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Studies on the Mode of Action of R 61837, an Antirhinovirus Compound.

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R 61837, or 3-methoxy-6-[4-(3-methylphenyl)-1-piperazinyl] pyridazine, is able to stabilize rhinoviruses by direct interaction with their capsid proteins. We studied the effect of this virus-drug interaction on early events in the entry process of rhinoviruses, using a variety of techniques. Experiments with HRV 1A and HRV 9, rendered light sensitive by growth in the presence of acridine orange, indicate that the compound indeed interferes with an early event in the viral replication. No effect on either viral RNA synthesis or viral protein synthesis was observed. The effect on the adsorption of HRV 1A and HRV 9 was studied using [35S]-labeled virus and infectious center assays. The absence of an effect on the adsorption of HRV 1A, despite the inhibition of an early event in the experiments using light-sensitive virus, suggests an effect on the uncoating event of HRV 1A . R 61837 inhibited the adsorption of HRV9, but an additional effect of R 61837 on the uncoating of HRV9 could not be excluded. Studies including more serotypes confirmed that the mode of action is serotype-specific . On the other hand, the mode of action does not appear to be related to receptor groups or antiviral groups.

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Isolation and Preliminary Characterisation of Chalcone Ro 09-0410 Resistant Human Rhinovirus Type 2.

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We have isolated a human rhinovirus type 2 (HRV-2) mutant that was resistant to the antiviral agent chalcone Ro 09-0410 (4'-ethoxy-2'-hydroxy-4 6'-dimethoxy-chalcone). This Ro 09-0410-resistant HRV-2 mutant (SR2-0410) exhibited altered biological properties when compared with the parental wild-type HRV-2. Thus, it was unstable when exposed to acid and heat in the presence of the drug, was incapable of producing plaques and produced early cytopathic effect (CPE) at high (37°C) temperature. Furthermore, compared with the parental wild-type, it showed reduced ability to be neutralized by an anti-HRV-2 polyclonal serum and monoclonal antibodies. This SR2-0410 mutant demonstrated cross-resistance to other synthetic antirhinovirus compounds which are also thought to bind to the viral capsid protein. Furth ermore, it was also resistant to various antiviral combinations synergistic against HRV-2. However, it was still sensitive to enviroxime [2-amino-1-(isopropyl sulphonyl)-6- benzimidazole phenyl ketone oxime] which has a different mode of action and interferes with viral RNA synthesis.