Rev. Inst. Med. trop. São Paulo
18(4):264-267, *julho-agosto*, 1976

UDC 616.995.122.22

EXPERIMENTAL CHEMOTHERAPY OF SCHISTOSOMIASIS

XI — Active derivatives of aminoethanethiols

David L. NELSON (1) and J. PELLEGRINO (2)

SUMMARY

A group of mono, di, and tri-substituted aminoethanethiols were selectively screened for activity on *Schistosoma mansoni* infection in mice by the oogram method. Compounds with secondary amino groups bearing small, apolar, spherical alkyl substituents were found to be active.

INTRODUCTION

During the process of blind screening of more than 5,000 compounds obtained from the Walter Reed Army Institute of Research, adamantyl-aminoethanethiol was observed to be active in mice experimentally infected with *Schistosoma mansoni*. Subsequent selective trials with other compounds of this class revealed that this was not a special case, but the activity was indeed more general. A study of the chemical structure-activity relationship was made based on trials performed with 37 compounds.

MATERIAL AND METHODS

Drugs — More than 5,000 non-selected compounds from the files of the Walter Reed Army Institute of Research (WRAIR) were screened in mice experimentally infected with *S. mansoni* for anti-schistosomal activity. After finding that adamantyl-aminoethanethiol displayed activity, other compounds of this class were obtained from WRAIR for a selective trial. Drugs were administered *per os*.

Infection of animals — The L.E. strain (Belo Horizonte) of *S. mansoni* was used throughout this study. Mice were exposed, by the tail immersion method (PELLEGRINO & KATZ [3]), to 100 ± 10 cercariae. Hamsters were infected via the cheek pouch with 80 ± 10 cercariae (PELLEGRINO, DE MARIA & FARIA [1]). Animals were dosed *per os*.

Primary screening — This was performed in mice weighing about 20 g in groups of 5 for each compound. When the LD_{50} was available, the schedule of treatment consisted in a daily oral dose corresponding to 1/5 of the LD_{50}, for 5 consecutive days. In all cases it was tried to give the maximum tolerated dose.

Secondary screening — This was performed in groups of 10 mice receiving different doses. Some active compounds were tested in hamsters.

This study was supported, in part, by the "Conselho Nacional de Pesquisas", Brazil, and the U.S. Army (Walter Reed Army Institute of Research). Contribution number 66 from the Schistosomiasis Research Unit

(1) Department of Biochemistry, Institute of Biological Sciences, Federal University of Minas Gerais

(2) Schistosomiasis Research Unit, Institute of Biological Sciences, Federal University of Minas Gerais and "Centro de Pesquisas René Rachou, INERu-FIOCRUZ"
Address for reprints: Caixa Postal 1404, 30.000 Belo Horizonte, MG, Brasil

Assessment of antischistosomal activity — For the primary screening in mice, the animals were sacrificed by cervical fracture 8 days after the beginning of treatment. The only parameter used was the oogram, performed in a fragment from the small intestine (PELLEGRINO & FARIA[2]). In the secondary screening of mice and in hamsters, the hepatic-shift of schistosomes (STANDEN[4]) and the percentage of oogram changes were considered. In all cases the animals were killed and examined 8 days after the beginning of dosing.

RESULTS AND DISCUSSION

From the data available, it is possible to make some tentative conclusions as to the structural characteristics necessary for activity, although some data are lacking. First of all, the data indicate that the amino group must be secondary. All compounds in which the nitrogen was trisubstituted were inactive. Data are lacking for the case of the primary amine. Secondly, the substituent on the nitrogen should be non-polar. Actually, in all cases where the carbon chain bore a polar group, the compound was inactive.

The results obtained in mice are included in Tables I and III.

Although data are lacking for various intermediate compounds, it appears that, within the series C_2 to C_{10}, the activity in mice increases to the *t*-butyl group (*4*) and then falls off again. Alkyl groups larger than C_{10} are inactive. The fact that the n-butylaminoethanethiol (*3*) is inactive while the n-octyl analog (*6*) shows activity is difficult to explain. It may be that more nearly spherical alkyl substituents are more active, as indicated by the high degree of activity of the *t*-butyl-(*4*) and adamantylamino ethanethiol (*16*). Although the lack of activity of the 2-bornyl (*14*) and 2-norbornylmethyl (*15*) analogs does not confirm this hypothesis, this could be due to the position of attachment of the amino group to the ring. Whether the lack of activity of the N-phenyl derivative (*11*) is due to the character of the substituent or to the low basicity of the amino group can not be determined with the data available. In general, the activity seems to increase with the hydrophobicity (lipophilicity) of the substituent bound to the nitrogen, but there is a limit to the allowable size of this group.

In the only case where an analog (*33*) bearing a substituent (methyl) alpha to the thiol group was tested while satisfying the above mentioned criteria, there appeared to be a slight increase in activity. With the data available, nothing can be said about the effect of substitution alpha to the amino group.

The activity of compounds *2*, *4*, and *5* in hamsters experimentally infected with *S. mansoni* parallels that observed in mice (Table II).

The mortality rate of the animals which received inactive substances as well as those which were dosed with active compounds shows that the schedule of treatment used was close to the maximum which could be tolerated. Among the active substances, the least toxic seemed to be compounds *4* and *33*. Of these compounds, the most interesting in terms of activity, low toxicity, and simplicity of structure was compound *4*.

RESUMO

Terapêutica experimental da esquistossomose. XI — Derivados ativos de aminoetanotiois

Um grupo de aminoetanotiois mono, di e trisubstituídos foram testados, de maneira seletiva, para detectar possível atividade sobre a infecção de camundongos pelo *Schistosoma mansoni*. O método do oograma foi usado como critério de atividade. Compostos com grupos amino secundários possuindo substituentes alquilas pequenos, esféricos e apolares mostraram atividade esquistossomicida.

TABLE I

Antischistosomal activity of compounds in mice experimentally infected with *S. mansoni*

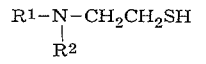
$$R^1-N(R^2)-CH_2CH_2SH$$

Compound	R^1	R^2	Dose (mg/kg/day) × 5, p.o.	Animals/dead	Schistosomes in the liver (%)	Oogram changes (%)
1	H	Et	600	5/2	—	0,0
2	H	i-Pr	300	10/4	52,0	50,0
			150	10/4	40,1	0,0
3	H	n-Bu	300	5/4	—	0,0
4	H	t-Bu	400	10/3	100,0	100,0
			200	10/2	45,0	25,0
			100	10/2	29,3	0,0
5 (*)	H	C_6H_{11}	600	10/8	—	100,0
			300	10/3	—	57,0
6	H	$n-C_8H_{17}$	300	10/7	53,7	33,3
7	H	$n-C_3H_{13}CHMe$	200	5/4	—	0,0
8	H	$n-C_{10}H_{21}$	400	5/3	—	0,0
9	H	$n-C_{12}H_{25}$	200	5/2	—	0,0
10	H	$n-C_{18}H_{37}$	600	5/3	—	0,0
11	H	Ph	50	5/1	—	0,0
12	H	$HO(CH_2)_5$	600	5/3	—	0,0
13	H	$PhOCH_2CHOHCH_2$	60	5/1	—	0,0
14	H	2-bornyl	90	5/2	—	0,0
15	H	2-norbornyl-CH_2	60	5/0	—	0,0
16	H	1-adamantyl	400	10/8	100,0	100,0
			200	10/5	88,8	80,0
17	H	1-piperidino-$(CH_2)_3$	400	5/4	—	0,0
18	H	$CH_3C(=O)$	200	5/2	—	0,0
19	H	$NH_2C(=O)CH_2CH_2$	520	5/3	—	0,0
20	H	$MeO(CH_2)_3$	400	5/4	—	0,0
21	H	$n-BuNHCH_2CH_2$	60	5/4	—	0,0
22	H	$EtCHOHCH_2$	600	5/1	—	0,0
23	H	$HOCH_2CHOHCH(CH_2OH)$	600	5/1	—	0,0
24	Et	Et	250	5/3	—	0,0
25	i-Pr	i-Pr	200	5/4	—	0,0
26	n-Bu	n-Bu	200	5/4	—	0,0
27	$n-C_8H_{17}$	$NH=C(NH_2)$	400	5/3	—	0,0
28	$R^1 + R^2 =$	$-(CH_2)-_6$	50	5/1	—	0,0
29	$R^1 + R^2 =$	$MeCHOHCH_2N(CH_2CH-_2)_2$	600	5/3	—	0,0

(*) Obtained from Aldrich Chemical Co.

TABLE II

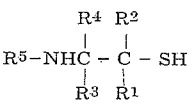
Antischistosomal activity of compounds *2*, *4*, and *5* in hamsters experimentally infected with *S. mansoni*



Compound	R^1	R^2	Dose (mg/kg/day) × 5, p.o.	Animals/ dead	Schistosomes in the liver (%)	Oogram changes (%)
2	H	i-Pr	500	5/3	90,5	100,0
			250	5/3	28,6	0,0
4	H	t-Bu	200	5/3	75,9	50,0
			100	5/3	49,5	50,0
5	H	C_6H_{11}	600	5/4	—	100,0
			100	5/1	—	0,0

TABLE III

Antischistosomal activity of compounds in mice experimentally infected with *S. mansoni*



Compounds	R^1	R^2	R^3	R^4	R^5	Dose (mg/kg/day) × 5	Route	Animals/ /dead	(%) Worms in the liver	(%) Oogram changes
30	Me	H	H	H	$EtOCOCH_2CHMe$	600	po	5/2	—	0,0
31	Me	H	H	H	$PhC(=O)SCH_2CH_2$	600	po	5/2	—	0,0
32	Me	H	H	H	$MeCHOHCH_2$	600	po	5/2	—	0,0
33	Me	H	H	H	$n-C_8H_{17}$	300	po	10/1	50,3	66,7
						150	po	10/1	12,0	0,0
34	Me	H	H	H	$PhC(=O)SCH_2CH_2$	600	po	5/1	—	0,0
35	H	H	$R^3+R^4=NH$		1-adamantylCH_2	35	po	5/3	0,0	—
36	H	H	$HOCH_2$	$HOCH_2$	H	600	po	5/2	0,0	—
37	Me	H	Me	H	H	600	po	5/1	0,0	—

REFERENCES

1. PELLEGRINO, J.; DE MARIA, M. & FARIA, J. — Infection of the golden hamster with *Schistosoma mansoni* cercariae through the cheek pouch. *J. Parasit.* **51**:1015, 1965.

2. PELLEGRINO, J. & FARIA, J. — The oogram method for the screening of drugs in schistosomiasis mansoni. *Amer. J. Trop. Med. Hyg.* **14**:363-369, 1965.

3. PELLEGRINO, J. & KATZ, N. — Experimental chemotherapy of schistosomiasis mansoni (Ed. Ben Dawes). *Adv. Parasitol.* **6**: 233-290, 1968.

4. STANDEN, O.D. — Experimental schistosomias s. III — Chemotherapy and mode of drug action. *Ann. Trop. Med. Parasit.* **47**: 26-43, 1953.

Recebido para publicação em 15/5/1975.