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Synthesis and in vitro antirhinoviral activity of broad spectrum 6-substituted-3-amino-pyridazines.

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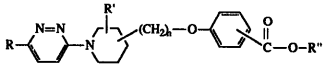
The discovery of two groups of rhinoviruses exhibiting differential susceptibility to pyridazinamines and WIN 51711 prompted us to synthesize a series of new compounds containing substructures of both chemical families.



A large series of 6-substituted-3-amino-pyridazines were prepared, some of which displayed a pronounced activity in vitro against both groups of rhinoviruses. Substituent- and chain length variations were investigated for their effect on the biological activity. The position of the ester function and the length of the spacer proved to be highly important for activity. The synthesis of these compounds and a structure-activity relationship will be presented. Based on these results R 77975 (ethyl 4-[2-[1-(6-methyl-3-pyridazinyl)-4-piperidinyl] ethoxy] benzoate) was shown to be the most promising compound and has been selected for further investigation.

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SCH 38057: A NEW MOLECULE WITH BROAD SPECTRUM INHIBITORY ACTIVITY AGAINST PICORNAVIRUSES

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The activity of a new molecule, SCH 38057 (1-[6-(2-chloro-4-methoxyphenoxy)hexyl] imidazole hydrochloride), against picornaviruses is described. In neutralization tests and tests determining inhibition of viral RNA synthesis, SCH 38057 exhibits broad activity against several enteroviruses and rhinovirus strains with IC_{50} values in the 3 to 35 µM range. The MIC for coxsackievirus B3 (CVB3) is 0.3 µM. Analysis of the effect of SCH 38057 on cellular processes indicates that the inhibitory activity of SCH 38057 is virus-specific and not due to cytotoxic effects. Studies using ^{3}H-SCH 38057 demonstrate that the molecule binds irreversibly to purified CVB3 in a ratio of 40 molecules : 1 virus particle. Binding of ^{3}H-SCH 38057 is competitively inhibited with nonradiolabelled SCH 38057. However, WIN 51711, a molecule that interacts with the capsid of picornaviruses (Smith et al., Science 233: 1286-1293), does not competitively inhibit binding of SCH 38057 to the virus capsid. A possible interpretation of this finding is that SCH 38057 binds to the virus capsid at a site different than that of WIN 51711. Experiments to determine the antiviral mechanism of SCH 38057 demonstrate that the molecule does not inhibit attachment of coxsackie- or polio- viruses to HeLa cells. Sucrose sedimentation of cellular lysates containing CVB3 treated with SCH 38057 establishes that the molecule does not inhibit uncoating of the virus. SCH 38057 also failed to stabilize CVB3 against thermal inactivation (47°, 40 min.). Addition of SCH 38057 to cells infected with CVB3 at different times after infection and analysis of the inhibitory effect on viral RNA synthesis indicates that the molecule exerts its antiviral effect at the stage of replication of the viral RNA. This was confirmed by showing that biochemically isolated viral replicase complexes treated with SCH 38057 fail to replicate viral RNA. Thus, although SCH 38057 interacts with the capsid of CVB3, no inhibitory effect could be directly attributed to this interaction. Instead, the major inhibitory site for SCH 38057 is the viral replicase complex.