Oral Session IV

Respiratory Virus Infections

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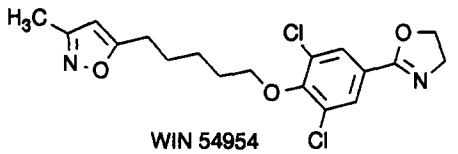
A Comparison of the Compound Binding Sites on Human Rhinovirus-14 and -1a; Examination of rigid analogues of Win 54954. G.D. Diana, J.P. Mallamo, D.C. Pevear and F.J. Dutko, Department of Medicinal Chemistry and Virology, Sterling Winthrop Pharmaceutical Research Division, Rensselaer, N.Y. 12144 USA

The binding sites in human rhinovirus type 14 and 1a for compounds related to disoxaril such as win 54954 have been shown by x-ray crystallography to consist of a hydrophobic pocket on the surface of the capsid protein. A comparison of the 3-dimensional structure of these serotypes, determined by Michael Rossmann, shows that the HRV-1A pocket is shorter and wider than that of HRV-14 which indicates that the relative sensitivity of these serotypes to analogues of disoxaril would be dependent upon the size of the molecule. It has been assumed that the flexibility of the hydrocarbon chain is critical for broad spectrum activity since through compression of the chain, the molecules could adapt to a variety of binding sites. To test this hypothesis, several analogues of win 54954 with rigidity incorporated into the chain have been evaluated against HRV-14 and -1A and the structures modeled in the respective binding sites. The differences in the sensitivity of these serotypes could be explained by examining interactions within the binding site.



WIN 54954