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FURTHER STUDIES ON THE CHEMOPROPHYLACTIC ACTIVITY OF PYRAZINOQUINOLINES IN EXPERIMENTAL SCHISTOSOMIASIS MANSONI

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SUMMARY

Eight pyrazinoquinolines synthesized at Pfizer Laboratories were tested as chemoprophylactic agents in mice experimentally infected with *Schistosoma mansoni*. All compounds were administered *per os* as a single dose. Animals were treated 3 hours after the intraperitoneal injection of 250 *S. mansoni* cercariae. Eight days later the mice were sacrificed for peritoneal washings and larval counts. There was a reduction in the number of living schistosomula, statistically significant at the level of $p < 0.01$, with all compounds. It was stressed the importance of pyrazinoquinolines as well as tetrahydroquinolines in the chemoprophylaxis of schistosomiasis.

INTRODUCTION

The activity of pyrazinoquinolines on early developing forms of *Schistosoma mansoni* has been recently reported (PELLEGRINO et al. [6]). Compounds U.K. 4210 and U.K. 5076 destroyed all larvae in the peritoneum of mice, while U.K. 5444 nearly killed all parasites. These data led us to ask to Pfizer Laboratories for other related compounds whose prophylactic activity is now reported.

MATERIAL AND METHODS

Infection of mice — Cercariae of *S. mansoni* (L.E. strain, Belo Horizonte) were shed by laboratory-reared and infected *Biomphalaria glabrata* and concentrated in sintered-glass crucibles (PELLEGRINO & MACEDO [5]). Aliquots containing about 250 cercariae in 1 ml were injected intraperitoneally in adult albino mice as described elsewhere (PEREIRA et al. [7]).

Drugs and treatment of animals — The chemical structure of the 8 pyrazinoquinolines used in this study are shown in Table I. All compounds were administered orally, as a single dose corresponding to 5 times that necessary to shift 50 to 90% of adult schistosomes toward the liver in mice experimentally infected. Drugs were administered 3 hours after the intraperitoneal injection of cercariae. The synthesis of these compounds was performed in England (Sandwich, Kent), at Pfizer Laboratories.

Assessment of activity — Animals were killed by cervical fracture 8 days after treatment for peritoneal washings and larval counts (PEREIRA et al. [7]).

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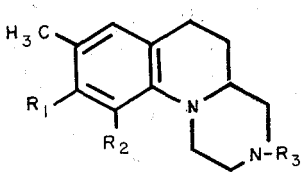
TABLE I

Chemical structure of pyrazinoquinolines



Compounds	R_1	R_2	R_3
U.K. 5066	Cl	H	H
U.K. 5378	NO_2	H	$-CH_2-CH=CH_2$
U.K. 5574	Cl	CH_3	$-CH(CH_3)_2$
U.K. 5585-11 (*)	Cl	CH_3	$-CH_2-CH_2=CH_3$
U.K. 5704	Cl	CH_3	$-CH_2-CH=CH_2$
U.K. 5778/11 (*)	Cl	CH_3	$-CH_2-CH_2OH$
U.K. 5876 (*)	Cl	CH_3	$-CH_2-CH_3$
U.K. 5925	Cl	CH_3	$-C(=O)-CH-CH-COOH$

(*) Maleate salt

TABLE II

Chemoprophylactic activity of pyrazinoquinolines assessed according to Pereira's method (schistosomula developed in the peritoneal cavity of mice)

Compounds	Dose mg/kg p.o.xl	Schistosomula in the peritoneal cavity	
		Number of living larvae per animal	Mean number of living larvae (control = 100)
U.K. 5066	125	2-0-2-4-2-0-0-0-0-2	1.5
U.K. 5378	250	0-0-0-81-10-7-49-4-3-39	23.9
U.K. 5574	250	0-0-0-3-0-0-0-0-0	0.4
U.K. 5585/11	250	0-0-0-1-0-0-0-0-0-0	0.1
U.K. 5704	62.5	42-22-39-25-8-13-25-17-27	29.9
U.K. 5778/11	250	0-0-0-0-0-0-0-0	0.0
U.K. 5876	62.5	6-6-7-30-18-22-41-19-33	25.0
U.K. 5925	250	0-0-0-0-0-0-0	0.0
Control	—	101-93-90-71-89-74-50-81-75-85	100.0

RESULTS AND COMMENTS

The results obtained are summarized in Table II. As can be seen, compounds U.K. 5778/11 and U.K. 5925 killed all larvae. The mean number of living schistosomula was reduced near to zero after treatment with U.K. 5066, U.K. 5574, and U.K. 5585/11. The reductions observed with U.K. 5378, U.K. 5704 and U.K. 5876, although less evident, were statistically significant at the level of $p < 0.01$. It is interesting to remark that 2 out of these 3 drugs (U.K.

PELLEGRINO, J.; MELLO, R. T. & PEREIRA, L. H. — Further studies on the chemoprophylactic activity of pyrazinoquinolines in experimental schistosomiasis mansoni. *Rev. Inst. Med. trop. São Paulo* **18**:149-151, 1976.

5704 and U.K. 5876) were administered at the lowest dose level (62.5 mg/kg).

In the last years numerous publications referred to the prophylactic activity of tetrahydroquinolines, especially U.K. 3883 and U.K. 4271 (oxamniquine) (CHEETHAM & MESMER [1]; FOSTER et al. [3]; PELLEGRINO & KATZ [4]; FOSTER [2]). It is interesting to mention that this property is also shared by pyrazinoquinolines (PELLEGRINO et al. [6]). The obtention of slow-release-derivatives is worthy to be pursued considering the public health importance of the chemoprophylaxis of schistosomiasis.

RESUMO

Estudos complementares sobre a atividade quimioprofilática de pirazinoquinolinas na esquistossomose mansônica

Oito pirazinoquinolinas, sintetizadas nos Laboratórios da Pfizer em Sandwich, Inglaterra, foram administradas em camundongos para testar sua atividade quimioprofilática na esquistossomose mansônica. Todos os compostos foram administrados por via oral, em dose única. Os animais foram tratados 3 horas após a infecção intraperitoneal com 250 cercárias de *S. mansoni*. Oito dias mais tarde, os camundongos foram sacrificados para coleta e contagem das larvas no peritôneo. Houve uma redução na média dos esquistossômulos, estatisticamente significativa ao nível de $p < 0,01$, com todos os compostos. Foi demonstrada a importância das pirazinoquinolinas assim como das tetrahidroquinolinas, na quimioprofilaxia da esquistossomose.

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