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Inhibitory Activity of Lipophilic 2',3'-Dideoxynucleoside Derivatives Against HIV.

M.D. Winther., H. Nakashima., N. Yamamoto and *E de Clercq. Scotia Pharmaceuticals Ltd, Guildford, UK and *Rega Institute for Medical Research, Katholieke Universiteit, Leuven, Belgium.

There are a wide range of nucleoside analogues active against HIV but whilst they may be very potent against HIV in vitro they are often less effective in clinical use. In particular nucleoside analogues tend to be poorly absorbed when given orally and are often rapidly eliminated from the body. We decided to produce lipophilic compounds of known antiviral compounds by the covalent attachment of fatty acid molecules. Fatty acid nucleoside derivatives are highly lipophilic (partition coefficient in hexane:water of greater than 10^3) and in many cases retain the antiviral activity of the parent nucleoside. This will alter the metabolism and distribution of such compounds in the body and the altered pharmacokinetics could be of therapeutic benefit. The fatty acid derivative of ddC, with linoleic acid linked through an amide bond to the 4 position of the cytosine ring had an increased activity in the MT-4 cell CPE assay when compared to ddC. The EC_{50} of ddC was determined to be 0.66μM and for the fatty acid derivative 0.08μM. In another series of experiments linoleic acid joined through a 5'ester linkage produced a derivative of AZT with equal potency but reduced cytotoxicity compared to AZT. This gave the derivative an increase in the selectivity index from 4,100 to 26,000 when tested against HIV1 and from 2,900 to 8,000 when tested against HIV2.

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Elucidation of a Polyphenolic Polymer with Antiviral Activity against Myxo- and Paramyxoviruses.

P.R. Wyde, L.R. Meyerson[1], M.W. Ambrose, J.B. Pfeifer, T.G. Voss and B.E. Gilbert. Baylor Col. Med., Houston, TX & Shaman Pharm.[1], San Carlos, CA, (USA)

Testing plant extracts in an antiviral screening program has elucidated a 3200 dalton polyphenolic polymer, SP303, which has antiviral activity in vitro against parainfluenza viruses type 1 (PI1) and 3 (PI3), respiratory syncytial virus (RSV), and both influenza A and B viruses. No significant antiviral activity was noted in vitro against adenovirus type 5 or rhinovirus type 13. The mean median toxic dose (ID_{50}), efficacious dose (ED_{50}) and selective index (S.I.; mean 3-11 replicate experiments) obtained for SP303 against the myxo- and paramyxoviruses in vitro were as follows:

Virus	Tissue	ID_{50} (ug/ml)	ED_{50} (ug/ml)	S.I.
PI3	HEp2	252	79	13
PI1	LLC	354	3	128
RSV	HEp2	299	14	35
Influenza A	MDCK	264	7	83
Influenza B	MDCK	277	14	46

SP303 also exhibited antiviral activity in cotton rats; the median efficacious dose ($CRED_{50}$) obtained for SP303 against both RSV and PI3 was 3 mg/kg/day when given i.p., and 10 mg/kg/day when given orally. Acute and subchronic toxicity testing in mice, rats and dogs indicated a safety multiple 50-100X the expected efficacious dose.