terestingly, were non-effective against the gram-negative bacteria included in this study. Most spectacular is their activity against *beta hemolytic Streptococcus,* the CLMH strain of which is 4-fold more sensitive to prianicins than to tetracycline. Structurally, prianicin A and B are alike in comprising a 6-membered ring cyclic peroxide but differ from each other in the stereochemistry of the propionic acid side-chain, on the one hand, and in the carbon skeleton of the $C_{15}H_{25}$-isoprenic side-chain, on the other hand. These differences are reflected in their antibacterial potency. Thus, (**2**) being 2.5-fold more effective than (**1**) against the CLMH strain of *beta hemolytic Streptococcus.*

Of particular interest is the activity of prianicins against the yeast species *Saccharomyces cerevisiae.* The importance of this observation lies in the ability of prianicins to prevent secondary infections due to pathogenic fungi.

The data now at hand strongly suggest that (**1**) and (**2**) are of therapeutic potential, meriting further study in the sense of structure-activity relationship. A study towards this end is currently in progress in our laboratory.

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2 Present addresses: S.S. 'Yissum', Hebrew University Company on Research and Development; V.U. Institute for Standardization and Control of Pharmaceuticals, Ministry of Health, Jerusalem, Israel; A.C. Hebrew University Marine Biology Laboratory, Elat.
3 To whom correspondence should be addressed.
4 B. Franco, M. Tsurnamal, A. Colorni and S. Halevy. in preparation.
5 *Prianos sp.* of the family *Hymeniacidonidae,* identified by Dr M. Tzurnamal of the Zoology Department, Hebrew University of Jerusalem.
6 W.C. Still, M. Kahn and A. Mitra, J. org. Chem. *43,* 2923 (1978).
7 Y. Kashman and M. Rotem, Tetrahedron Lett. *1979,* 1707.
8 S. Sokoloff, I. Tamir, S. Halevy and S. Sarel, submitted.
9 a) M. Albericci, J.C. Braekman, D. Daloze and B. Tursch, 3rd int. Symp. Marine nat. Prod., p.P-14. Bruxelles, Sept. 1980, abstracts; b) M. Albericci, M. Collart-Lempereur, J.C. Braekman, D. Daloze, B. Tursch, J.P. Declercq, G. Germain and M. Van Meersche, Tetrahedron Lett. *1979,* 2687.
10 M.C. Bryant. Antibiotics and their Laboratory Control, Butterworths, London 1972.

The efficacy of a novel compound, (*E*)-1-(4′-bromo-4-biphenylyl)-1-(4-chlorophenyl)-3-dimethylaminoprop-1-ene against *Trypanosoma cruzi* in mice

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Summary. The biological properties of a novel compound 353C with high activity against *Trypanosoma cruzi,* are described. The compound was about 10 times and 20 times more effective than either benznidazole or nifurtimox respectively, in producing radical cure in mice. 353C had a long half-life and showed anti-trypanosomal properties when given to mice at weekly intervals.

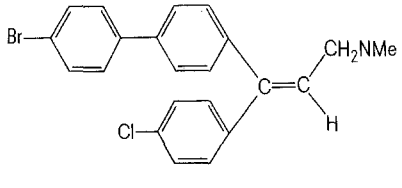
South American trypanosomiasis (Chagas' disease), which is caused by the protozoan *Trypanosoma cruzi,* is primarily vector-borne and is transmitted by reduviid bugs of the sub-family *Triatominae.* It has been estimated[1] that some 12 million persons are affected by the disease, which is an important cause of morbidity and mortality in endemic areas in South and Central America (particularly Brazil, Venezuela and Argentina). Current therapy of the disease is unsatisfactory[2]. Only 2 drugs (nifurtimox and benznidazole) are in general use. However both produce a high incidence of side-effects at therapeutic dose levels (10 mg kg^{-1} day^{-1} for 60–90 days, and 5–10 mg kg^{-1} day^{-1} for 30–60 days respectively). Both drugs are less effective in the chronic stages of the disease than they are in the acute phase. We report here the synthesis and biological activities of (*E*)-1-(4′-bromo-4-biphenylyl)-1-(4-chlorophenyl)-3-dimethylaminoprop-1-ene (353C) (fig.), one of a series of more than 130 1,1-diaryl-3-aminoprop-1-enes possessing high efficacy against *T. cruzi* in experimentally infected animals.

Synthesis of 353C was achieved by the Wittig reaction between 4′-bromo-4-biphenylyl 4-chlorophenyl ketone and the ylid from 2-(dimethylamino)ethyl triphenylphosphonium bromide. After separation from the accompanying (Z)-isomer, 353C was converted into the tartrate salt m.p. 163 °C.

Following conventional techniques[3], the activity of 353C (as tartrate salt) in mice (strain CDI) was determined using an oral regimen of 5 once-daily doses. The drug was shown to be highly effective in suppressing infections induced by 5 stocks of *T. cruzi,* with ED_{50}-values which ranged from 0.5 mg $kg^{-1} \times 5$ to 3.0 mg $kg^{-1} \times 5$ (as base).

In experiments designed to examine the ability of the drug to effect radical cure (sterilization) of *T. cruzi* infections, mice were infected with a variety of stocks of the parasite. When the infection was established, 353C was administered orally once daily for 30 days, then 30 days after the last dose, blood from each mouse was collected, cultured and examined for the presence of parasites[3]. The results obtained (table) indicated that 353C was about 10 times more potent than benznidazole and about 20 times more active than nifurtimox.

In mice (strain CDI) infected with a Peruvian stock of *T. cruzi,* 353C (as tartrate) appeared to be a unique trypanocide, in that it cured > 90% of infected animals when it was administered orally as 7 once-weekly doses of 25 mg kg^{-1} (as base).



Sterilisation[3] of *T. cruzi* infections in mice

Drug	Dose[b] mg kg^{-1} day^{-1}	Proportion of mice sterilized with stocks of *T. cruzi*[a]				
		BG	Peru	Ml	Y	Total of all stocks (%)
353C	20	n.d.	n.d.	12/12	9/10	21/22 (95)
	10	24/40	7/11	10/12	11/11	52/64 (81)
	5	n.d.	n.d.	5/11	4/9	9/20 (45)
Nifurtimox	120[c]	1/6	7/11	0/0	4/4	12/21 (57)
	60	n.d.	0/12	n.d.	5/11	5/23 (22)
	30	n.d.	n.d.	2/12	3/10	5/22 (23)
Benznidazole	120	15/16	8/10	11/12	9/12	43/50 (86)
	30	2/16	0/12	1/12	1/11	4/51 (8)

[a] BG, old laboratory strain; Peru, Peruvian human strain; Ml, Argentinian strain; Y, Brazilian human strain. [b] Drug administered for 30 days; sterilization evaluated by haemoculture 30 days after the last dose; control mice all died before the end of the treatment period. [c] Drug related toxicity caused deaths in experiments with stock BG 6/14, Peru 1/12, Ml 12/12 and Y 6/10. n.d., not done.

Drug metabolism studies showed that 353C tartrate was well absorbed after oral administration, and that the primary metabolic step appeared to be demethylation to the corresponding secondary amine; trace amounts of the primary amine were also detected. In mice, significant accumulation of parent drug and metabolites occurred within 5 days when 353C tartrate was administered at 3 or 23 mg kg^{-1} day^{-1} although no cumulation could be demonstrated after 3 once-weekly doses of 50 mg kg^{-1}. Similar results were obtained with daily dosing in rats, dogs, and *Erythrocebus patas* monkeys, indicating that 353C had a relatively long half-life in each of these species. Plasma and whole blood levels were always much lower than tissue levels.

In toxicity studies in rats and beagle dogs, oral doses of 3 or 10 mg kg^{-1} day^{-1} for 30 days produced no haematological, biochemical or histopathological effect, although all the dosed dogs did suffer some loss in weight.

Further studies are in hand to evaluate the full potential of this novel trypanocide which, in contrast to most drugs possessing activity against *T. cruzi*, is not a nitro-heterocyclic derivative.

1 J.A. Walsh and K.S. Warren, New Engl. J. Med. *301*, 967 (1979).
2 J.R. Cançado and Z. Brener, in: *Trypanosoma cruzi* e Doença de Chagas, p.362. Ed. Z. Brener and Z. Andrade. Guanabara Koogan SA, Rio de Janeiro Brazil 1979.
3 E. Beveridge, I.C. Caldwell, V.S. Latter, R.A. Neal, V. Udall and M.M. Waldron, Trans. R. Soc. trop. Med. Hyg. *74*, 43 (1980).

Sequence organization in the DNA of three Selachians

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Summary. The DNA interspersion pattern in 3 Selachians *(R. asterias, T. marmorata* and *S. stellaris)* has been studied through the reassociation kinetics of short (0.3 Kb) and long (2.5 Kb) DNA fragments. Preliminary results show that most of the DNA (approximately 80%) of these organisms is arranged according to a short-period interspersion pattern. A notable resemblance to the pattern previously described in the teleostean *Salmo trutta* has been observed.

It has been observed that the 'original' vertebrate DNA interspersion pattern is Xenopus-like. In fact, a similar pattern has been found also in Amphioxus and, though sometimes with some variations, in almost all the classes of vertebrates as well[1] except the birds[2,3]. As for the fishes, thus far only the genome organization of a teleostean, *Salmo trutta*[4], has been studied. Therefore, we have deemed it interesting to undertake a study on the DNA interspersion pattern of the Selachians, which are among the most primitive vertebrates. Their DNA values are much higher than those of trout and are among the highest so far found in the subphylum[5,6]. This study will give further information on the evolutionary trend followed by the genome organization in vertebrates and, in particular, in fish.

Material and methods. DNA renaturation kinetics of short (0.3 Kb) and long (2.5 Kb) DNA fragments has been studied in 3 Selachians: *Raja asterias, Torpedo marmorata* (Batoidea) and *Scyliorhinus stellaris* (Galeomorphii). The specimens were kindly supplied to us by the Zoological Station of Naples.

DNA was extracted from blood, liver and testis cells of 1 or 2 samples per species using Marmur's technique[7] partially modified by the addition of several enzymatic digestions and phenol deproteinization[8]. DNA was fragmented by sonication with a Branson sonifier B 12 cell-disruptor. Fragment lengths were examined by agarose gel electrophoresis according to Elsevier et al.[9], using as standard lambda DNA digested with ECO R_1 and HIND III[10].

The reassociation kinetics of 0.3 Kb DNA fragments was carried out by the optical method for Cot-values from 0.5×10^{-3} to 3×10^{-1} and by hydroxyapatite chromatography for Cot-values from 1×10^{-1} to 1×10^{4}. The reassociation kinetics of 2.5 Kb fragments was performed by HAP chromatography. Reassociation kinetics by the optical method was performed by Britten et al.[11]. HAP chromatography was performed according to the batch method[12]. *E. coli* DNA, used as reference, had a $Cot_{0.5}$ value of 5.75 msec and a rate of 0.174 M^{-1} sec^{-1}. For further technical details see also Olmo et al.[13].

Results and discussion. The reassociation curves of short (0.3 Kb) and long (2.5 Kb) DNA fragments of the 3 species assayed are represented in the figure.