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Glycosyl phosphotriesters of 5-FdU : synthesis, transmembrane transport and antiviral activity.

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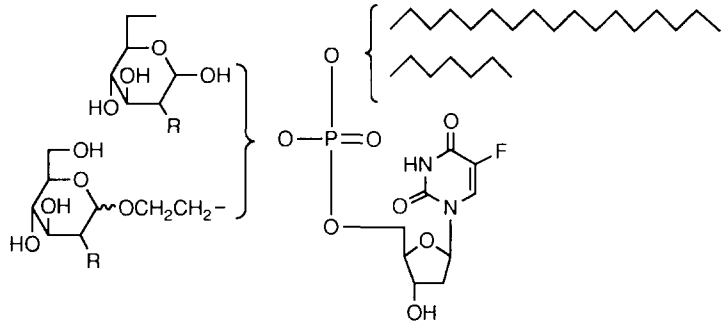
A series of alkyl glycosyl phosphate derivatives of 5-fluoro-2'-deoxy-uridine was prepared as lipophilic prodrugs. The influence of the hydrophobic chain in the transmembrane transport inside large unilamellar vesicles was investigated by NMR spectroscopy (^1H, ^{31}P). These compounds were evaluated for their inhibitory effect on herpes virus eidolon : a significant activity was shown with in vitro screening, implying a metabolization of the phosphotriester bond in biological milieu. The most promising derivative of the series, hexadecyl 2-(2-deoxy-D-glucopyranosidyl)ethyl 5-fluoro-2'-deoxy-5' uridinyl phosphate was selected for in vivo test and it presented a more potent activity than acyclovir or 5-FdU on mice.



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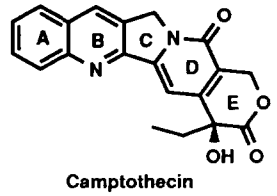
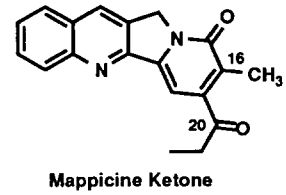
Novel Non-nucleoside Inhibitors of Herpes Viruses: Antiviral Activity, Structure-activity Relationships, and Pharmacokinetics of Mappicine Ketone and its Derivatives. R. Hertzberg, D. Berges, G. Gallagher, J. Taggart, R. Johnson, G. Hofmann, M. Mattern, S. Petteway, S. Barney, R. Wittrock, A. Breen, F. McCabe, D. Lambert, and W. Kingsbury, SmithKline Beecham Pharmaceuticals, Research and Development, King of Prussia, PA, USA, 19406.

Mappicine ketone is a novel and selective inhibitor of HSV-1, HSV-2, human cytomegalovirus, and varicella zoster virus replication. This compound is derived from the mammalian topoisomerase I inhibitor camptothecin but lacks the critical E-ring lactone. As a result, mappicine ketone has no activity against the mammalian enzyme. Compounds of this class have broad-spectrum activity against herpes viruses but are not active against other DNA or RNA viruses. In HSV-infected cells, mappicine ketone produces lesions selectively in viral DNA; no damage to cellular DNA occurs. The structural features of mappicine derivatives required for antiviral activity include a carbonyl or hydroxyl group at position 20 and a methyl group at position 16. With a few exceptions, substitution of the A and B-rings generally affords compounds with reduced antiviral activity . The pharmacokinetic properties of several analogs of this class were evaluated in mice. The relationship between chemical structure and pharmacokinetic profile will be presented.



Camptothecin



Mappicine Ketone