Brief Articles

Quinolones: Novel Probes in Antifilarial Chemotheraphy[+,⊥]

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Quinolones have been discovered in our laboratory as a new class of antifilarial agents. This has led to the design, synthesis, and antifilarial evaluation of a number of N-substituted quinol-4(1*H*)-one-3-carboxamide derivatives **4**−**6**. The macrofilaricidal activity of the target compounds was initially evaluated in vivo against *Acanthoeilonema viteae* by oral administration of 200 mg/kg × 5 days. Among all the synthesized compounds, 13 displayed activity, with the most potent compound (**4a**) exhibiting 100% macrofilaricidal and 90% microfilaricidal activities. Compound **4e** elicited significant macrofilaricidal (80%) response while compound **5c** showed 100% sterilization of female worms. Finally, the two most potent macrofilaricidal compounds, namely **4a** and **4e**, have been screened for their potency against DNA topoisomerase II, and it has been observed that both have the capability to interfere with this enzyme at 10 μmol/mL concentration. The structure−activity relationship (SAR) associated with position-3 and aryl ring substituents is discussed.

Introduction

The chemotherapy of filariasis is not possible due to the nonavailability of macrofilaricidal agents.[1−6] The age-old drug diethyl carbamazine (DEC) removes almost all the microfilariae from the blood stream and has a lethal effect on the adult worms.[6] Ivermectin is highly effective in reducing microfilariae, but it does not irreversibly damage the adult filarial worms.[6] As a result, in 1995 the World Health Organization (WHO) adopted a goal to develop a nontoxic macrofilaricidal agent, or at least an agent which could sterilize filariae permanently.[7] Such an agent would block further transmission of infection, and to this end a screening program based on *Acanthoeilonema viteae* infection was initiated.[7] In a continuation of our earlier studies toward the search for a potential macrofilaricidal agent,[1,3,5] we have developed a range of quinolones as a new class of antifilarial agents. The details of the design, synthesis, and antifilarial evaluation of this study are presented here.

Recently, the presence of ATP-dependent DNA topoisomerase II activity in the filarial parasites has been demonstrated in our laboratory.[8,9] As yet the effect of chemotherapeutic agents on this newly discovered biochemical target site has not been extensively explored, although bacterial DNA topoisomerase II inhibitors, and particular quinolone antibacterials, have shown an ability to inhibit this enzyme in filarial parasites.[10] To ascertain the actual utility of quinolone in the filarial chemotherapy, potent compounds are required. However, the optimal structural requirements for potent macrofilaricidal activity have not yet been determined, and therefore, in order to define the structural modification important for activity, it was considered essential to evaluate N-substituted quinol-4(1*H*)-one-3-carboxamides (Figure 1).

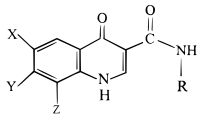

Figure 1.

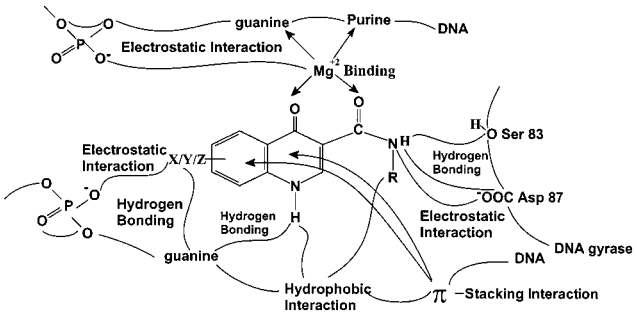

Figure 2. Proposed DNA gyrase-N-substituted quinol-4(1*H*)-one-3-carboxamide interaction model.

The prototype N-substituted quinol-4(1*H*)-one-3-carboxamides (Figure 1) have been envisaged to interact in biophase, mimicking the model proposed for bacterial DNA gyrase (DNA topoisomerase II)−quinolone interactions published previously.[11] The hypothetical picture of this interaction is presented in Figure 2. The main concern of this model is to view the quinolone derivative in a three-dimensional structure after its binding with magnesium. It is apparent that a large number of factors contribute to this picture; however, the key

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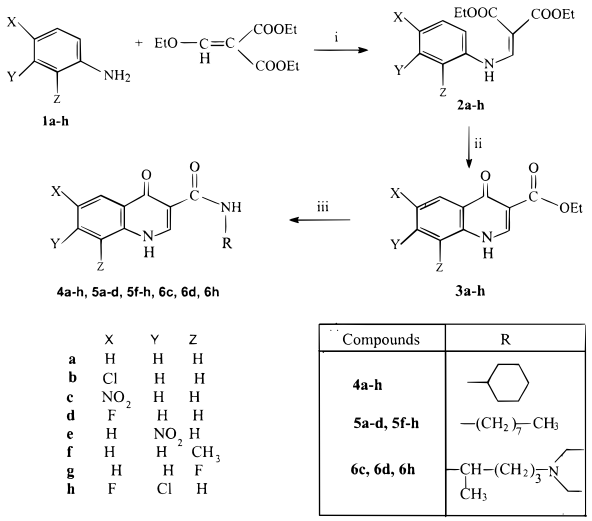
Scheme 1[a]



[a] Reagents and conditions: (i) neat; (ii) Dowtherm in a ratio 1:10 with the solvent, reflux, 250 °C; (iii) amine (RNH_2), pyridine, 125 °C, under pressure.

points of concern for the present study are π-stacking interactions of the heterocyclic nucleus and the interaction of the amide nitrogen with the receptor.

Chemistry

The synthetic strategy for constructing the molecular framework of quinolone ring **3a**−**h** is outlined in Scheme 1. First diethyl ethoxymethylenemalonate was reacted with the anilines **1a**−**h** to yield the corresponding enamine diesters[12] **2a**−**h**. This was followed by thermal cyclization in Dowtherm in a ratio of 1:10 with the solvent at 250 °C to afford ethyl quinol-4(1*H*)-one-3-carboxylates[13] **3a**−**h**. Compounds **3a**−**h** were treated separately with primary amines (RNH_2) in pyridine in a steel bomb at 125 °C to furnish their respective N-substituted quinol-4(1*H*)-one-3-carboxamides **4a**−**h**, **5a**−**d**, **5f**−**h**, **6c**, **6d**, and **6h** (Scheme 1).

Antifilarial Evaluation

All the synthesized componds **4**−**6** were evaluated for their antifilarial activity in vivo against *A. viteae* at 200 mg/kg × 5 days by oral administration (po). The model used in this experiment was *Mastomys coucha* since this model has been recommended by WHO for the experimental chemotherapy of filariasis.[7,14] The antifilarial activities of N-substituted quinol-4(1*H*)-one-3-carboxamides **4**−**6** against *A. viteae* are summarized in Table 1. The effect of compounds **4a** and **4e** on DNA topoisomerase II of filarial parasite was assessed at 10 μmol/mL concentration.

Results and Discussion

The micro- and macrofilaricidal activities in quinol-4(1*H*)-ones with various substituents at position-3 and in the aromatic ring were monitored as follows. With a particular substituent at position-3, the effect of various substituent in the aromatic ring of quinol-4(1*H*)-ones was monitored.

Among the *N*-cyclohexylquinol-4(1*H*)-one-3-carboxamide derivatives **4a**−**h**, the most potent compound was the one with no substituent on the aromatic ring (**4a**). It exhibited 100% macro- and 90% microfilaricidal activities. This compound was also the most potent compound among all the N-substituted quinol-4(1*H*)-one-3-carboxamides in the present study. Introduction of a nitro group at position-6 in this compound resulted compound **4c**, which showed only 54% microfilaricidal response. However, the introduction of a nitro group at position-7 (**4e**) resulted in 80% macrofilaricidal activity and 24% microfilaricidal effect. It was interesting to note that *N*-cyclohexyl 6-fluoroquinol-4(1*H*)-one-3-carboxamide (**4d**) showed 50% micro- and 31% macrofilaricidal activities along with 36% sterilization of female worms. The methyl group at position-8 in cyclohexyl quinol-4(1*H*)-one-3-carboxamide (**4f**) was less effective since it showed only 54% microfilaricidal activity. The other compounds of this series such as *N*-cyclohexyl 6-chloro (**4b**), 8-fluoro (**4g**), and 7-chloro 6-fluoro (**4h**) quinol-4(1*H*)-one-3-carboxamides did not elicit any antifilarial activity.

Unlike the *N*-cyclohexyl quinol-4(1*H*)-one-3-carboxamide series (**4a**−**h**), among *N*-octyl quinol-4(1*H*)-one-3-carboxamides (**5a**−**d**, **5f**−**h**), the most active derivative was N-octyl 6-nitroquinol-4(1*H*)-one-3-carboxamide (**5c**). Compound **5c** exhibited 100% sterilization of female worms along with 40% micro- and 38% macrofilaricidal activities. The compound with no substituent in its aromatic ring (**5a**) produced insignificant microfilaricidal (25%) activity. Substituents such as chloro (**5b**) or fluoro (**5d**) at position-6 did not produce any significant antifilarial response, with **5b** exhibiting 50% macro- and 30% microfilaricidal activities while compound **5d** showed 48% microfilaricidal activity only. The compound with a fluoro group at position-8 (**5g**) showed 47% macro- and 37% microfilaricidal activities along with 25% sterilization of female worms while the corresponding methyl derivative **5f** caused insignificant microfilaricidal (17%) response. Compound **5h** failed to elicit any antifilarial response.

None of the *N*-(*N*′,*N*′-diethylamino-1′-methyl)butyl quinol-4(1*H*)-one-3-carboxamide series (**6c**, **6d**, **6h**) showed any interesting antifilarial activity. For example, compounds **6c** and **6h** exhibited only 54% and 60% microfilaricidal activity, respectively.

Table 1. Antifilarial in Vivo Activity of N-Substituted Quinol-4(1*H*)-one-3-carboxamides **4**−**6** against *A. vteae* at 200 mg/kg × 5 days (po)

	antifilarial activity[b] (% reduction in parasites load)		
compound[a]	mif.	maf.	sterl. of ♀
4a	90	100	NA
4c	54	0	0
4d	50	31	36
4e	24	80	0
4f	54	0	0
5a	25	0	0
5b	30	50	0
5c	40	38	100
5d	48	0	0
5f	17	0	0
5g	37	47	25
6c	54	0	0
6h	60	0	0
DEC[c] citrate	90	0	0

[a] Inactive compounds are not listed here. [b] mif. = microfilariae; maf. = macrofilariae; sterl. = sterilization; ♀ = female worms; NA = not applicable; 0 = inactive. [c] DEC = diethylcarbamazine (standard antifilarial drug).

The most potent macrofilaricidal compounds, namely **4a** and **4e**, were screened for their DNA topoisomerase II activity at 10 μmol/mL concentration. Compound **4a** displayed >80% enzyme inhibition while compound **4e** exhibited >70% inhibitory activity. These data clearly indicate that both compounds have the capability to interact with filarial DNA topoisomerase II and could provide an important tool for future drug design.

However, the highlight of the present study was the discovery of quinol-4(1*H*)-one-3-carboxamides as a new class of antifilarial agents. For the macrofilaricidal efficacy in particular, the optimum pharmacophoric requirement of the substituent on the amide nitrogen was the cyclohexyl moiety. Studies are now underway to further explain the SAR of this series and generate compounds with improved potency.

Experimental Section

Chemistry. The compounds were routinely checked for their purity by thin-layer chromatography (TLC) on silica gel G. R_f values were determined using 4% MeOH−$CHCl_3$. Visualization was achieved by I_2 vapor. Column chromatography separations were carried out on Merck silica gel (230−400 mesh), and the eluent was 0.5−1% MeOH−$CHCl_3$. Melting points (mp) were determined in capillary tubes on an electrothermal melting point Toshiniwal CL-03001 apparatus and are uncorrected. Infrared (IR) spectra were run on a Beckman-Acculab-10 spectrophotometer (ν_{max} in cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded on either Bruker-400-FT or 300-FT or 200-FT instruments, and chemical shifts (δ in ppm) were reported relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.23 ppm, and DMSO in DMSO-d_6 at 2.49 ppm) or TMS. Signals were designated as follows: s, singlet; bs, broad signal; d, doublet; t, triplet; m, multiplet. EI mass spectra were recorded on a JEOL-JMS-D-300 spectrometer. Chemical analyses were carried out on a Carlo-Erba EA 1108 elemental analyzer. Reagents and solvents were purchased from commercial suppliers and used as received. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated with a Buchi rotary evaporator at low pressure. Yields were of purified product and were not optimized.

***N*-Cyclohexyl Quinol-4(1*H*)-one-3-carboxamide (4a).** A solution of ethyl quinol-4(1*H*)-one-3-carboxylate (**3a**) (0.55 g, 2.5 mmol) and cyclohexylamine (0.3 mL, 2.62 mmol) in pyridine (1.5 mL) was heated at 125 °C in a steel bomb for 30 h. The reaction mixture was then poured in water and extracted with chloroform (3 × 100 mL). The chloroform extract was washed by water, dried over Na_2SO_4, and concentrated to furnish an oil which was washed by hexane and after purification afforded **4a**: 0.37 g (53.1%); R_f 0.84; mp 46 °C; IR (KBr) 2930, 1642, 1202, 706 cm^{-1}; MS *m*/*z* 270 (M); ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.55 (d, 1H, J = 7.7 Hz, NH), 8.95 (s, 1H, H-2), 8.43 (d, 1H, J = 7.9 Hz, ArH), 7.71−7.41 (m, 3H, ArH), 4.08 (bs, 1H, N-CH), 2.14−1.36 (m, 10H, CH_2). Anal. ($C_{16}H_{18}N_2O_2$) C, H, N.

***N*-Cyclohexyl 6-Chloroquinol-4(1*H*)-one-3-carboxamide (4b).** Reaction of ethyl 6-chloroquinol-4(1*H*)-one-3-carboxylate (**3b**) (0.76 g, 3 mmol) and cyclohexylamine (0.4 mL, 3.5 mmol) in pyridine (2.5 mL) using a procedure identical to that described for **4a** furnished **4b**: 0.45 g (48.8%); R_f 0.76; mp 52 °C; IR (KBr) 2916, 1652, 1252, 730 cm^{-1}; MS *m*/*z* 304 (M); ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.48 (d, 1H, J = 6.6 Hz, NH), 8.94 (d, 1H, J = 7.2 Hz, H-2), 8.40 (s, 1H, ArH), 7.69−7.53 (m, 2H, ArH), 4.15 (bs, 1H, N-CH), 2.28−1.45 (m, 10H, CH_2). Anal. ($C_{16}H_{17}ClN_2O_2$) C, H, N.

***N*-Cyclohexyl 6-Nitroquinol-4(1*H*)-one-3-carboxamide (4c).** A solution of ethyl 6-nitroquinol-4(1*H*)-one-3-carboxylate (**3c**) (0.48 g, 1.83 mmol) in pyridine (1 mL) and cyclohexylamine (0.2 mL, 1.9 mmol) was reacted as for **4a** to afford **4c**: 0.35 g (60.8%); R_f 0.78; mp 48 °C; IR (KBr) 3030, 2931, 1645, 1215, 759 cm^{-1}; MS *m*/*z* 315 (M); ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.18 (bs, 1H, NH), 10.16 (d, 1H, J = 6.0 Hz, NH), 9.30 (s, 1H, H-2), 8.89 (s, 1H, ArH), 8.46 (d, 1H, J = 4 Hz, ArH), 7.76 (d, 1H, J = 6.0 Hz, ArH), 4.08 (bs, 1H, N-CH), 2.10−1.92 (m, 2H, CH_2), 1.86−1.74 (m, 2H, CH_2), 1.48−1.28 (m, 6H, CH_2). Anal. ($C_{16}H_{17}N_3O_4$) C, H, N.

***N*-Cyclohexyl 6-Fluoroquinol-4(1*H*)-one-3-carboxamide (4d).** Compound **4d** was prepared from ethyl 6-flouroquinol-4(1*H*)-one-3-carboxylate (**3d**) (0.58 g, 2.47 mmol) and cyclohexylamine (0.3 mL, 2.62 mmol) in pyridine (1.5 mL) by following the method as described for **4a**: 0.43 g (61.5%). R_f 0.79; mp 41 °C; IR (KBr) 3018, 2935, 1647, 1215, 758 cm^{-1}; MS *m*/*z* 289 (M + 1), 288 (M); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.41 (d, 1H, J = 6.0 Hz, NH), 8.80 (s, 1H, H-2), 8.09 (m, 1H, ArH), 7.66−7.36 (m, 2H, ArH), 4.05 (bs, 1H, N-CH), 1.98−1.90 (m, 2H, CH_2), 1.79−1.42 (m, 4H, CH_2), 1.35−1.11 (m, 4H, CH_2). Anal. ($C_{16}H_{17}FN_2O_2$) C, H, N.

***N*-Cyclohexyl 7-Nitroquinol-4(1*H*)-one-3-carboxamide (4e).** Ethyl 7-nitroquinol-4(1*H*)-one-3-carboxylate (**3e**) (0.50 g, 1.90 mmol) was treated with cyclohexylamine (0.24 mL, 2.20 mmol) in pyridine (1.5 mL) as for **4a** to provide **4e**: 0.33 g (54.8%); R_f 0.68; mp 63 °C; IR (KBr) 3020, 2934, 1636, 1350, 788 cm^{-1}; MS *m*/*z* 315 (M); ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6) δ 9.89 (d, 1H, J = 7.8 Hz, NH), 8.88 (d, 1H, J = 6.5 Hz, H-2), 8.55−8.45 (m, 2H, ArH), 8.26−8.11 (m, 1H, ArH), 3.99 (bs, 1H, N-CH), 2.25−1.04 (m, 10H, CH_2). Anal. ($C_{16}H_{17}N_3O_4$) C, H, N.

***N*-Cyclohexyl 8-Methylquinol-4(1*H*)-one-3-carboxamide (4f).** By a procedure similar to that for **4a**, compound **4f** was obtained from ethyl 8-methylquinol-4(1*H*)-one-3-carboxylate (**3f**) (0.50 g, 2.17 mmol) and cyclohexylamine (0.30 mL, 2.60 mmol) in pyridine (1.0 mL): 0.38 g (61.6%); R_f 0.89; mp 56 °C; IR (KBr) 3010, 2928, 1632, 1200, 760 cm^{-1}; MS *m*/*z* 281 (M − 3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.11 (bs, 1H, NH), 10.35 (d, 1H, J = 8.0 Hz, NH), 8.91 (d, 1H, J = 6.6 Hz, H-2), 8.26 (d, 1H, J = 8.0 Hz, ArH), 7.48 (d, 1H, J = 7.0 Hz, ArH), 7.31 (t, 1H, J = 8.8 Hz, ArH), 3.99 (bs, 1H, N-CH), 2.59 (s, 3H, CH_3), 2.22−1.38 (m, 10H, CH_2). Anal. ($C_{17}H_{20}N_2O_2$) C, H, N.

***N*-Cyclohexyl 8-Fluoroquinol-4(1*H*)-one-3-carboxamide (4g).** Ethyl 8-flouoroquinol-4(1*H*)-one-3-carboxylate (**3g**) (0.50 g, 2.13 mmol) and cyclohexylamine (0.3 mL, 2.62 mmol) in pyridine (1.5 mL) were reacted in a manner similar to that described under **4a** to afford **4g**: 0.35 g (57.6%); R_f 0.74; mp 55 °C; IR (KBr) 3012, 2928, 1652, 1360, 774 cm^{-1}; MS *m*/*z* 286 (M − 2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.25 (d, 1H, J = 7.8 Hz, NH), 9.90 (s, 1H, H-2), 8.17−8.02 (m, 1H, ArH), 7.49−7.35 (m, 2H, ArH), 4.20 (bs, 1H, N-CH), 1.95−1.73 (m, 2H, CH_2), 1.60−1.25 (m, 8H, CH_2). Anal. ($C_{16}H_{17}FN_2O_2$) C, H, N.

***N*-Cyclohexyl 7-Chloro-6-fluoroquinol-4(1*H*)-one-3-carboxamide (4h).** Ethyl 7-chloro-6-flouoroquinol-4(1*H*)-one-3-carboxylate (**3h**) (0.58 g, 2.15 mmol) and cyclohexylamine (0.25 mL, 2.20 mmol) in pyridine (1.5 mL) were reacted as for **4a** to afford **4h**: 0.39 g (56.6%); R_f 0.65; mp 49 °C; IR (KBr) 3066, 2929, 1647, 1253, 798 cm^{-1}; MS *m*/*z* 322 (M); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (s, 1H, H-2), 8.16 (d, 1H, J = 9.0 Hz, ArH), 7.77 (d, 1H, J = 6.0 Hz, ArH), 4.08 (bs, 1H, N-CH), 2.04−2.01 (m, 2H, CH_2), 1.81−1.78 (m, 2H, CH_2), 1.63−1.47 (m, 2H, CH_2), 1.39−1.26 (m, 2H, CH_2). Anal. ($C_{16}H_{16}FClN_2O_2$) C, H, N.

***N*-Octyl Quinol-4(1*H*)-one-3-carboxamide (5a).** Compound **3a** (0.55 g, 2.5 mmol) and *n*-octylamine (0.50 mL, 3.2 mmol) in pyridine (1.5 mL) were treated as for **4a** to provide **5a**: 0.47 g (61.4%); R_f 0.82; mp 59 °C; IR (KBr) 3008, 2926, 1640, 1210, 702 cm^{-1}; MS *m*/*z* 300 (M); ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.56 (t, 1H, J = 5.4 Hz, NH), 8.89 (d, 1H, J = 6.6 Hz, H-2), 8.43 (d, 1H, J = 8.0 Hz, ArH), 7.63−7.40 (m, 3H, ArH), 3.53 (m, 2H, N-CH_2), 1.73−1.22 (m, 12H, CH_2), 0.8 (t, 3H, J = 6.2 Hz, CH_3). Anal. ($C_{18}H_{24}N_2O_2$) C, H, N.

***N*-Octyl 6-Chloroquinol-4(1*H*)-one-3-carboxamide (5b).** In a manner similar to the preparation of **4a**, compound **5b** was obtained from compound **3b** (0.8 g, 3.19 mmol) and *n*-octylamine (0.58 mL, 3.0 mmol) in pyridine (2.0 mL): 0.47 g (43.9%); R_f 0.69; mp 57 °C; IR (KBr) 3018, 2958, 1680, 1210, 830 cm^{-1}; MS *m*/*z* 300 (M − Cl + 1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.39 (bs, 1H, NH), 8.82 (s, 1H, H-2), 8.51 (s, 1H,

ArH), 7.62−7.52 (m, 2H, ArH), 3.51 (m, 2H, N-CH_2), 1.66−1.25 (m, 12H, CH_2), 0.86 (m, 3H, CH_3). Anal. ($C_{18}H_{23}ClN_2O_2$) C, H, N.

***N*-Octyl 6-Nitroquinol-4(1*H*)-one-3-carboxamide (5c).** Compound **3c** (0.48 g, 1.83 mmol) was reacted with *n*-octylamine (0.3 mL, 1.9 mmol) in pyridine (1.0 mL) as described for **4a** to afford **5c**: 0.42 g (66.7%); R_f 0.70; mp 51 °C; IR (KBr) 3118, 2925, 1651, 1494, 758 cm^{-1}; MS *m*/*z* 345 (M); ^1H NMR (400 MHz, $CDCl_3$) δ 12.06 (bs, 1H, NH), 10.56 (t, 1H, J = 3.0 Hz, NH), 8.72 (s, 1H, H-2), 7.59 (s, 1H, ArH), 7.44 (d, 1H, J = 6.0 Hz, ArH), 7.02 (m, 1H, ArH), 3.49 (m, 2H, N-CH_2), 1.64−1.23 (m, 12H, CH_2), 0.85 (t, 3H, J = 4.0 Hz, CH_3). Anal. ($C_{18}H_{23}N_3O_4$) C, H, N.

***N*-Octyl 6-Fluoroquinol-4(1*H*)-one-3-carboxamide (5d).** By an analogous procedure as described for **4a**, compound **5d** was obtained from compound **3d** (0.68 g, 2.89 mmol) and *n*-octylamine (0.50 mL, 3.2 mmol) in pyridine (1.5 mL): 0.64 g (69.3%); R_f 0.72; mp 43 °C; IR (KBr) 3080, 2929, 1647, 1533, 752 cm^{-1}; MS *m*/*z* 318 (M); ^1H NMR (400 MHz, $CDCl_3$) δ 12.30 (bs, 1H, NH), 10.18 (bs, 1H, NH), 9.28 (s, 1H, H-2), 8.91 (s, 1H, ArH), 8.46 (d, 1H, J = 10.0 Hz, ArH), 7.76 (d, 1H, J = 10.0 Hz, ArH), 3.50 (m, 2H, N-CH_2), 1.90−1.58 (m, 4H, CH_2), 1.50−1.08 (m, 8H, CH_2), 0.88 (t, 3H, J = 5.0 Hz, CH_3). Anal. ($C_{18}H_{23}FN_2O_2$) C, H, N.

***N*-Octyl 8-Methylquinol-4(1*H*)-one-3-carboxamide (5f).** In an analogous procedure as described for **4a**, compound **5f** was obtained from compound **3f** (1.0 g, 4.34 mmol) and *n*-octylamine (0.80 mL, 5.0 mmol) in pyridine (3.0 mL): 0.81 g (59.5%); R_f 0.82; mp 48 °C; IR (KBr) 3020, 2934, 1686, 1644, 774 cm^{-1}; MS *m*/*z* 314 (M); ^1H NMR (200 MHz, $CDCl_3$) δ 10.27 (t, 1H, J = 5.4 Hz, NH), 8.79 (d, 1H, J = 6.9 Hz, H-2), 8.11 (d, 1H, J = 7.7 Hz, ArH), 7.36 (d, 1H, J = 6.8 Hz, ArH), 7.19 (t, 1H, J = 7.8 Hz, ArH), 3.32 (m, 2H, N-CH_2), 2.37 (s, 3H, CH_3), 1.51−1.15 (m, 12H, CH_2), 0.77 (t, 3H, J = 6.3 Hz, CH_3). Anal. ($C_{19}H_{26}N_2O_2$) C, H, N.

***N*-Octyl 8-Fluoroquinol-4(1*H*)-one-3-carboxamide (5g).** In a manner similar to the preparation of **4a**, compound **5g** was prepared from compound **3g** (0.65 g, 2.77 mmol) and *n*-octylamine (0.56 mL, 3.4 mmol) in pyridine (1.5 mL): 0.48 g (53.8%); R_f 0.66; mp 54 °C; IR (KBr) 3040, 2982, 1680, 1416, 764 cm^{-1}; MS *m*/*z* 318 (M); ^1H NMR (200 MHz, $CDCl_3$) δ 10.20 (t, 1H, J = 4.9 Hz, NH), 8.98 (d, 1H, J = 6.4 Hz, H-2), 8.19−8.15 (m, 1H, ArH), 7.46−7.33 (m, 2H, ArH), 3.48 (m, 2H, N-CH_2), 2.23−2.17 (m, 2H, CH_2), 1.67−1.60 (m, 2H, CH_2), 1.56−1.24 (m, 8H, CH_2), 0.85 (t, 3H, J = 6.2 Hz, CH_3). Anal. ($C_{18}H_{23}FN_2O_2$) C, H, N.

***N*-Octyl 7-Chloro-6-fluoroquinol-4(1*H*)-one-3-carboxamide (5h).** Compound **3h** (0.58 g, 2.15 mmol) and *n*-octylamine (0.36 mL, 2.2 mmol) in pyridine (1.5 mL) were reacted as for **4a** to provide **5h**: 0.47 g (61.8%); R_f 0.64; mp 53 °C; IR (KBr) 3060, 2925, 1645, 1356, 798 cm^{-1}; MS *m*/*z* 344 (M − F − 1); ^1H NMR (200 MHz, $CDCl_3$) δ 10.15 (bs, 1H, NH), 8.90 (s, 1H, H-2), 8.10 (m, 1H, ArH), 7.85 (m, 1H, ArH), 4.02 (m, 2H, N-CH_2), 1.70−1.52 (m, 12H, CH_2), 0.88 (t, 3H, J = 6.0 Hz, CH_3). Anal. ($C_{18}H_{22}ClFN_2O_2$) C, H, N.

***N*-(*N*′,*N*′-Diethylamino-1′-methyl)butyl 6-Nitroquinol-4(1*H*)-one-3-carboxamide (6c).** By an analogous procedure as described for **4a**, compound **6c** was prepared from the compound **3c** (0.53 g, 2.02 mmol) and 2-amino-5-diethylaminopentane (0.50 mL, 2.6 mmol) in pyridine (1.0 mL): 0.44 g (58.9%); R_f 0.62; mp 42 °C; IR (KBr) 3108, 2920, 1635, 1028, 758 cm^{-1}; MS *m*/*z* 374 (M); ^1H NMR (200 MHz, $CDCl_3$) δ 10.28 (bs, 1H, NH), 8.90 (s, 1H, H-2), 8.20−7.70 (m, 3H, ArH), 4.50 (m, 1H, N-CH), 3.20−2.50 (m, 6H, CH_2), 2.40−2.10 (m, 4H, CH_2), 1.80 (m, 3H, CH_3), 1.50−0.85 (m, 6H, CH_3). Anal. ($C_{19}H_{26}N_4O_4$) C, H, N.

***N*-(*N*′,*N*′-Diethylamino-1′-methyl)butyl 6-Fluoroquinol-4(1*H*)-one-3-carboxamide (6d).** In a manner similar to the preparation of **4a**, compound **6d** was synthesized from the compound **3d** (0.65 g, 2.76 mmol) and 2-amino-5-diethylaminopentane (0.55 mL, 2.85 mmol) in pyridine (1.5 mL): 0.57 g (59.8%); R_f 0.66; mp 40 °C; IR (KBr) 3142, 2925, 1636, 1035, 798 cm^{-1}; MS *m*/*z* 348 (M + 1), 347 (M); ^1H NMR (90 MHz, $CDCl_3$) δ 10.25 (bs, 1H, NH), 8.80 (s, 1H, H-2), 8.10−7.90 (m, 1H, ArH), 7.80−7.50 (m, 2H, ArH), 6.25 (bs, 1H, NH), 4.40−4.41 (m, 1H, N-CH), 3.30−2.70 (m, 6H, CH_2), 2.65−2.10 (m, 4H, CH_2), 1.75−1.50 (m, 3H, CH_3), 1.40−1.20 (m, 3H, CH_3), 1.10−0.90 (m, 3H, CH_3). Anal. ($C_{19}H_{26}FN_3O_2$) C, H, N.

***N*-(*N*′,*N*′-Diethylamino-1′-methyl)butyl 7-Chloro-6-fluoroquinol-4(1*H*)-one-3-carboxamide (6h).** By a procedure similar to that described for **4a**, compound **6h** was obtained from the compound **3h** (0.65 g, 2.41 mmol) and 2-amino-5-diethylaminopentane (0.50 mL, 2.55 mmol) in pyridine (1.5 mL): 0.59 g (64%); R_f 0.69; mp 45 °C; IR (KBr) 3018, 2929, 1647, 1215, 759 cm^{-1}; MS *m*/*z* 381 (M); ^1H NMR (400 MHz, $CDCl_3$) δ 10.18 (bs, 1H, NH), 8.75 (s, 1H, H-2), 8.16−7.88 (m, 2H, ArH), 6.20 (bs, 1H, NH), 3.50 (m, 1H, N-CH), 3.00−2.70 (m, 4H, CH_2), 1.84−1.50 (m, 6H, CH_2), 1.49−0.9 (m, 9H, CH_3). Anal. ($C_{19}H_{25}ClFN_3O_2$) C, H, N.

Materials and Method for Antifilarial Evaluation. *A. viteae* infection was transmitted to 6 weeks old male *M. coucha* through the vector *Ornithodorus moubata* by the method as reported in the literature.[15] The micro- and macrofilaricidal activities of the compounds **4**−**6** were assessed at 200 mg/kg (po) for five consecutive days according to literature methods.[16,17] The effect of compounds, namely **4a** and **4e**, on DNA topoisomerase II of filarial parasite has been assessed at 10μmol/mL concentration, and the procedure for topoisomerase II assay was as reported in the literature.[8−10]

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