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ANTIVIRAL ACTIVITY OF SYNTHETIC 3-METHOXYFLAVONES

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3-Methoxyflavones were found to be responsible for the pronounced and specific antiviral activity of several medicinal plant extracts against picornaviruses. Preliminary SAR studies of naturally occurring 3-methoxyflavones showed the 3-methoxy- and 4'-hydroxygroups to be essential for the antiviral activity. Therefore, a series of 4'-hydroxy-3-methoxyflavones, of which the A-ring was substituted with one or two electron-withdrawing functions such as halogens and nitrogroups or electron-releasing groups such as alkyl, hydroxy, methoxy and aminofunctions were prepared.
The antiviral activity was determined by means of the endpoint titration technique (EPTT) in liquid medium using VERO-cells. The results showed that none of the synthetized compounds had a better therapeutic ratio than the naturally occurring 3-methoxyflavones, viz. 3-methylquercetin (3-MQ) and 3,3',7-trimethylquercetin (3,3',7-TMQ). Polysubstitution of the latter compounds, however, with methoxyfunctions in the 6,7 and 8 positions and a hydroxygroup at the 5-position, giving a 5,6,7,8-substitution pattern of the A-ring markedly decreased cytotoxicity without affecting much antiviral potency, which resulted in more selective antipoliovirus 3-methoxyflavones.

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Selective Inhibition of HIV-1 Envelope Glycoprotein-Induced Syncytium Formation. R. J. Owens and R. W. Compans, University of Alabama at Birmingham, Birmingham, AL USA.

The human immunodeficiency virus (HIV-1) envelope glycoprotein is essential for virus entry and the formation of multinucleated giant cells by cell fusion, the major virus-induced cytopathic effect. To study the effects of potential fusion inhibitors, a recombinant vaccinia virus expressing the envelope glycoprotein was generated and used to infect a HeLa cell line (HeLa $T4^+$) which constitutively expresses the CD4 receptor molecule. Syncytium induction was observed as early as 4 hours post-infection and continued until the entire monolayer was fused. Several fusion glycoproteins of enveloped viruses are activated by a proteolytic cleavage event which produces a new N-terminal stretch of hydrophobic amino acids that is thought to mediate fusion of the viral envelope with a cellular membrane; such a sequence is present at the N-terminus of the gp41 subunit of the HIV-1 envelope protein. Peptides which were homologous to this hydrophobic terminal domain of the F_1 protein of paramyxoviruses were reported to inhibit virus-induced cell fusion. Therefore, we synthesized a series of oligopeptides based on the deduced amino acid sequence of gp41 and determined their ability to inhibit HIV-1 -induced cell fusion in HeLa $T4^+$ cells. One hexapeptide was found to almost completely prevent virus-induced cell fusion. In contrast, a peptide which differed by a single amino acid insertion showed almost no inhibitory effect. These results indicate that oligopeptides which are related to the fusion peptide of HIV inhibit virus-induced cytopathology, and should be evaluated further as potential antiviral agents.