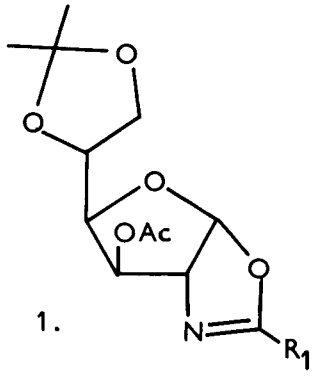
THE DEVELOPMENT OF NOVEL CARBOHYDRATE UPTAKE INHIBITORS FOR THE TREATMENT OF ONCHOCERCIASIS (RIVER BLINDNESS)

E J Gray, J W Powell, P S Raines and R A Watt, Pharmaceutical Chemistry Department, The School of Pharmacy, Brunswick Square, London WC1N 1AX.

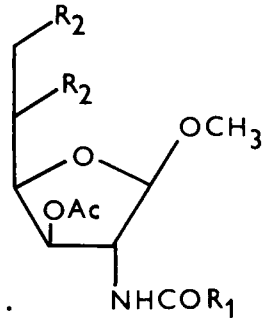
Onchocerciasis (River Blindness), a tropical disease caused by infection with the filarial nematode Onchocerca volvulus is currently estimated to affect some 20-40 million people and represents a major cause of blindness (Edwards 1984). Drug treatment is traditionally with Diethylcarbamazine (DEC), a microfilaricide, and Suramin, a macrofilaricide, both of which are far from ideal in terms of toxicity and ease of treatment. The recently introduced microfilaricide Ivermectin has proved to be effective but is not recommended for use in certain patient groups including children and there remains a need for an effective macrofilaricide (Hay et al 1989).

As part of a continuing programme to develop new macrofilaricides, the uptake and primary carbohydrate metabolism of glucose has been studied in Onchocerca and a series of related model filarial worms including Brugia pahangi and Dipetalonema vitae. The methods have included use of ^{13}C-Nuclear magnetic resonance spectroscopy to monitor the rate and routes of metabolism of labelled glucose non-destructively in intact filariae in vitro. A number of differences between parasite and mammalian host metabolism have been identified revealing the potential for selective drug design. (Watt et al 1987) Parasite selective effects of two competitive carbohydrate uptake inhibitors, 2-Deoxy-D-glucose (k_i = 0.2 mM) and 5-thio-D-glucose (k_i = 0.135 mM) on glucose uptake have been quantified.

From this data, a number of synthetic targets have been identified as potentially efficient inhibitors of glucose uptake. One novel route to one of the primary targets, 2-deoxy-5-thio-D-glucose, commenced with the cheap, readily available monosaccharide, D-glucosamine. A series of substituted 1,2-oxazoline derivatives (1), (R_1 = CH_3,$CH(CH_3)_2$,$C(CH_3)_3$, Ph etc) has been prepared, partly to assess the relative acid stability of these functions. In these intermediates the carbohydrate is "locked" in the furanose ring form, a configuration essential to free C5 for substitution. These intermediates or their related ß-methyl glycosides can then be converted to the 5,6-dihydroxy (2), (R_2 = OH) and 5,6-dihalo derivatives (2), (R_2 = Cl). Selective halogen displacement with thioacetate has much shortened conventional approaches to thio sugar synthesis. (Guthrie et al 1981)



1.



2.

Edwards, G. (1984) TIPS, 5; 192-195
Hay, J. and Burr, A. (1989) Pharm. J., 243; 296-298
Watt, R.A. et al (1987) Mol. Biochem.Parasitol, 24; 125-130
Guthrie, R.D and O'Shea, K. (1981) Aust. J. Chem. 34; 2225-30