented.

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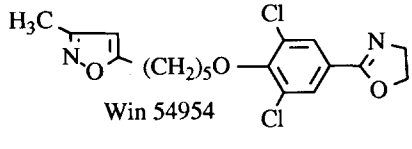
The Synthesis and Antipicornaviral Activity of Tetrazole Analogues of Win 54954. G.D. Diana, D.M. Volkots, D. Cutcliffe, R.C. Oglesby, T.R. Bailey, J.P. Mallamo, T.J. Nitz and D.C. Pevear. Sterling-Winthrop Pharmaceutical Research Division, Rensselaer, New York 12144, USA

The acid lability of the oxazoline ring of Win 54954, a broad spectrum antipicornaviral agent has lead to the evaluation of several heterocyclic replacements. This effort has resulted in the discovery that the 2-methyl tetrazole analogues exhibit comparable activity to the oxazolines and are acid stable. A structure activity evaluation has been performed on this series of compounds. Several of these compounds have demonstrated potent activity against both rhino- and enteroviruses. X-ray studies have been performed on one member of this series bound to human rhinovirus-14 which show the position of the compound in the binding site on the viral capsid. The hydrophobic interaction of the side chain of this analogue with several residues within the compound binding site may enhance the binding energy and account for the potency of this compound.



Win 54954