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IN VIVO POTENT ANTIFILARIAL ß-CARBOLINES

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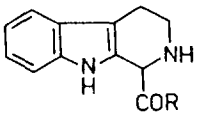
Abstract: 1-Methoxycarbonyl/carboxamido/cyano-9H-pyrido (3,4-b)indoles have been found to exhibit interesting *in vivo* filaricidal activity against *Litomosoides carinii* and *Acanthocheilonema viteae* in rodents.

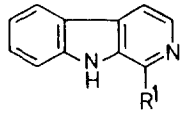
Lymphatic filariasis, a disease of tropical and subtropical countries, caused by filarial worms, is one of the most neglected, public health and socio-economic problems of the world. Over 900 million people are living in endemic areas and more than 80 million people are infected with this disease caused by *Wuchereria bancrofti, Brugia malayi* and *B. timori*[1].

For 50 years, the chemotherapy of filariasis has been based on treatment with diethylcarbamazine (DEC), which kills microfilariae but has little or no effect on most of the adult filarial species and causes side effects[2]. A semisynthetic macrocyclic lactone antibiotic, ivermectin which has recently been used successfully to treat Onchocerciasis, also has effect only on the microfilarial stage of filarial parasites[3,4]. A large number of benzimidazole-2-carbamates were found to possess macrofilaricidal activity by parenteral routes but suffer from several shortcomings[5,6]. No drug yet has been found to be effective against the adult worm. Thus, there is urgent need to search newer structural prototypes with broad range macrofilaricidal activity.

In continuation of our endeavors to develop an ideal adulticide, substituted 1-H/1-phenyl-9H-pyrido [3,4-b] indoles[7] exhibited interesting filaricidal activity against *L. carinii* and *A. viteae* in rodents. Herein, we report the synthesis and *in vivo*

antifilarial activity of 1-methoxycarbonyl/carboxamido/cyano-9H-pyrido [3,4-b] indoles. 1-Methoxycarbonyl/ carboxamido/cyano-9H-pyrido[3,4-b]indoles (**4-6**) have been obtained from 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole 1-carboxylic acid (**1**) according to literature method[8,9].





1 R = OH
2 R = OCH_3
3 R = NH_2

4 R^1 = $COOCH_3$
5 R^1 = $CONH_2$
6 R^1 = CN

Table 1 : Antifilarial activity of 1-substituted-ß-carbolines (2-6) and diethyl carbamazine citrate

Compound	Activity Against					
	L. Carinii			*A. Viteae*		
	Dose mg/kg x 5 days (i.p.)	% Death mif	maf	Dose mg/kg x 5 days (i.p.)	%Death mif	maf	Sterl. of O +
2	30	0	81	50	96	0	0
3	30	0	0	50	0	84	0
4	30	0	0	50	96	0	0
5	30	0	0	50	100	50	100
6	30	59	78	50	0	50	0
DEC Citrate	6	> 90	0	350(i.p.)	> 90	0	0

'O' inactive '-' not done 'o' female worms, 'mif' microfilariae, 'maf' macrofilariae

In vivo **antifilarial activity:** All the compounds were evaluated against *L. carinii* in cotton rats (Sigmodon hispidus) and *A. viteae* in *Mastomys natalensis* as described earlier[7]. The compounds being insoluble in water were made fine suspensions with 1% Tween 80. Two to three animals were used for each dose level study and atleast two replicates were used for confirming the activity.

Results and Discussion

Amongst the compounds tested, only compounds **2** and **6** showed significant filaricidal action against *L. carinii* at 30 mg/kg x 5 days (i.p.) (Table 1). Compound **2** exhibited 81% adulticidal activity and **6** showed 59% micro- and 78% macrofilaricidal activity.

Whereas in general, all the 1-substituted compounds exhibited a wide range of activity against filarial parasite *A. viteae* in *M. natalensis* at 50 mg/kg x 5 days (i.p.) (Table 1). In 1,2,3,4-tetrahydro series-1-carbomethoxy substituted compound **2** showed 96% microfilaricidal activity and 1-carboxamido compound **3** exhibited 84% adulticidal activity. Compound **4** containing 1-carbomethoxy substituent obtained from **2** showed 96% microfilaricidal activity, whereas compound containing 1-carboxamido group obtained from aromatisation of **3** exhibited 100% micro-and 50% macrofilaricidal activity alongwith 100% sterilization of surviving female worms. Conversion of carboxamido derivative **5** into 1-cyano derivative **6** showed only 50% adulticidal activity.

The examination of *in vivo* activity profile of different 1-substituted-9H-pyrido[3,4-b]indoles against rodent filariids (*L. carinii* and *A. viteae*) point out to the structure— activity correlation, which may be summarized as follows. Compounds containing 1-carbomethoxy group exhibited microfilaricidal activity against *A. viteae*, whereas compounds with carboxamido function showed promising micro and macrofilaricidal activity. Introduction of cyano function showed the reduction in micro filaricidal activity, while it maintains the adulticidal activity. This indicates that substitutent at 1

position in tetrahydro or aromatised ß-carbolines play an important role in eliciting antifilarial activity in rodents.

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