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Anthelmintic activity of several 5-substituted benzimidazolyl carbamates against *Hymenolepis nana* cysticercoids

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Summary. Several benzimidazolyl carbamate derivatives effective against *Hymenolepis nana* cysticercoids were found.

There is still today a scarcity of anthelmintics which are effective against larval tapeworms. In recent years a number of benzimidazole derivatives with promising anthelmintic properties have been discovered. Among these, 5-substituted benzimidazolyl carbamates have been found active in preventing, inhibiting and curing various metacestode infections[1-7]. Here we report the discovery of additional 5-substituted benzimidazolyl carbamate derivatives with cestocidal properties (table). All compounds were synthesized in our laboratory[8]. Three of them (II, IV and V) have been made for the first time, and their synthesis and properties will be published elsewhere. The 2 remaining compounds (I and III) have been synthesized before by a somewhat different method[9], but were never tested against cestodes.

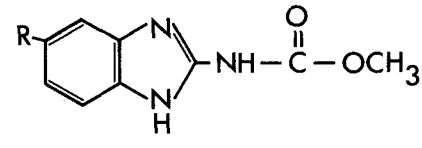
To test these compounds for anthelmintic activity we used the *Tribolium confusum* - *Hymenolepis nana* system. The flour beetles infected with *H. nana* eggs were fed continuously from day 1 to day 10 post infection on mixtures of 9 parts flour and 1 part drug, the concentration used previously[2,3] in studies with mebendazole, another benzimidazolyl carbamate. Control beetles received only four.

On day 10 post infection the beetles fed compounds I, II, III and IV contained significantly ($p < 0.001$) fewer postoncosphere stages than the controls. Also, whereas all the parasites in the control beetles had become fully developed cysticercoids, many of those in the drug-treated groups were retarded. This inhibiting effect varied with the drug tested. The most potent drug proved to be compound I where all the parasites (100%) failed to reach the fully developed cysticercoid stage, followed by compounds II, III, IV and V with decreasing potency in that order. Haemocoel contents of hosts treated with compounds I, II, III and IV contained in addition to the various postoncospheral stages many oncospheres that were alive but had not progressed beyond this stage of development. Their presence indicated that these compounds, though they drastically arrested the development of larvae, did not kill them. No oncospheres were found in control beetles or beetles fed compound V. The mean number of postoncospheral stages in beetles fed compound V was comparable to those in the controls ($p > 0.05$), yet 17% of them were underdeveloped larvae, suggesting the weak, but still noticeable effect of this drug. None of the compounds tested caused beetle mortality.

Thus the results with the first 4 compounds presented here are comparable to those reported for *H. nana* and mebendazole[2,3,6].

Although the larval stages of *H. nana* seem to have some resistance to benzimidazolyl carbamates, it is known that the adults of this parasite are easily expelled by mebendazole from the intestinal lumen of mice[6] and humans[7]. It is reasonable then to assume that the compounds reported here might also be useful against *H. nana* in man.

Unlike hymenolepidid larvae, metacestodes such as *Echinococcus multilocularis*, *E. granulosus*, *Taenia crassiceps*, *T. pisiformis* and *Mesocestoides corti* are highly susceptible to treatment with many benzimidazoles[1,4,5]. Therefore the compounds presented in this study should also be tested for possible activity against other larval cestodes.



Compound	R	Mean number postoncosphere stages per beetle (± SE)*	p	Total number postoncosphere stages	Underdeveloped stages (%)	Fullydeveloped cysticercoids (%)
Control	No treatment	17.40 ± 1.19	-	1035	0	100
I	$-Cl$	0.54 ± 0.12	< 0.001	35	100	0
II	$-OCH_3$	0.26 ± 0.07	< 0.001	17	88	12
III	$-CH_3$	0.81 ± 0.25	< 0.001	56	73	27
IV	$-NO_2$	6.87 ± 1.20	< 0.001	482	32	68
V	$-CO_2H$	18.37 ± 1.34	> 0.05	1182	17	83

* Summarized results from 3 replicate experiments. All groups contained 25 beetles when the experiments began and at least 20 live beetles at day 10 post infection when the experiments were terminated.

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Mass expulsion of zooxanthellae by heat-stressed reef corals: a source of food for giant clams?

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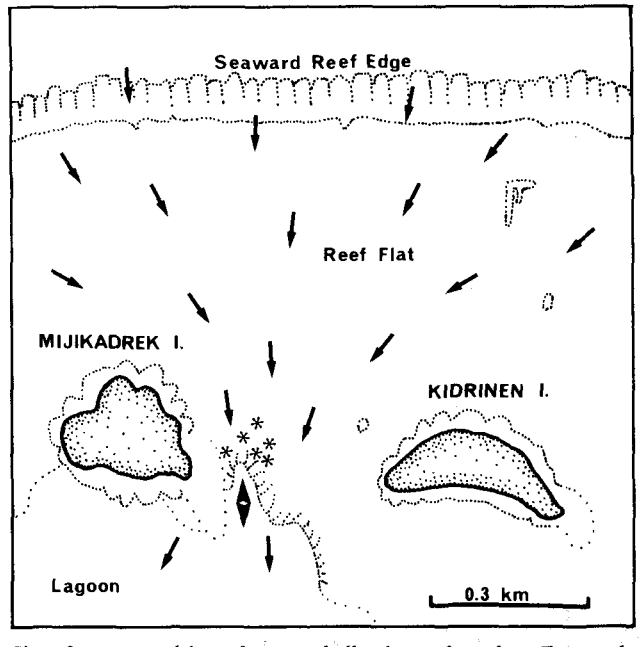
Summary. Symbiontic zooxanthellae found in the stomach of the giant clam *Tridacna gigas* are of exogenous origin. They become available to the clam following their mass expulsion from heat-stressed hermatypic corals. The frequent appearance of these mini-plankton blooms also permits the primary production of zooxanthellae to become an available food source for other filter-feeding reef organisms rather than remaining imprisoned within the tissues of corals.

Giant clams are hosts to endosymbiotic algae called zooxanthellae which inhabit the subepithelial haemal spaces of their hypertrophied siphons. As this animal-plant association is presently understood, the relationship is mutualistic with both participants accruing physiological advantages[1,2]. Zooxanthellae have also been found in the stomachs of giant clams, and it has been assumed that these algae have originated from the clam's blood spaces[3,4]. The more parsimonious explanation, that the material found in guts has been eaten, has been disregarded. In this paper, we report that the reason zooxanthellae occur in the stomachs of giant clams is indeed that they have filtered these algae from the surrounding sea water and eaten them. As to the origin of ingested zooxanthellae, it is evident that they have arisen from cohabitating hermatypic corals which have expelled their algal symbionts in response to the thermal stress of tidal exposure.

To explain the means by which zooxanthellae migrate from siphonal blood spaces to the lumen of the stomach, several ingenious mechanisms have been proposed including a reverse digestion process[3] and the presence of special canals linking the stomach to the siphons[4]. At Enewetak Atoll, Marshall Islands, we have frequently found the stomach of *Tridacna gigas* to be full of zooxanthellae. However, exhaustive thin sectioning of the stomach's digestive diverticula failed to substantiate a build-up of zooxanthellae adjacent to that tissue or the transport of these algal cells into the stomach lumen, which Morton[3] has reported for *Tridacna crocea*. Furthermore, the canals figured by Mansour[4] between the hypertrophied siphons and the stomach of *Tridacna* do not exist[5,6].

Tridacnid clams typically inhabit shallow coral reef waters within the Indo-Pacific geographical region[7]. Like these bizarre molluscs, the vast majority of reef-building corals (the hermatypic Scleractinia) live symbiontically with zooxanthellae[8,9]. However, whereas only 1% or less of the biomass of *Tridacna* consists of zooxanthellae[10], in some hermatypic corals this figure approaches 50%[11]. During mid-day low tides, reef corals are exposed to intense tropical sunlight and may experience temperature elevations exceeding 36 °C; they respond to this stress by expelling masses of algal symbionts into the surrounding sea water[8]. We observed this phenomenon during several mid-day low tide periods in August, 1979 at Enewetak Atoll.

While collecting specimens of *Tridacna gigas* between the islets of Mijikadrek and Kidrinen (figure), we noted the incoming tide, manifested by a line of brown froth, spill over the recently-exposed seaward reef edge, join waters of the reef flat, and advance towards the atoll lagoon. Seen underwater, the tidal flood appeared as a cloudy-green vertical front, about 2 m deep, advancing across the reef flat at 1–2 knots. Underwater visibility was reduced from about 40 m to 3 m as the front passed by. The temperature of the tidal front was conspicuously higher than ambient. In fact, so much so that when free-diving about 100 m to the lee of the reef edge, one of us (P.V.F.) experienced a transient burning sensation as the tidal water touched has skin. Microscopic examination of the sea water revealed the presence of numberous zooxanthellae along with bits of filamentous algae, miscellaneous protozoa, polychaete setae and molted crustacean cuticles. On the following day,



Site of mass expulsion of zooxanthellae by reef corals at Enewetak Atoll. Direction of tidal flooding is indicated by arrows. * Designates a specimen of *Tridacna gigas* while black diamond represents the research vessel Rontak.