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*

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Antifilarial Activity, ß-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 (ß-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 viteae 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 D L-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 mm³ 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 sacrificed 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).
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. x 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 = C₆H₅, R¹ = R² = R³ = R⁴ = 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 l-phenyl-9H-pyrido[3,4-b]indoles (I).

<table>
<thead>
<tr>
<th>Compd.* No.</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>L. carinii 30 mg/kg×5 (i.p.)</th>
<th>A. viteae 50 mg/kg×5 (i.p.)</th>
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<tbody>
<tr>
<td></td>
<td>%Death</td>
<td></td>
<td>Sterl.</td>
<td></td>
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<tr>
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</table>

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 = R1 = R2 = R3 = R4 = 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 acetamide 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.
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