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A Solid Phase Approach to Quinolones using the DIVERSOMER® Technology.

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Abstract: The first example of a library of the quinolone antibacterial agents prepared by solid phase organic synthesis is described. Results of these studies and the parallel synthesis, isolation, purification and analysis of eight quinolones are discussed. Copyright © 1996 Elsevier Science Ltd

The discovery and development of a new drug takes on average 12 years at an estimated cost of $357 million. [1] However, the advent of combinatorial chemistry has provided a means for the preparation of hundreds, or even thousands, of diverse chemical libraries at a fraction of the normal cost and time. A recent phenomenon, combinatorial chemistry has resulted in the successful preparation of oligomeric libraries,[2] and has also been applied to small molecule libraries such as the benzodiazepines,[3,4] hydantoins,[4] thiazolidines,[5] and ß-lactams. [6]

In order to increase the number of solid phase organic reactions, we studied a solid phase approach to the quinolone antibacterial agents which represent a class of highly potent, broad-spectrum antibiotics. Their mode of action is believed to involve inhibition of DNA gyrase[7] and more recently they have been shown to have *in vitro* activity against *M.tuberculosis*.[8,9] Herein, we report a general and straightforward method for synthesizing the quinolones on a solid support and subsequently the generation of eight structurally related quinolones using the DIVERSOMER® technology. [10]

Several synthetic routes have been reported for the quinolones and our initial objective was validation and optimization of a solution phase route which was also amenable to solid phase organic synthesis (SPOS). Typically, reaction conditions were designed to exploit the advantages of solid phase synthesis while at the same time circumventing the disadvantages of the polystyrene solid support. For example, the use of resin swelling solvents and low to ambient temperatures.

Preliminary work involved the SPOS of Ciprofloxacin® by the cycloaracylation process.[11] The applicability of this route proved to be most attractive since it provided a direct pathway for attachment to a functionalized polystyrene solid support via the ß-keto ester **2** as shown in Figure 1.

The ß-keto ester starting material, 2,4,5-trifluorobenzoylacetic acid ethyl ester **2** was prepared by a method described by Clay *et al.*[12] Initially, transesterification of **2** to *p*-benzyloxybenzyl alcohol (Wang) resin **1** was achieved by heating the mixture in toluene with a catalytic amount of N,N-dimethylaminopyridine (DMAP) at 110°C for 72 hours. However, analysis of the resin-bound product **3** by gel phase ^{13}C-NMR and IR confirmed that the reaction had gone to completion after only 18 hours.

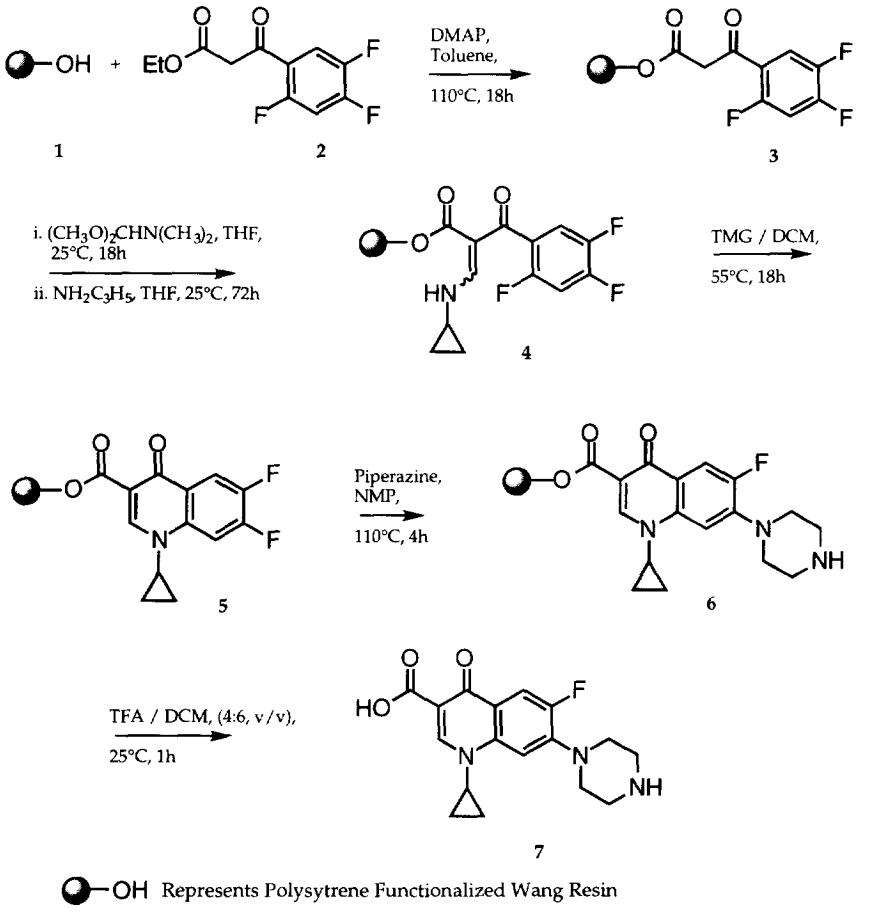


Figure 1. SPOS of Ciprofloxacin®.

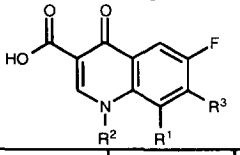
Preparation of the resin-bound enamide **4** was achieved by activation of the resin-bound ß-keto ester **3** with dimethylformamide dimethyl acetal followed by *in situ* addition of cyclopropylamine at 25°C, for 18 hours and 72 hours respectively. The resulting product was subsequently confirmed by gel phase ^{13}C-NMR. Cyclization of **4** in a solution of tetramethylquanidine (TMG) and dichloromethane (DCM) at 55°C for 18 hours provided the corresponding resin-bound quinolone **5**. In addition to gel phase ^{13}C-NMR analysis, further confirmation of the reaction was achieved by cleavage of **5** with 40% TFA in DCM at 25°C for 1 hour, and analysis of the filtrates by both ^{1}H-NMR and MS.

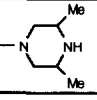
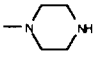
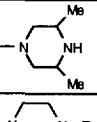
The final step in the preparation of the quinolones by traditional solution phase routes, involves nucleophilic substitution in the presence of the carboxylic acid. However, in our designed SPOS route, this reaction must occur in the presence of the resin-bound ester **5**. Thus, **5** was reacted with a solution of

piperazine in N-methylpyrrolidinone (NMP) at 110°C for 4 hours and the resin-bound Ciprofloxacin® **6** identified by gel phase ^{13}C-NMR. Treatment of **6** under the resin cleavage conditions confirmed the isolated product as crude Ciprofloxacin® **7**.

Following the successful SPOS of Ciprofloxacin®, a library of 8 quinolones was generated by the DIVERSOMER® technology. Using a DIVERSOMER® synthesizer compatible with up to 800mg of resin and eight reactions (8-800 synthesizer), 500 mg of functionalized Wang resin afforded sufficient product in order to purify and characterize our library. Initially, the crude library was confirmed by TLC and RP-HPLC, however a major objective of our work is to provide high purity products for full analysis and biological testing.[13] Following exhaustive chromatographic purification protocols, RP-HPLC methods yielded the pure products as shown in Table 1. The corresponding products were characterized by both ^{1}H-NMR and MS analysis. This library has subsequently been submitted for full biological analysis and the results will be disclosed in due course.

Table 1. Eight Quinolones Synthesized using the DIVERSOMER® Technology.



Cpd. No.	R^1	R^2	R^3	Yield (mg)	Yield %[i]	Purity %[ii]	MS (M+1)
A1	H			14.8	13	96	332
A2	H			30.4	24	90	360
A3	H			15.8	12	93	360
A4	H			22.8	19	76	346
B1	H			7.9	6	86	386
B2	H			7.8	6	92	414
B3	H			5.6	4	94	414
B4	H			9.8	7	83	400

i. Isolated yields following purification by preparative RP-HPLC (based on a resin loading of 0.70mmol/g).
ii. Qualitative purity based on RP-HPLC.

In conclusion, our work has successfully demonstrated the first application of a SPOS route to the quinolones. This work illustrates new solid phase chemistries such as reductive amination and nucleophilic aromatic substitution. Furthermore, the compatibility of the DIVERSOMER® synthesizer with a wide range of reagents and reaction conditions including, reflux, high temperatures, acidic and caustic environments has been shown.

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References and Notes

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