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SOLID PHASE SYNTHESIS OF QUINOLONES+

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Abstract: *Solid phase syntheses of ethyl 6-carboxyquinol-4(1H)-one-3-carboxylate (5) and N-substituted 6-carboxyquinol-4(1H)-one-3-carboxamides* ***7a-d*** *have been described. Antifilarial in vitro activities of* ***5,7a-d*** *against Brugia malayi have also been delineated.* © 1999 Elsevier Science Ltd. All rights reserved.

Solid phase synthesis of small organic molecules for the potential use in combinatorial chemistry is relatively new area and has current focus of research[1]. This technique has been successfully applied to the preparation of a variety of heterocyclic structures including benzodiazepines, hydantoins, thiazolidinones, pyrrolidines, oxazoles, imidazoles, indoles, tetrahydrocarbolines and 1,4-dihydropyridines and several other compound classes based on adaptions of known solution phase syntheses[2]. Here, we report solid phase synthesis of ethyl 6-carboxyquinol-4(1H)-one-3-carboxylate due to their great importance in the pharmaceutical field[3,4]. Design and synthesis of N-substituted 6-carboxyquinol-4(1H)-one-3-carboxamide was based on their recent exploration in filarial chemotherapy[5]. The details are presented here.

Synthetic strategy for quinolones has been described in Scheme 1. Cesium salt of 4-aminobenzoic acid was linked with ***Merrifield resin*** (1,0.9 meq/g) to provide **2**[6]. On treatment of **2** with diethyl ethoxymethylenemalonate afforded polymer-bound malonate **3** and which on cyclisation in Dowtherm at 260°C using the procedure reported in solution[7,8] yielded polymer-bound quinolone **4** in which keto group, ester, carbonyl and the NH could be utilized as centers of diversity to generate libraries of quinolone derivatives for potential use in combinatorial chemistry. Here, it was interesting to note that the resin was stable at this reaction temperature and performed the cyclisation in the favourable direction. However, Polymer-bound quinolone **4** was then elaborated in two ways. First, cleavage[9] from the resin with TFA/CH_2Cl_2 (1:1) gave ethyl 6-carboxyquinol-4(1H)-one-3-carboxylate (**5**) in 98% yield. Although compound **5** was known[3] but the synthesis of **5** on solid phase was not yet reported.

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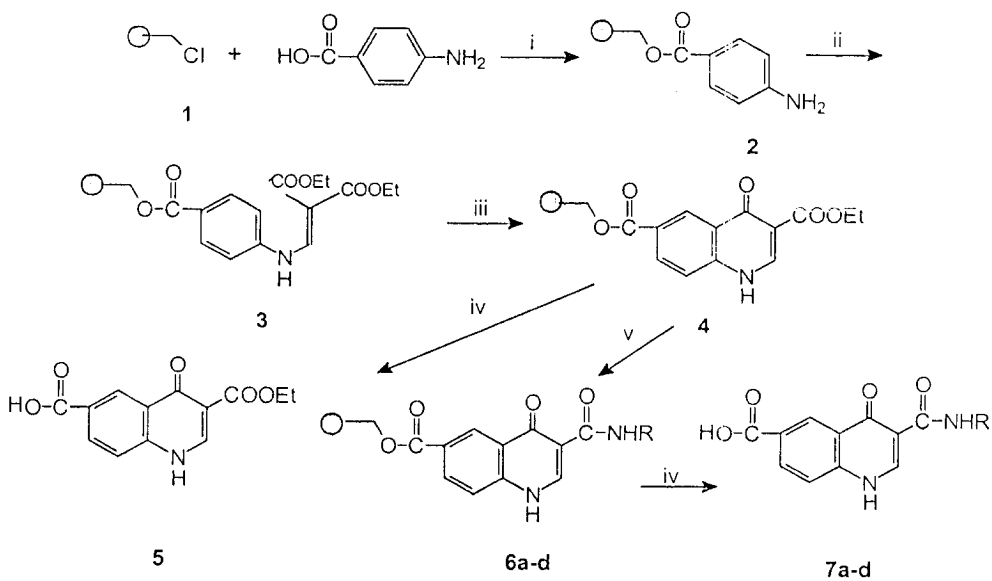
Scheme 1

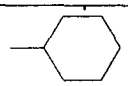
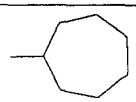


Reagents/Condition : i. Cs_2CO_3,DMF, *Merrifield resin*, ii. Diethyl ethoxymethylenemalonate, DMF, iii. Dowtherm, 260°C, iv. TFA/CH_2Cl_2 (1:1), reflux , v. RNH_2, pyridine, 120°C

In the second, nucleophilic substitution of amines with **4** based on method reported in solution[10], provided their respective polymer-bound N-substituted quinolone-3-carboxamides **6a-d** which upon subsequent treatment with TFA/CH_2Cl_2, as for **5**, yielded N-substituted 6-carboxyquinol-4(1H)-one-3-carboxamides **7a-d** as in scheme 1. The final purified yields are reported in Table 1. The rest of material in solution would, possibly, be either quinolone-3,6-dicarboxamides or **7a-d** or the mixture of both. However, these were not isolated since we were mainly concentrated towards the solid phase syntheses of quinolone-3-carboxamides **7a-d** because the reasons stated earlier. The purity of final compounds **5,7a-d** was typically excellent (>90% as determined by NMR and TLC). Compounds **7a-d** the new and all the synthesized compounds were characterized by spectroscopic and analytical techniques[11].

Antifilarial activity : *In vitro* antifilarial activity of **5,7a-d** was evaluated against adult worms of *B. malayi* using motility assay and MTT reduction potential assay as parameters according to the method described in the literature[12,13]. The motality of the worms was scored as active (+3), sluggish (+2), paralised (+1) and dead (D). 'D' was taken as end point criterion. For compounds causing less than 25% inhibition in MTT reduction potential of worms was considered inactive.

Table 1 : Physical data and antifilarial activity of synthesized compounds against adult worms of *Brugia malayi* at 100 μM concentration

Compd.	R	Yield[a] (%)	Antifilarial activity			
			Motality scored of parasite		% Inhibition in MTT reduction potential of parasite	
			Female	Male	Female	Male
5	NA	98	+3	+3	0	0
7a		72	+3	+3	0	0
7b	$-(CH_2)_7-CH_3$	78	D	D	84.80	62.81
7c		69	+3	+3	0	0
7d	$-(CH_2)_5-CH_3$	68	D	D	64.80	58.75

[a] Isolated yields after preparative TLC purification; NA = not applicable ; MTT = 3-(4,5-dimethylthiazolyl-2-yl)-2,5-diphenyl tetrazolium bromide; O = inactive

Results and Discussion

Motality and MTT reduction assays revealed that at 100 μM concentration, two of the five compounds affected adult parasites of *B. malayi* (Table 1). An overview of the antifilarial data clearly indicated that N-octyl (**7b**) and N-hexyl (**7d**) 6-carboxy quinol-4(1H)-one-3-carboxamides showed interesting antifilarial activity while other substituents such as cyclohexyl and cycloheptyl at amide nitrogen at position-3 in 6-carboxy quinol-4(1H)-one-3-carboxamide did not exert any significant antifilarial response. Ethyl 6-carboxy quinol-4(1H)-one-3-carboxylate also failed to show any promising response.

It was concluded that alkyl substituent at amide nitrogen in 6-carboxy quinol-4(1H)-one-3-carboxamide plays an important role in eliciting antifilarial response and therefore, this class of compounds may provide a useful 'lead' which might be developed as an antifilarial drug. Moreover, the present strategy describes an efficient and clean preparation of quinolones on solid support which provides a scaffold for

other useful synthetic transformations for the potential use in combinatorial chemistry. Application towards the synthesis of more biologically interesting quinolones using this strategy will be reported in due course.

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11. **5**; IR (KBr) : 3072, 2696, 1694, 1522, 770 cm^{-1}; ^1H NMR (TFA, 200 MHz) : δ 9.58 (s, 1H, H-2), 8.99-8.89 (m, 1H, ArH), 8.42-8.26 (m, 2H, ArH), 4.81 (q, 2H, OCH_2, J=6.9 Hz), 1.65 (t, 3H, CH_3, J=7.1 Hz); MS m/z 261 (M^+), 215 (M^+-CO_2+1), Anal. Calcd for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.25; N, 5.36. Found : C, 59.92; H, 4.32; N, 5.22. **7a**; M.P. 42°C; IR (KBr) : 3028, 2692, 1696, 1652, 1546, 764 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) : δ 8.90 (s, 1H, H-2), 8.08-7.71 (m, 3H, ArH), 3.06 (bs, 1H, N-CH), 2.03-1.63 (m, 4H, CH_2), 1.45-0.96 (m, 6H, CH_2); MS m/z : 314 (M^+), 272 (M^+-CO_2+2), Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; H, 8.91. Found : C, 64.78; H, 5.81; N, 8.74.
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