Structure-Antifilarial Activity Relationship of 5/6/7/8-Mono- or Disubstituted 1H/1-Phenyl-9H-pyrido[3,4-b]indoles – A New Class of Potential Filaricides*

Alka Agarwal[a], Shiv K. Agarwal[a], Som Nath Singh[b], Nigar Fatma[b] and R. K. Chatterjee[b]

Divisions of [a] Medicinal Chemistry and [b] Parasitology, Central Drug Research Institute, Lucknow 226001, India

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Antifilarial Activity, β-Carbolines, Substituted 9H-Pyrido[3,4-b]indoles

Antifilarial activity of 5/6/7/8-mono- or disubstituted 1H/1-phenyl-9H-pyrido[3,4-b]indoles (**I**) has been described. The 1,6- and 8-substituted 9H-pyrido[3,4-b]indoles (**I**) elicited interesting filaricidal activity against *Litomosoides carinii* and *Acanthocheilonema viteae* in rodent hosts.

Introduction

The successful treatment of filariasis, a disease of many tropical and subtropical areas, is jeopardized, due to lack of suitable chemotherapeutic agents capable of eliminating both microfilariae and adult worms with least toxicity to the host (Agarwal *et al.,* 1993). Benzimidazole class of compound possessing high order of activity against intestinal and to the extent against tissue dwelling helminths (Sharma and Abuzar, 1983) have several set backs (Townsend and Wise, 1990) and thus there is need for search for new structural prototypes having macrofilaricidal property.

In our earlier studies, substituted 9H-pyrido-[3,4-b]indoles (β-carbolines) (Agarwal *et al.,* 1989, 1990a, 1990b; Kumar *et al.,* 1990) exhibited promising anthelmintic activity against intestinal helminths. Therefore, it is proposed to explore this class of compounds for filarial chemotherapy. Accordingly, 5/6/7/8-mono- or disubstituted 1H/1-phenyl-9H-pyrido[3,4-b]indoles (**I**) were synthesized and evaluated for antifilarial activity against *Litomosoides carinii* and *Acanthocheilonema vitae* in rodents.

Materials and Methods

Synthesis

The various 5/6/7/8-mono- or disubstituted 1H/1-phenyl-9H-pyrido[3,4-b]indoles (**I,** Table I) were synthesized starting from DL-tryptophan according to literature procedures (Agarwal *et al.,* 1989, 1990a).

Parasites and hosts

All the compounds were evaluated against *L. carinii* in cotton rats *(Sigmodon hispidus)* and *A. viteae* in *Mastomys natalensis.* As the compounds were insoluble in water fine suspensions of each one of them was made in presence of 1% Tween 80 (Katiyar *et al.,* 1984). Two to three animals were used for each dose level study and at least two replicates were used for confirmation of activity.

Evaluation of antifilarial activity

1. *Litomosoides carinii*

The infection was transmitted to 6 weeks old male cotton rats *(Sigmodon hispidus)* through the vector *Liponyssus bacoti* by the literature method (Hawking and Sewell, 1948). Animals showing 250 or more microfilariae per 5 mm^3 of blood were chosen for screening. Blood samples of experimental and control animals were examined for microfilariae before starting the treatment and thereafter at weekly interval till day 42. All the compounds were given 30 mg/kg intraperitoneally for 5 consecutive days. On day 42, all the treated and control animals were sacrified and the condition of adult male and female worms observed. The micro- and macrofilaricidal action were assessed by literature method (Lämmler *et al.,* 1971; Misra *et al.,* 1981).

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Reprint requests to Dr. S. K. Agarwal.
Telefax: 91-522-243405.

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2. *Acanthocheilonema viteae*

The *A. viteae* infection was transmitted to 6 weeks old male *M. natalensis* through the vector *Ornithodorus moubata* by the method of Worms *et al.* (1961). The micro- and macrofilaricidal activities of the compounds were assessed against *A. viteae* in *M. natalensis* as described for *L. carinii* at 50 mg/kg i.p. for 5 consecutive days.

Results

Activity against L. carinii

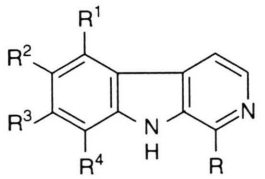
Amongst the compounds tested, only compounds **2, 5, 6** and **14** showed significant filaricidal action (>90% micro- and/or macrofilaricidal action or sterilization of female worms) at 30 mg/kg i.p. × 5 days. Compound **2** (**I,** 6-nitro) exhibited 100% micro- and 97.2% macrofilaricidal activity.

Introduction of 1-phenyl substituent in compound **1** led to compound **5** (**I,** R = C_6H_5, R^1 = R^2 = R^3 = R^4 = H) which showed 100% micro- and 66.4% macrofilaricidal activity along with 100% sterilization of the surviving female worms. Nitration of **5** afforded 6-nitro-1-phenyl-9H-pyrido-[3,4-b]indole (**6**) which exhibited 77% adulticidal activity with sterilization of all the surviving female worms. 8-Acetamido-1-phenyl-9H-pyrido[3,4-b]indole (**14**) showed 94.7% microfilaricidal activity but no adulticidal activity.

Activity against A. viteae

In general, all the substituted 9H-pyrido[3,4-b]-indoles except compounds **7, 11** and **13** exhibited a wide range of activity against filarial parasite, *A. viteae* in *M. natalensis* at 50 mg/kg i.p. × 5 days.

Table I. Antifilarial activity of 5/6/7/8-mono- or disubstituted 1H/1-phenyl-9H-pyrido[3,4-b]indoles (**I**).



Compd.* No.	R	R^1	R^2	R^3	R^4	*L. carinii* 30 mg/kg×5 (i.p.) % Death mf	maf	Sterl. ♀	*A. viteae* 50 mg/kg×5 (i.p.) % Death mf	maf	Sterl. ♀
1	H	H	H	H	H	0	0	0	0	84.4	0
2	H	H	NO_2	H	H	100	97.2	0	100	68.8	0
3	H	H	$NHCOCH_3$	H	H	0	0	0	42	0	0
4	H	H	$NHCOOCH_3$	H	H	0	0	0	0	50	100
5	Ph	H	H	H	H	100	66.4	100	92.8	81.5	0
6	Ph	H	NO_2	H	H	0	77	100	97	80**	0
7	Ph	H	NH_2	H	H	0	0	0	0	0	0
8	Ph	H	$NHCOCH_3$	H	H	0	0	0	0	68.8 (100 ♀)***	0
9	Ph	H	$NHCOOC_2H_5$	H	H	0	0	0	87.3	0	100
10	Ph	NO_2	$NHCOCH_3$	H	H	0	0	0	0	67.7	0
11	Ph	NO_2	NH_2	H	H	0	0	0	0	0	0
12	Ph	H	H	H	NO_2	0	0	0	0	76.5	0
13	Ph	H	H	H	NH_2	0	0	0	0	0	0
14	Ph	H	H	H	$NHCOCH_3$	94.7	0	0	0	75	0
15	Ph	H	H	H	$NHCOOC_2H_5$	0	0	0	56.6	81.3	0
16	Ph	H	H	NO_2	$NHCOCH_3$	0	0	0	0	67.5	75

0, inactive; *, compounds **1–16** described in references (Agarwal *et al.*, 1989, 1990a); **, on ♀ only; ***, death of ♀'s only; mf, microfilaricidal activity; maf, macrofilaricidal activity.

Compounds **1–4** without any substituent at 1-position (Table I) exerted filaricidal activity. The compounds (**1–4**) caused 42–100% death of microfilariae and/or 50–84% adulticidal activity at a dose of 50 mg/kg. The most potent compounds **1** and **2** showed 84.4% and 68.8% adulticidal activity, respectively. Compound **4** exhibited 50% adulticidal action along with sterilization of all the surviving female worms. However, compound **3** did not exert any adulticidal activity.

Incorporation of a phenyl substituent at 1-position in 9H-pyrido[3,4-b]indole (**I,** R = R^1 = R^2 = R^3 = R^4 = H) provided compounds **5–16.** These compounds were found to have pronounced effect in evoking biological response against *A. viteae.* In general, compounds **5–16** exhibited potent adulticidal activity except compounds **7, 11** and **13** which have an amino function at position 6 and 8 in 1-phenyl-9H-pyrido[3,4-b]indole, respectively. These compounds have no filaricidal action. Compound **5** showed 92.8% microfilaricidal and 81.5% adulticidal activity against *A. viteae* infection. Amongst 6-substituted 1-phenyl-9H-pyrido[3,4-b]-indoles (**6–9**), compound **6** with a nitro function was equipotent to its parent compound **5.** Reduction of nitro compound **6** to the corresponding amino compound **7** led to complete loss of biological response. Filaricidal activity was improved upon converting an amino compound **7** into acetamido derivative **8** and carbamate derivative **9,** but these compounds showed low order of activity in comparison to **5.** Nevertheless, compound **8** showed 68.8% adulticidal activity (death of all the female worms), whereas **9** exhibited 87.3% microfilaricidal activity along with sterilization of 100% female worms.

Introduction of substituents at position 8 in 1-phenyl-9H-pyrido[3,4-b]indole showed better adulticidal activity against *A. viteae* infection. The compounds **12–15** exhibited 75–81% adulticidal activity. Carbamate derivative **15** also showed 56.6% microfilaricidal activity along with 81.3% adulticidal activity.

However, 1,5,6-/1,7,8-substituted compounds (**10, 11, 16**) failed to improve the filaricidal activity. Compounds having both nitro and acetamido functions (**10, 16**) exhibited around 67% adulticidal activity. Compound **16** also showed 75% sterilization of female worms. Hydrolysis of acetamido compound **10** into amino compound **11** was devoid of any filaricidal activity.

Discussion

The principal objective of evaluating 5/6/7/8-mono- or disubstituted 1H/1-phenyl-9H-pyrido-[3,4-b]indoles (**I; 1–16**) as the possible filaricides was to develop new structural prototypes in the filarial chemotherapy, which may have better profile of activity with minimal side effects.

The examination of activity profile of different 5/6/7/8-mono- or disubstituted 1H/1-phenyl-9H-pyrido[3,4-b]indoles (**I**) against rodent filariids (*L. carinii* and *A. viteae;* Table I) point out to the structure activity correlate, which may be summarized as follows. 5/6/7/8-Mono- or disubstituted 1H/1-phenyl-9H-pyrido[3,4-b]indoles (**I**) have shown better activity profile against *A. viteae* in *M. natalensis* than *L. carinii* in cotton rats. Compounds with 1-phenyl and/or 6-nitro substituents exhibited more pronounced effect against *L. carinii* and *A. viteae.* Complete loss of adulticidal activity was observed in amino compounds (**7, 13**). Reduction in biological response was also seen in compounds with substituents other than nitro group. This would indicate that 1-, 6- and 8-substituents play an important role in adulticidal activity. 1,8-Disubstituted compounds irrespective of the nature of substituents, exhibited better adulticidal activity. Thus, this class of compound may provide a useful lead to carry out further molecular modifications in β-carbolines to generate better drugs to combat filariasis.

Agarwal A., Agarwal S. K., Bhakuni D. S., Gupta S. and Katiyar J. C. (1989), Antiparasitic agents: Part VIII. Synthesis of 1,6- and 1,8-disubstituted 9H-pyrido-[3,4-b]indoles and 2-substituted 9-phenyl-1(3),10-dihydropyrido[3,4-b]imidazo[4,5-g]indoles and their anthelmintic activity. Indian J. chem. **28B,** 943–949.

Agarwal A., Agarwal S. K. and Bhakuni D. S. (1990a), Antiparasitic agents: Part X. Synthesis of 2,7-disubstituted 1,6-dihydropyrido[3,4-b]imidazo[4,5-e]indoles as anthelmintic agents. Indian J. Chem. **29B,** 843–847.

Agarwal A., Agarwal S. K., Bhakuni D. S., Gupta S. and Katiyar J. C. (1990b), Antiparasitic agents: Part XIII. Synthesis and anthelmintic activity of 6- and 8-(2,4-dioxoquinazolin-3-yl)-1-substituted 9H-pyrido[3,4-b]-indoles, 6- and 8-(2-methyl-5-acetamidobenzimidazol-1-yl)-1-substituted 9H-pyrido[3,4-b]indoles and 6-[2-carbomethoxyamino-5-(N,N′-dicarbomethoxy)guanidinobenzimidazol-1-yl]-1-phenyl-9H-pyrido[3,4-b]-indole. Indian J. Chem. **29B,** 848–854.

Agarwal A., Agarwal S. K., Bhakuni D. S., Singh S. N. and Chatterjee R. K. (1993), Antiparasitic agents: Part XVI. Synthesis of 5(6)-substituted benzimidazole-2-carbamates as anthelmintic agents. Indian J. Chem. **32B,** 453–456.

Hawking F. and Sewell P. (1948), The maintenance of filarial infection *(Litomosoides carinii)* for chemotherapeutic investigations. British J. Pharmacol. **3,** 285–296.

Katiyar J. C., Visen P. K. S., Misra A., Gupta S. and Bhaduri A. P. (1984), Methyl 5(6)-[4-(2-pyridyl)-piperazinocarbomoyl]benzimidazole-2-carbamate, a new broad spectrum anthelmintic. Acta Tropica **41,** 279–286.

Kumar P., Agarwal S. K. and Bhakuni D. S. (1990), Antiparasitic agents: Part XI. Synthesis and anthelmintic activity of 6- and 8-[β-carbomethoxyamino)benzimidazole]-5-carbonylamino-1-substituted 9H-pyrido-[3,4-b]indoles. Indian J. Chem. **29B,** 1077–1080.

Lämmler G., Herzög H. and Schutze H. R. (1971), Chemotherapeutic studies on *Litomosoides carinii* infection in *M. natalensis.* I. The filarial action of 2,6-bisbenzimidazole. Bull. WHO **44,** 751–756.

Misra S., Chatterjee R. K. and Sen A. B. (1981), Antifilarial action of Furazolidone. Indian J. Med. Res. **73,** 725–728.

Sharma S. and Abuzar S. (1983), The benzimidazole anthelmintics, chemistry and biological activity. Prog. Drug Res. **27,** 85–161.

Townsend L. B. and Wise D. S. (1990), The synthesis and chemistry of certain anthelmintic benzimidazoles. Parasitology Today **6,** 107–112.

Worms M. J., Jerry R. J. and Terry A. (1961), *Dipetalonema witei,* filarial parasite of the Jirds *Meriones libycus.* I. Maintenance in the laboratory. J. Parasit. **47,** 963–970.

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