RESEARCH NOTE

Efficacy of a New Schistosomicidal Agent 2-[(methylpropyl)amino]-1-octanethiosulfuric Acid against an Oxamniquine Resistant *Schistosoma mansoni* Isolate

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The schistosomicidal activity of one alkylaminoalkanethiosulfuric acid was studied against a recently described oxamniquine resistant strain of *Schistosoma mansoni*. This drug exhibited an activity against the resistant strain (R_1) similar to that shown against non-resistant, standard LE strain.

PMZ Coelho et al. (1997 *Rev Inst Med Trop S Paulo 39*: 101-106) have recently described a natural strain of *S. mansoni* partially resistant to oxamniquine (Mansil, Pfizer) one of the drugs of choice in the treatment of schistosomiasis. When given to infected mice, a 250 mg/kg dose of oxamniquine killed all the worms of the LE strain (standard) known to be susceptible to oxamniquine at this treatment schedule, but some worms of the resistant strain, designed as R_1, were recovered from mice treated with the same dose. The resistance was more evident when the dose of 200 mg/kg was used, since the recoveries of male and female worms of the LE strain were 1.1% and 20.6% and for the R_1 strain, 18.6% and 61.1%, respectively. The dose of 500 mg/kg of praziquantel (Cestox, Merck), also an important drug for the treatment of schistosomiasis, was equally efficient in mice against both these *S. mansoni* strains when administered orally (R Gönnert & P Andrews 1977 *Ztschr f Parasitenk 52*: 129-150).

The schistosomicidal activity of alkylaminoalkanethiosulfuric acids was first described by DL Nelson and J Pellegrino (1976 *Rev Inst Med Trop S Paulo 18:* 365-370). Since then, the efficacy of newly synthesized compounds of this group has been studied in order to determine their utility as a cheaper, alternative schistosomicidal drug (WY Liu 1981 *Síntese de Ácidos N-alquilamino-alcanotiossulfúricos Potencialmentes Ativos contra* Schistosoma mansoni, MSc Thesis, Universidade Federal de Minas Gerais, Belo Horizonte xii+179 pp., MG Cardoso 1988 *Síntese de ácidos alquilamino-heptanotiossulfúricos e di-(N-alquilamino) propanotiossulfúricos potencial-mente ativos contra* Schistosoma mansoni, MSc Thesis, Universidade Federal de Minas Gerais, Belo Horizonte xiv+126 pp., MLO Penido et al. 1990 *J Braz Chem Soc 1:* 35-39).

One of these compounds, 2-[(methylpropyl)amino]-1-octanethiosulfuric acid, obtained by Penido et al. (1990 *loc. cit.*) (I, Fig.), has proved to be effective against *S. mansoni* in mice at a dose range of 600 to 800 mg/kg, with a preferential activity against the female worms, that have been eliminated from infected mice at a level of 90 to 95%, whereas the males were reduced to 50-60% (MLO Penido et al. 1994 *Mem Inst oswaldo Cruz 89:* 595-602). MLO Penido et al. (1995 *Parasitology 111:* 177-185) also showed that this compound is taken up by the worm and metabolized into a hydrophobic substance identified as the disulphide derivative of the parent compound.

As much as the living standards of the susceptible human populations have improved, chemotherapy is still important for the control of schistosomiasis (N Katz 1998 *Mem Inst Oswaldo Cruz 93:* 33-35). However, the increased use of the two main schistosomicidal drugs by larger populations could result in the appearance of resistant strains of *S. mansoni* (FF Stelma et al. 1995 *Am J Trop Med Hyg 53:* 167-170, PG Fallon et al. 1995 *Am J Trop Med Hyg 53:* 61-62, Coelho et al. *loc. cit.*). The discovery of new, effective compounds should be encour-

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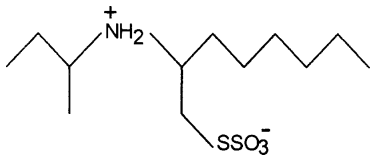

Structure of the 2-[(methylpropyl)amino]-1-octanothiosulfuric acid (I)

aged as alternatives for the control of the disease, specially cheaper, effective compounds which could be used in chemotherapy control programs (S Archer et al. 1990 *Mol Biochem Parasitol 43:* 89-96, Katz *loc. cit.*).

The present work was designed to study the efficacy of the new schistosomicidal agent 2-[(methylpropyl)amino]-1-octanothiosulfuric acid (I) against the R_1 oxamniquine resistant *S. mansoni* strain described by Coelho et al. (*loc. cit.*). In a comparative study of the efficacy of (I), the LE oxamniquine-susceptible strain of *S. mansoni* which has been maintained in the Schistosomiasis Research Unit, UFMG, Brazil for more than 30 years, and is considered as a standard in drug trial experiments, and the R_1 strain, isolated from faecal material obtained from a patient (Coelho et al. *loc. cit.*) and maintained at the same Schistosomiasis Research Unit, were used. Two groups of 30 albino (defined breed) Swiss mice were infected with LE and R_1 cercariae. On day 60 of infection, 15 mice of each group were treated *per os* with 700 mg/kg of (I) as a suspension in 1% cremophor El (an emulsifying agent used as vehicle - Sigma). The two remaining groups were maintained as controls and were treated only with the vehicle. The mice were sacrificed 30 days after treatment for worm recovery as described by J Pellegrino and AF Siqueira (1956 *Rev Bras Malariol 3:* 589-597). Data obtained were evaluated using the Kruskal-Wallis non parametric method.

The results of worm burden recovery from each group are shown in the Tables I and II. Table III shows the percentage reductions in the mean number of female, male and total worm burdens for both strains, LE and R_1.

The reduction observed in the number of female worms of the LE (93%) and R_1 (88%) strains, as compared with their respective control groups was similar to those observed in previous experiments (Penido et al. 1994 *loc. cit.*). Table III shows that the percentage reduction of female worms was the same for both strains. A slightly statistical significant difference (P = 0.05) can be noted between the percentage reductions for males, indicating that compound (I) may be more active against oxamniquine resistant R_1 strain (25%) than LE oxamniquine sensitive LE strain (15%). The small reduction in the male worm burdens was an

TABLE I

Number of male (m) and female (f) worms recovered from mice infected with the LE strain of *Schistosoma mansoni*. The two groups are control and treated with 700 mg/kg of 2-[(1-methylpropyl)amino]-1-octanethiosulfuric acid (I) on day 60 after infection and perfused for worm recovery 30 days later

	Number of recovered worms					
	Control			Treated		
Mouse number	m	f	Total	m	f	Total
1	3	3	6	7	1	8
2	7	7	14	3	0	3
3	8	4	12	3	0	3
4	5	5	10	11	0	11
5	9	9	18	3	0	3
6	12	12	24	11	1	12
7	6	5	11	6	0	6
8	10	8	18	5	0	5
9	8	7	15	13	3	16
10	9	5	14	4	0	4
11	5	5	10	12	1	13
12	9	8	17	6	0	6
13	*	*	*	2	0	2
Total	91	78	169	86	6	92
M±	7.58	6.50[a]	14.08	6.61	0.41[a]	7.07
SD	2.50	2.50	4.77	3.86	0.87	4.53

a: indicates a statistically significant difference between the control and treated means; P<0.000001 calculated with T test; * animal died before perfusion.

TABLE II

Number of male (m) and female (f) worms recovered from mice infected with the R_1 strain of *Schistosoma mansoni*. The two groups are control and treated with 700 mg/kg of (2-[(methylpropyl)amino]-1-octanothiosulfuric acid (I) on day 60 after infection and perfused for worm recover 30 days later

	Number of recovered worms					
	Control			Treated		
Mouse number	m	f	Total	m	f	Total
1	6	4	10	6	0	6
2	6	4	10	2	0	2
3	4	2	6	6	0	6
4	10	3	13	4	0	4
5	3	1	4	4	0	4
6	6	5	11	3	0	3
7	5	4	9	1	1	2
8	7	6	13	4	0	4
9	2	1	3	1	2	3
10	8	6	14	5	0	5
11	4	2	5	10	2	12
12	4	3	7	*	*	*
13	8	7	15	*	*	*
Total	73	48	121	46	5	51
M±	5.61	3.69[a]	9.30	4.18	0.45[a]	4.63
SD	2.25	1.93	3.88	2.60	0.82	2.80

a: indicates a statistically significant difference between the control and treated means; $P < 0.00002$ calculated with T test; * animal died before perfusion.

TABLE III

Comparative reduction in male, female and total worm burdens of R_1 and LE strains of *Schistosoma mansoni* after treatment of mice with 2-[(methylpropyl)amino]-1-octanothiosulfuric acid (I), 700 mg/kg, in relation to the mean numbers of males (m) and females (f) recovered from untreated control mice

Sex of worms	LE	R_1	P
f	93%	88%	0.49[a]
m	15%	25%	0.05[b]
m+f	50.2%	49.7%	0.06[c]

LE: susceptible strain of *S. mansoni*; R1: resistant strain of *S. mansoni*. Values of P were calculated with Kruskal-Wallis test; *a* and *c*: indicate no statistically significant differences between the reductions in female and total worm burdens in either strain; *b*: (a threshold value for P) may indicate a slightly statistical significant difference for male worm reductions between both strains.

unexpected result as compared to the nearly 50% reductions observed previously.

These results together with previous data (Penido et al. 1994 *loc. cit.*) emphasize the need to test the alkylaminoalkanethiosulfuric acids in other experimental models, such as monkeys, to evaluate its potential as an alternative clinical schistosomicidal drug. The apparently large dose of (I) will certainly be smaller in heavier animals than with mice, since the rate of liver metabolism in the former is lower, as demonstrated for praziquantel (Gönnert & Andrews *loc. cit.*). As pointed out by D Ciolli et al. (1993 *Parasitol Today 9:* 162–166, 1995 *Pharmacol Therap 68:* 35-85), the emergence of strains of *S. mansoni* resistant to conventional drugs stimulates and justifies the search of new alternative compounds. Also, acute and chronic toxicities should be studied to evaluate safety of this compound for human use.