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Expeditious solution phase synthesis of fluoroquinolone antibacterial agents using polymer supported reagents

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Abstract—The first example of a library synthesis of novel quinolone antibacterial agents using a polymer supported base (Amberlite 900-Cl) is described.

The use of polymer supported reagents and scavenging reagent systems has become routine in organic synthesis. These techniques are widely considered to be reaching maturation, partly due to the recent demonstration that these reagent systems can be used in multi-step synthesis and their development has resulted in a dramatic impact in the creation of chemical libraries.[1]

With an aim towards the generation of new chemical entities active against fluoroquinolone resistant antibacterial strains, we recently introduced a synthesis programme towards the creation of chemical libraries of novel fluoroquinolones (R^1 = F, R^2 = amines).[2] Herein we wish to report a straightforward method to realise these goals using a polymer supported ion-exchange base in a key nucleophilic displacement step.

In our initial experiments the *N*-cyclopropyl-6,7,8-trifluoroquinolonecarboxylic acid[3] was treated with excess piperazine in various solvents (DCM, MeCN, toluene, DMSO) with a range of polymer supported bases **1a**–**d**.[4] Much to our delight it was shown that in each case the product could be isolated in excellent purity (>95% by HPLC and NMR analysis) after filtration and evaporation of the reaction mixture, and via this route it was possible to isolate significant quantities (>20 mg) of pure material, although in each case the yield of the product was disappointingly low (<10%).[5]

Screening of commercially available ion-exchange bases revealed that Amberlite 900-Cl (resin **1e**, Table 1, entry 5) showed a dramatic improvement in the reaction, and in the event, the desired product was isolated in quantitative yield and excellent purity (>95%) under mild conditions.[6] Representative examples, from a library of 200 compounds prepared, are shown which were prepared from a range of cyclic secondary amines that had no functionality adjacent to the *N*-atom (Fig. 1). From these examples it can be seen that the scope of the

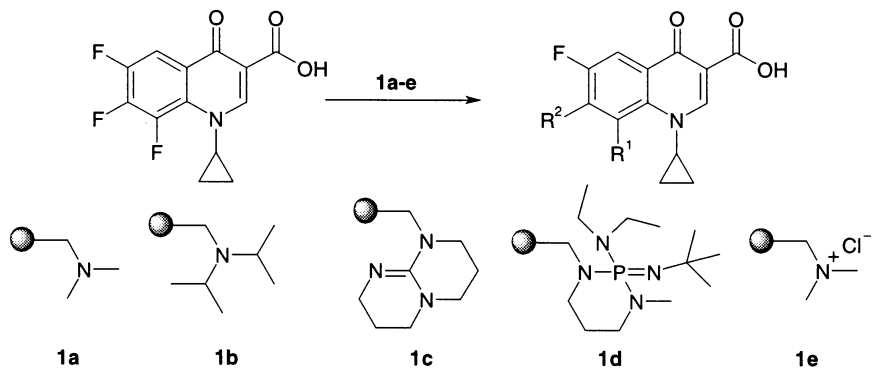

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Table 1.

Entry	Resin **1**	Reaction conditions	Equiv. **1**	Yield (%)
1	**a**	Piperazine (1.5–3.0 equiv.), MeCN, rt, 1 h	1.1–3.0	10[a] (75)[b]
2	**b**	Piperazine (1.5–3.0 equiv.), MeCN, rt, 1 h	1.1–3.0	6[a] (69)[b]
3	**c**	Piperazine (1.5–3.0 equiv.), MeCN, rt, 1 h	1.1–3.0	9[a] (81)[b]
4	**d**	Piperazine (1.5–3.0 equiv.), MeCN, rt, 1 h	1.1–3.0	8[a] (77)[b]
5	**e**	Piperazine (4.0 equiv.), MeCN, rt to 60°C, 2 h	2.0	98[a]

[a] Yield after filtration and evaporation to afford pure product.
[b] Yield after acidification.

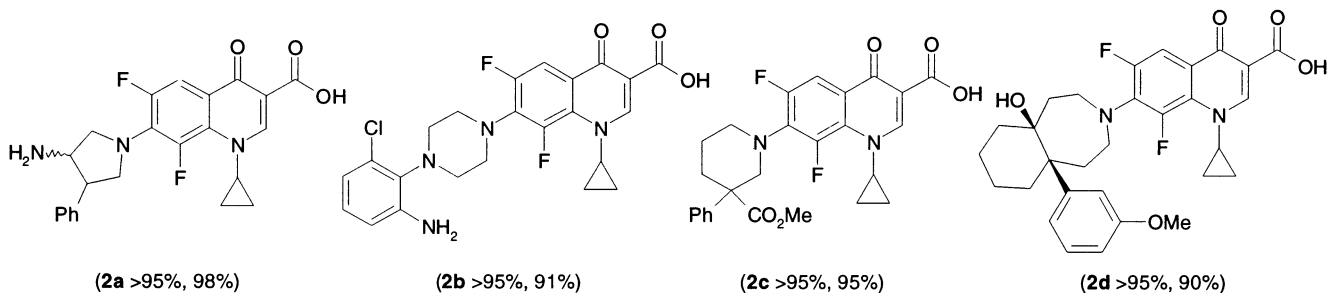

Figure 1. Selected examples (purity, yield based on HPLC, NMR spectroscopy).[7]

reaction is wide and can tolerate other functionalities (primary amines and anilines, alcohols, ester, etc.) without altering the outcome of the reaction.

In conclusion a new straightforward method for the solution phase synthesis of a library of fluoroquinolone anti-infective agents has been achieved. The reaction proceeds under mild conditions using a basic resin (Amberlite 900-Cl) and no chromatography is necessary in order to achieve high purity products in excellent yield.

References

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2. Previously two independent groups have reported the library synthesis of potential anti-infective agents. (a) Frank, K. E.; Jung, M.; Mitscher, L. A. *Comb. Chem. High Throughput Screening* **1998**, *1*, 73–87. (b) MacDonald, A. A.; DeWitt, S. H.; Hogan, E. M.; Ramage, R. *Tetrahedron Lett*. **1996**, *37*, 4815–4818.
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4. The resins **1a–d** were commercially available and were purchased from Fluka.
5. Treatment of the resin with dilute HCl followed by washing with DCM resulted in an improved recovery of the product (overall yields approaching 90%) but unfortunately this was met with a reduction in the purity (69–81%) since the mixture included significant amounts of unreacted starting material. Increasing the reaction temperature resulted in no improvement in yield.
6. ***Typical experimental conditions***: The Amberlite 900-Cl resin **1e** was purchased from Fluka. For best results, prior to use, the resin was washed with consecutive portions of MeOH (×3), DCM (×3) and MeOH (×1) and dried overnight under vacuum. To a mixture of the trifluoroquinolone **2** (0.05 mmol) in acetonitrile (0.5 ml) was added the amine (1.0–4.0 equiv.) followed by the resin **1e** (2.0 equiv.) and the resulting mixture heated at 60°C. Once the reaction was complete (30 min to 2 h, as judged by HPLC) the mixture was cooled to room temperature, filtered and evaporated to afford the product used directly for antibacterial testing.
7. All new compounds gave satisfactory ^{1}H, ^{13}C NMR and MS data. Selected ^{1}H NMR spectroscopic data: **2a** (300 MHz, DMSO-d_6) δ 14.51 (br s, 1H), 8.72 (s, 1H), 7.80 (d, *J* 9, 1H), 7.52–7.32 (m, 5H), 5.11 (br s, 2H), 4.31 (m, 1H), 4.22–3.21 (m, 6H), 1.33–1.24 (m, 4H); **2b** δ 12.21 (br s, 1H), 8.81 (s, 1H), 7.96 (d, *J* 9, 1H), 6.87 (t, 1H), 6.64 (d, 1H), 6.45 (d, 1H), 5.50 (br s, 2H), 4.11 (m, 1H), 3.66 (dt, 2H), 3.31 (m, 4H), 2.82 (d, 2H), 1.43 (m, 4H); **2c** δ 13.01 (br s, 1H), 8.74 (s, 1H), 7.94 (d, *J* 9, 1H), 7.43 (m, 5H), 4.23 (m, 1H), 3.94 (d, 1H), 3.74 (s, 3H), 3.33–2.94 (m, 4H), 2.13 (dt, 1H), 1.94 (dt, 1H), 1.66 (dt, 1H), 1.44 (m, 4H); **2d** δ 11.05 (br s, 1H), 8.84 (s, 1H), 7.80 (d, *J* 9, 1H), 7.60 (m, 1H), 7.31 (d, 1H), 7.08 (t, 1H), 6.73 (dd, 1H), 4.43 (br s, 1H), 4.22 (m, 1H), 3.72 (s, 3H), 2.82–2.62 (m, 4H), 2.11–1.42 (m, 12H), 1.32 (m, 4H).