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Syntheses and Antifilarial Profile of 7-Chloro-4-(substituted Amino) Quinolines: a New Class of Antifilarial Agents†

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Abstract—The syntheses of 7-chloro-4-(substituted amino) quinolines (**2**–**22**) and their antifilarial activities are delineated. Some of the screened compounds have shown promising filarial response and sterilization effect on female *Acanthocheilonema viteae* in rodents. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Problem associated with the chemotherapy of filariasis is the non-availability of non-toxic macrofilaricide or at least an agent which can sterilize filariae permanently and thus blocking the further transmission of infection.[1,2] Associated with this problem is the kinetics of the death of microfilariae (mf) which must not allow anaphylactic or side reactions. The candidate drug Diethylcarbamazine (DEC) which kills mf but has no effect on most of the adult filarial species and causes side effects.[3] No drug yet has been found to be effective against adult worms.[4,5] Therefore, R&D activities are involved for the search of a new molecular structure as macrofilaricidal or at least an sterilizing agent. In our earlier efforts in search for macrofilaricidal agent, we have explored 2,4,6-substituted triazines,[4] 5-amino and 5,8-diaminoisoquinolines,[6] aplysinopsin derivatives,[7] 1,1-dicyano-2-substituted-ethylenes,[8] 1,3-disubstituted pyrido indoles,[9] and quinolones.[10] Extensive work has been done on 4-aminoquinolines as antimalarials but no sincere efforts have been carried out in exploring this pharmacophore as antifilarial.

In this present work, we have explored, 4-aminoquinoline derivatives (**2**–**22**) as a new lead compounds in antifilarial chemotherapy. The design of these 7-chloro-4-(substituted amino) quinolines (**2**–**22**) is based on the observation that Amodiaquine exhibits strong therapeutic effect against adult forms of *L. carinii* in Mongolian gerbils[11,12] and other 4-aminoquinolines also exhibited antifilarial activity in vivo.[13] The details of the synthesis and antifilarial potential in vivo of adult *A. viteae* are reported here.

Chemistry

The synthetic strategy to obtain the molecular frame work of 7-chloro-4-(substituted amino) quinolines **2**–**22** can be divided into two (Schemes 1 and 2). Compounds **2**, **3** and **6** were prepared by reacting 4,7-dichloroquinoline **1** with appropriate amines in dry methanol. Nitration of compound **6** with fuming HNO_3 produced the nitro derivative **7**. The compound **6** was reacted at 0 °C with $SOCl_2$ in dry benzene to furnish compound **8**. This could be made to react with excess anhydrous piperazine in dry methanol to furnish mono-substituted derivative **11**. Compounds **9**, **10** and **12** were obtained by refluxing the mixture of **8** with *para*-substituted phenols and substituted piperazine respectively, in dry DMF: K_2CO_3 in a ratio 1:1. Elaboration of compound **11** was carried out by coupling with *N*-Boc aminoacids in presence of HOBT and DCC to yield compound **13**–**17** and their deprotection by 50% trifluoroacetic acid in methylene chloride gave compounds **18**–**22**. Bisquinolines **4** and **5** were obtained by refluxing compound **1** with 1,4-diaminobutane and L-Lysine hydrochloride in presence of triethylamine and *N*-methyl pyrrolidene-2 as solvent in a ratio of 2:1:2 respectively. All the compounds were characterized by spectroscopic analysis.[14]

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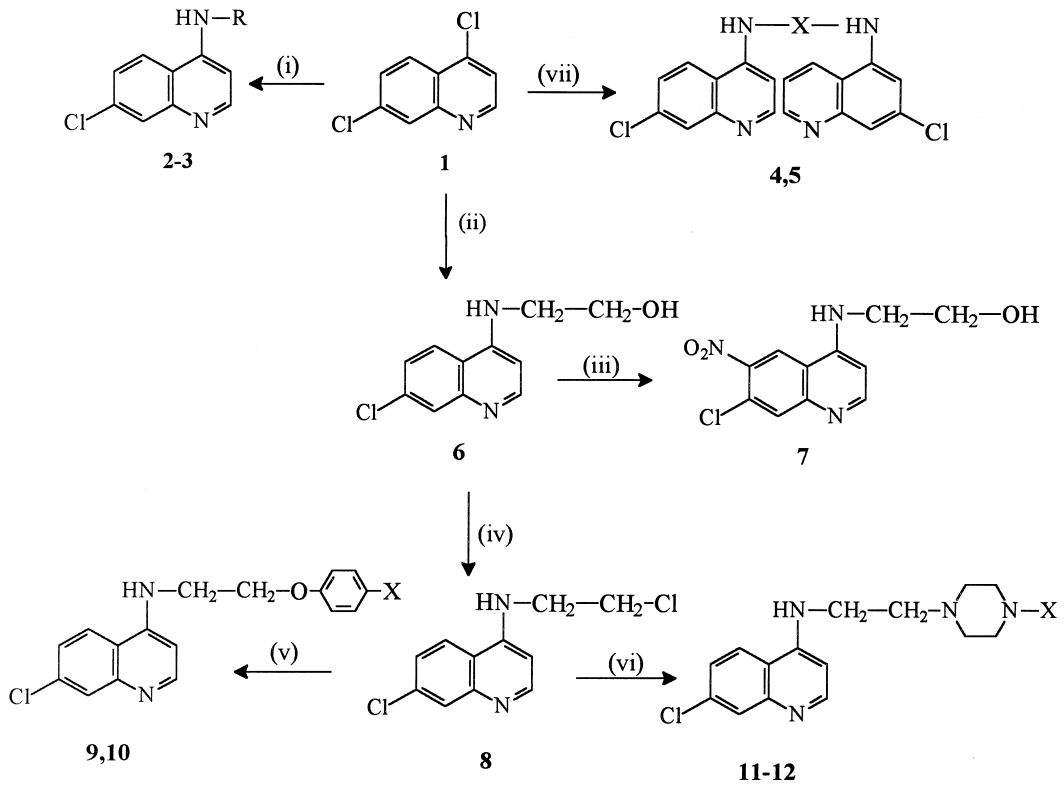
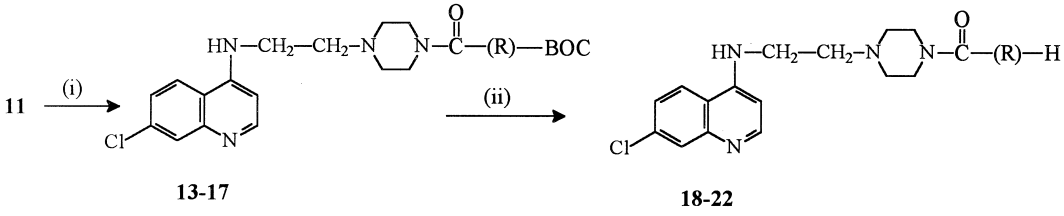


Scheme 1. Reagents and conditions: (i) Primary amines, dry methanol, reflux; (ii) Ethanolamine, reflux, NaOH; (iii) Concd H_2SO_4, fuming HNO_3, stirring at 0 °C, liquid. Ammonia; (iv) $SOCl_2$, stirring at 0 °C, Dry benzene, NH_4OH; (v) Dry DMF, K_2CO_3, substituted phenol, reflux; (vi) Dry Methanol/Dry DMF, K_2CO_3, substituted Piperazine; (vii) Diamines, *N*-methylpyrrolidone, Et_3N, reflux.



Scheme 2. Reagents and conditions: (i) Dry DMF, DCC, HOBT, *N*-Boc (Gly, Ala, Phe, Ile, Pro), Stirring at 0 °C; (ii) CF_3CO_2H, CH_2Cl_2, ether, stirring at room temperature.

Material and methods

The micro- and macrofilariacidal activities of the synthesised compounds were evaluated in vivo against *A. viteae* infection in *Mastomys natalensis*.[15] Compounds being insoluble in water were made fine suspension with 1% Tween 80. Two of the three animals were used for each dose level studied and at least two replicates were used for confirmation of activity.

Results and Discussion

All the synthesised compounds (**2**–**7**, **9**–**22**) were examined in vivo against *A. viteae* but only nine compounds **2**, **4**, **5**, **6**, **7**, **9**, **13**, **15** and **19** were found active (Tables 1 and 2).

Compound **2** having nitrophenyl hydrazine group at position 4 of quinoline ring has maximum 78% adulticidal activity along with 50% sterilization of female worms. Compound **19** has shown maximum sterilization (100%) of female worms. Compound **5** having aminoacid L-Lysine has 85% microfilaricidal and compound **6** having ethanolamine has 86% microfilaricidal activity along with 22% adulticidal activity, respectively. Whereas incorporation of NO_2 group in compound **6** enhanced its adulticidal activity (**7**, 58%). Compound **9** having *p*-cyano phenoxy group has 56% adulticidal activity while compound **10** having *p*-nitro phenoxy group is inactive. Compound **4** (bisquinoline) having simple 1,4 diamino butane is 47% adulticidal, while compound **5** (bisquinoline) having aminoacid L-Lysine is 85% microfilaricidal. Compound **11** and **12** are inactive, while exploring compound **11** to furnish Boc-protected glycine, i.e., **13** has shown 63% sterilization whereas **15** and **19** has shown

Table 1.

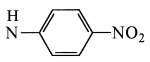
Compound	R	Compound	R
2		**12**	
3		**13**, **18**	CH_2—NH
4	$(CH_2)_4$	**14**, **19**	
5		**15**, **20**	
9		**16**, **21**	
10	NO_2	**17**, **22**	
11	H		

Table 2. Antifilarial in vivo activity of 7-chloro-4-substituted aminoquinolines (**2**–**22**) against *A. viteae* at 200 mg/kg×5 days (po)

Compound[a]	Antifilarial activity (% reduction in parasite load)		
	Mif.	Maf.	Sterl. of ♀
2	41	78	50
4	0	47	0
5	85	0	0
6	86	22	0
7	0	58	0
9	0	56	0
13	0	0	63
15	0	0	50
19	0	0	100
DEC[b] citrate	90	0	0

[a]Inactive compounds are not listed here; mif = microfilariae; maf. = macrofilariae; sterl. = sterilization; ♀ = female worms; O = inactive.
[b]DEC = Diethylcarbamazine (Standard Antifilarial Drug).

50% and 100% sterilization, respectively. One interesting observation is that among the modified peptide derivatives of quinoline **13**–**22** only three compounds i.e., **13**, **15** and **19** were found active and that also in sterilization only. From the SAR of the 4-(substituted amino) analogues, we can conclude that nitrophenyl hyrazaine at position 4 of quinoline ring plays an important role in eliciting biological response against *A. viteae* and the compound **2**, **4**, **5**, **9**, **13**–**22** having bulky substitution at 4th position of quinoline ring were found active as antifilarials. The novel modified peptide derivative of quinoline having Boc-protected glycine **13**, Boc-protected phenylalanine **15** and Boc-free alanine **19** showed good sterilization of female worms which provides useful lead to conduct further modification to generate sterilizing agent to combat filarial infection. Therefore, there is need of reevaluation of 7-chloro-4-(substituted amino) quinolines as well as bisquinolines as antifilarials.

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14. Spectroscopic data for representative compounds **2**: yield 63%; mp 215°C (dec.); MS: *m*/*z* (M^+ +2, 316,Cl^{37}), (M^+ 314, Cl^{35}) ; IR (KBr): 3442, 3151, 2750, 1510, 1332, 1109, 839 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 9.80 (bs, 1H, NH), 8.71 (d,1H, *J* = 8Hz). 8.50 (d, 1H, *J* = 8Hz), 8.19 (d, 1H, *J* = 10Hz), 7.95 (bs, 1H, NH), 7.68 (d, 1H, *J* = 10 Hz), 7.04–6.93 (m, 4H). **5**: yield 46%, mp 262° (dec), FAB MS: *m*/*z* 492 [M + Na^+], 470 [M + H]$^+$; IR (KBr): 3370, 3228, 3060, 1635, 1609, 1455, 1205, 858 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6): δ 8.56 (bs, 1H, NH), 8.44–8.36 (m, 4H), 7.83–7.80 (m, 2H), 7.55–7.45 (m, 2H), 6.63 (d, 1H, *J* = 6.6 Hz), 6.44 (d, 1H, *J* = 6Hz), 4.25–4.23 (m, 1H, NH), 2.49–2.47 (m, 1H, CH), 2.49–2.47 (m, 2H), 2.08–2.97 (m, 2H), 1.77–1.49 (m, 4H); 9: yield 83%; mp 178 °C; MS: *m*/*z* (M^{+} +2, 325, Cl^{37}), (M^+ 323, Cl^{35}); IR (KBr): 3840, 3269, 3068, 2925, 2360, 2225,1579, 1506,1452, 1253, 1051, 837 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$); δ 8.80 (d, 1H, *J* = 6Hz), 8.17 (d, 1H, *J* = 4.8 Hz), 8.07 (d, 1H, *J* = 1.2 Hz), 7.60 (t, 2H, *J* = 2.8 Hz), 7.26 (t, 1H, *J* = 8Hz), 7.19–6.89 (m, 2H), 6.74 (d, 1H, *J* = 6 Hz), 4.85 (bs, 1H, NH), 4.53 (t, 2H, *J* = 4Hz, OCH_2), 4.07 (t, 2H, *J* = 4Hz, NCH_2), **13**: yield 76%, mp 201 °C, FAB MS: *m*/*z* 448 [M + H] $^+$; IR (KBr): 3754, 3340, 2290, 2877, 1706, 1620, 1456, 1166, 1020 cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$): δ 8.53 (d, 1H, *J* = 6Hz), 7.97 (d, 1H, *J* = 2Hz), 7.75 (d, 1H, *J* = 10 Hz), 7.66 (d, 1H, *J* = 8 Hz), 6.39 (d, 1H, *J* = 4 Hz), 5.84 (bs, 1H, NH), 5.50 (bs, 1H, NH), 3.86 (dd, 2H, *J* = 6, 12 Hz, CH_2), 3.35 (t, 4H, *J* = 6 Hz, NCH_2), 2.81 (t, 2H, *J* = 6 Hz, CH_2), 2.55 (d, 4H, *J* = 4.4 Hz, NCH_2), 1.45 [s, 9H, O-C(CH_3)$_3$], 1.12 (t, 2H, *J* = 6Hz, $COCH_2$), 19: Yield 47%, mp 115 °C (dec); FABMS:

m/*z* 362 $[M+H]^+$; IR (KBr): 3816, 3759, 3149, 1631, 1406, 1074, 1029 cm^{-1}; ^1H NMR (200 MHz, D_2O): 8.26 (d, 1H, $J=7.2$ Hz), 8.25 (d, 1H, $J=10$ Hz), 7.73 (d, 1H, $J=2$Hz), 7.59–7.49 (m, 1H), 6.73 (d, 1H, $J=7.2$ Hz), 4.44–4.37 (m, 1H, COCH), 3.96 (t, 2H, $J=9$Hz, NCH_2), 3.79–3.27 (m, 10H, NCH_2, $NHCH_2$), 1.43–1.18 (m, 3H, CH_3).

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