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Oxathiin Carboxanilide, A Novel Potent Inhibitor of HIV Reproduction. J.P. Bader, J.B. McMahon, R.J. Schultz, V.L. Narayanan, M.R. Boyd; Developmental Therapeutics Program, DCT, NCI, Bethesda, Maryland 20852, USA; O.S. Weislow, Program Resources Inc., FCRF, Frederick, Maryland 21701, USA; J.B Pierce, Uniroyal Chemical Co., Middlebury, Connecticut, USA; W.A. Harrison, Uniroyal Chemical Ltd, Guelph, Ontario, Canada.

Oxathiin Carboxanilide (NSC 615985) was highly active in preventing HIV-induced cytopathicity as detected in the AIDS antiviral screening program of the National Cancer Institute. The compound also inhibited virus reproduction; infectious virus, extracellular viral p24 antigen, and extracellular viral reverse transcriptase were reduced at concentrations (0.5 µM) of NSC 615985 far below those which produced cytotoxicity (>100 µM). NSC 615985 had no direct effect on virions of HIV, or on the enzymatic activities of HIV reverse transcriptase or HIV protease. The point of action of NSC 615985 within the virus reproductive cycle was different from that of active nucleosides (e.g., azidothymidine or dideoxycytidine); limited treatment of newly infected cells with NSC 615985 had little effect on the progress of infection, while late addition and continued treatment effectively prevented virus-induced effects. The compound, benzoic acid, 2-chloro-5-[5,6-dihydro-2-2-methyl-1,4-oxathiin-3-yl) carbonyl] amino-isopropyl ester, was originally synthesized as a potential fungicide. A large number of structural analogs have been tested and structure-activity relationships will be discussed.

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF 3-(DIALKYLAMINO) ISOXAZOLES

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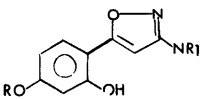

I

R = H, CH3, C2H5, COCH3

R1 = NEt2, NMet2, N

3-(dialkylamino)isoxazoles (I) were synthesized treating 2-(dialkylamino)-7-alkoxy-chromones with hydroxylamine- HCl in refluxing ethanol in the presence of pyridine for 24 hours. The yields ranged from 65 to 75%. While ineffective on DNA viruses, most compounds selectively inhibited in vitro the multiplication of RNA viruses. None of the title compounds, however, inhibited HIV-1 replication.