Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 313–314

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

# Secondary Amines as New Pharmacophores for Macrofilaricidal Drug Design†

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Received 24 March 1999; accepted 25 November 1999

**Abstract**—Several secondary amines exhibit promising macrofilaricidal response in vivo through oral route of administration against *Acanthocheilonema viteae* in which *N*-hexylcyclohexylamine (**1**) shows 100% macrofilaricidal activity while a tertiary amine such as **9** elicits predominantly microfilaricidal (93%) response. 

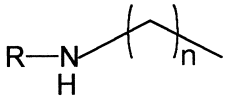
## Introduction

Filariasis contributes the highest morbidity of human population of many tropical and subtropical countries of the world.[1–4] More than 900 million people are directly exposed to the risk of filariasis[4] and for more than 50 years the chemotherapy of filariasis is based on the diethylcarbamazine (DEC) which kills the microfilariae but has no effect on the adult filarial worms.[5] The search for new molecular structures associated with macrofilaricidal activity as lead molecule is, therefore, needed.

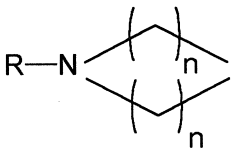
Design of the molecular framework of a new macrofilaricidal agent requires simulation of appropriate bioactive pharmacophore which is normally not projected in scientific publications. However, during the search of such chemical entities, we have been able to identify *N*-alkylamines as new pharmacophores for antifilarials and, in particular, the secondary amines fulfill the requirements for macrofilaricidal drug design to a greater extent. The details are presented here.

## Chemistry

The syntheses of *N*-mono (**1**–**6**) and *N*,*N*-dialkylamines (**7**–**9**) have been carried out using the procedure reported in the literature.[6]




**1-6**




**7-9**

## Antifilarial Activity

The micro- and macrofilaricidal activities of the synthesized compounds (**1**–**9**) are evaluated in vivo against *Acanthocheilonema viteae* in *Mastomys coucha*.[7] Compounds being insoluble in water are made fine suspension with 1% Tween 80. Two to three animals are used for each dose level study and at least two replicates are used for confirmation of activity.[7]

## Results and Discussion

The in vivo antifilarial activities of compounds **1**–**9** are given in Table 1. It is interesting to note that all the amines exhibit antifilarial activity against *A. viteae* at 200 mg/kg × 5 days by oral route and, in particular, the secondary amines show promising macrofilaricidal response while the tertiary amines elicit microfilaricidal action. For example, the most potent secondary amine is *N*-hexylcyclohexylamine (**1**) which exhibits 100% adulticidal activity while a tertiary amine such as *N*,*N*-dibutylcyclohexylamine (**9**) shows 93% microfilaricidal activity along with 50% sterilization of female worms.

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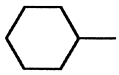
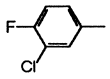
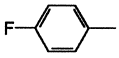
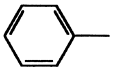
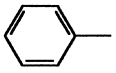
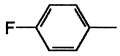
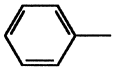
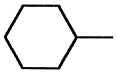
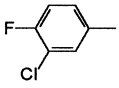
0960-894X/00/$ - see front matter 
PII: S0960-894X(99)00687-3

**Table 1.** Antifilarial in vivo activity of *N*-alkylamines (**1**–**9**) against *A. viteae* through oral route of administration at 200 mg/kg×5 days

| Compound | R | *n* | Activity (% reduction in parasites load) | | | Compound | R | *n* | Activity (% reduction in parasites load) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | mif[a] | maf[b] | Sterilization of ♀[c] | | | | mif | maf | Sterilization of O |
| **1** |  | 5 | 0 | 100 | 0 | **6** |  | 3 | 32 | 0 | 0 |
| **2** |  | 5 | 0 | 50 | 0 | **7** |  | 3 | 77 | 0 | 55 |
| **3** |  | 5 | 58 | 50 | 0 | **8** |  | 3 | 81 | 0 | 50 |
| **4** |  | 6 | 69 | 0 | 0 | **9** |  | 3 | 93 | 0 | 50 |
| **5** |  | 5 | 50 | 88 | 0 | DEC citrite | | | 90 | 0 | 0 |

[a]mif = microfilariae.
[b]maf = macrofilariae or adult worms.
[c]♀ = female worms, O = inactive.

Aromatic secondary amines do not show any significant activity except 3-chloro-4-fluoro-*N*-hexylaniline (**5**) which shows 88% macro- and 50% microfilaricidal activity while its *N*-butyl derivative **6** exhibits only 32% microfilaricidal activity. *N,N*-Dibutylaniline (**7**) shows 77% microfilaricidal activity along with 55% sterilization of female worms while its other derivatives such as *N*-hexyl (**3**) and *N*-heptylanilines (**4**) show only 58 and 69% microfilaricidal activity, respectively. In addition, the former also exhibits 50% adulticidal activity. *N,N*-dibutyl-4-fluoroaniline (**8**) shows 81% microfilaricidal and 50% death of female worms are also observed, whereas 4-fluoro-*N*-hexylaniline (**2**) elicits only 50% macrofilaricidal action.

The present study clearly indicates two results: (i) the secondary amines having longer alkyl chain ($n>5$) would be responsible for eliciting macrofilaricidal activity; (ii) the tertiary amines having dialkyl chain ($n=3$) show a vital role in predominantly microfilaricidal action. Therefore, it might be presumed that these functionalities would play a vital role during the designing of an antifilarial agent because amines could easily be incorporated in the selected molecular architecture.

## Acknowledgements

SKS is thankful to CSIR, New Delhi for the award of Senior Research Fellowship and grateful to RSIC, Lucknow for providing spectroscopic data.

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