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STRUCTURALLY DIVERSE 2,6-DISUBSTITUTED QUINOLINE DERIVATIVES BY SOLID-PHASE SYNTHESIS

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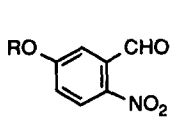
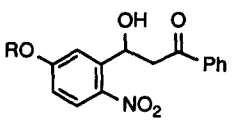
Summary. 2,6-Disubstituted quinoline derivatives **12** are generated by parallel synthesis in seven steps, the last five of which proceed on a polymeric support. Variable building blocks are selected from three commercially available classes of compounds: ω-functionalized fatty acids, aryl methyl ketones, and primary amines.

The development of high-throughput screening assays against important pharmacological targets and the steady production of large numbers of new test compounds represent major challenges for all disciplines contributing to the drug discovery/optimization process. Since a powerful assay may handle as many as 10^4-10^5 individual compounds within a few weeks, medicinal chemistry is increasingly relying on combinatorial synthesis and automation to meet these stringent demands.[2] A mainstay of peptide chemistry ever since its inception,[3] solid-phase synthesis should also play a dominant role in the assembly of large compound libraries containing non-peptide drug-like entities.[4,5] At present, however, the repertoire of organic reactions successfully utilized in multi-step solid-phase syntheses remains limited and somewhat inflexible. In fact, the functional group responsible for tethering intermediates to a polymeric support must survive lengthy reaction sequences but lend itself to smooth scission on completion of the synthesis. Against such odds, we are currently exploring polymer-based synthetic approaches to heterocyclic frameworks of potential therapeutic value. As a part of these efforts, we herein disclose essential features of a study aiming at 2,6-disubstituted quinoline derivatives.[6]

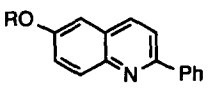
Retrosynthetic considerations identified 5-hydroxy-2-nitrobenzaldehyde (**1**) as a promising building block for the benzo-ring of the quinoline nucleus.[7] Noteworthy properties of this key component include excellent formyl group reactivity towards nucleophiles and a phenolic hydroxyl group which allows coupling to a functionalized polymeric support by way of a suitable linker. According to our strategy, pyridine ring construction was to proceed via aldol reaction followed by reductive cyclization. The fundamental issue of structural diversity in final products is addressed at three different sites on the heterocyclic core and beyond. Obviously, the synthetic design just outlined offers ample opportunities to vary substituents at positions C(2) and C(6). It should be noted that C(6) is occupied by variable linker-type appendages which form integral parts of our target molecules. Derivatizations of the linker termini at the polymer-substrate juncture provide a third option to incorporate diversity during release from the solid support.



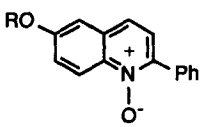
1 R = H
2 R = $(CH_2)_4COOEt$



3 R = $(CH_2)_4COOEt$



4 R = $(CH_2)_4COOEt$

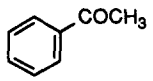


5 R = $(CH_2)_4COOEt$

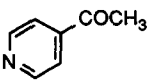
For one representative set of components, the feasibility of the overall synthetic scheme was thoroughly checked in solution and optimized as it became necessary. Toward this end, ethyl 5-bromovalerate was anchored to **1** under standard alkylation conditions (CH_3CN, K_2CO_3, reflux, 16h; 84%). Gratifyingly, reaction conditions were uncovered which guarantee smooth aldol addition between acetophenone and **2** in a variety of solvents and combinations thereof (CH_3CN, K_2CO_3, 22°C; 78%). Exposure of the resulting crystalline hydroxy ketone **3** to

Scheme 1. Building Blocks Utilized for the Assembly of Quinoline Derivatives.

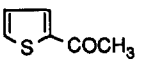
Aryl Methyl Ketones



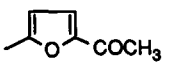
6a



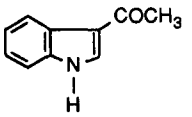
6b



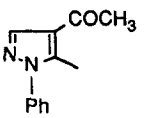
6c



6d

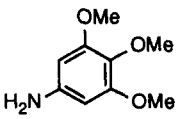


6e

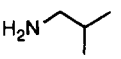


6f

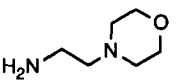
Primary Amines



6α

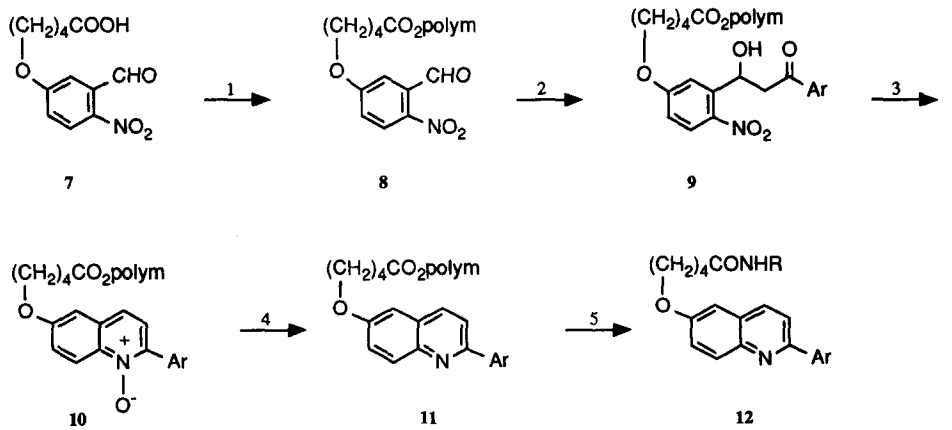


6β



6γ

Scheme 2. Polymer-Supported Reaction Sequence Affording Quinoline Derivatives.



7 8 9

10 11 12

Reagents and Conditions. (1) CH_2Cl_2, DIPC, DMAP, hydroxyethyl polystyrene, 22°C, 24h. (2) THF, K_2CO_3, $ArCOCH_3$, reflux, 48h. (3) CH_2Cl_2, C_2H_5OH, $SnCl_2$-$2H_2O$, reflux, 4h. (4) CH_2Cl_2, toluene, $TiCl_3$, 22°C, overnight. (5) CH_2Cl_2, toluene, $(CH_3)_3Al$, RNH_2, 22°C, overnight.

tin(II) chloride in refluxing ethanol for two hours furnished the desired reductive cyclization product **4** and the corresponding quinoline *N*-oxide **5**, the latter predominating (**4/5**, 1:8, 90% overall yield) as determined by chromatographic separation on silica gel (dichloromethane/ethyl acetate, 4:1).[8] In a second run, the major component was shown to deoxygenate in high yield upon subjection of the crude product mixture to titanium(III) chloride.[9] Taking advantage of the ester functionality, a final combinatorial element was introduced by aminolysis[10] with 3,4,5-trimethoxyaniline (**6**α), (toluene, $(CH_3)_3Al$, 22°C, 20h; 82%), to mention a specific example, **4**→**12a**α. Based on its excellent performance in solution, an ester group should prove equally effective as a polymer-substrate interface.

The stage was thus set to adapt this five-step synthetic protocol to a suitable solid support. As matters worked out, a commercially available hydroxyethyl substituted polystyrene resin gave most satisfactory results in our hands.[11] A total of twelve separate quinoline derivatives was approached in parallel fashion by selecting six distinct aryl methyl ketone building blocks for the aldol addition step and two primary amines for the final cleavage operation (Scheme 1). Although additional linker candidates might obviously be recruited in the class of ω-substituted fatty acids or related compounds, we restrict ourselves to the aforementioned valerate motif for the sake of brevity. With this lay-out in mind, **2** was saponified (CH_3OH, THF, H_2O, KOH, 22°C; 83%) and the resulting acid **7** subsequently immobilized on a single batch of hydroxyethyl resin by re-esterification (Scheme 2). A conceptually more intriguing, stepwise construction of the linker/aldehyde hybrid on bead was also pursued but the reaction sequence for the acetophenone/*i*-butylamine couple afforded the final product in lower overall yield. Luckily, all key reactions involve carbonyl group transformations amenable to close monitoring by FT-IR spectroscopy. To conduct the crucial series of aldol additions, the modified resin was split into six equal parts, each of which was suspended in a separate reaction vessel containing a mixture of dichloromethane/-tetrahydrofuran (1:4) and charged with the respective ketone (**6**a-f) and potassium carbonate. After stirring the resulting slurries at reflux temperature for two days, all transformations appeared to be complete as judged by IR analysis. In each case, the solid remnants were collected in a fritted disc funnel and washed thoroughly with THF and water to remove excess reagents. Before drying in vacuo to constant weight, all polymer batches underwent five additional washing cycles employing solvents (water, ethanol, acetone, ether, dichloromethane) in a decreasing order of polarity, a manipulation that recurred after each transformation. Next, reductive cyclizations were accomplished with ethanolic tin(II) chloride under reflux upon pre-swelling the resin samples in dichloromethane. The derivatized polymeric supports were filtered off from the hot reaction mixtures, washed with ethanol, and processed as described above. A second reductive step served to generate homogeneous, *N*-oxide-free quinoline populations on bead, **10**→**11**. The final release from the polymer was effected on one half of each batch at room temperature within 20 hours by *i*-butylamine/$(CH_3)_3Al$, on the remaining half by *N*-(2-aminoethyl)morpholine/$(CH_3)_3Al$. Aqueous work-up delivered twelve discrete crude products the majority of which was in a state of purity close to 80% (HPLC). Further purifications by chromatography on silica gel led to a set of spectroscopically homogeneous, crystalline compounds **12** in overall yields ranging from 20-65%. Examples which give a low recovery of the desired product correlate with the presence of a sensitive indole/-furan substituent at C(2), thereby revealing some drawbacks in the later stages of our protocol.[12]

In conclusion, this work demonstrates that certain 2,6-disubstituted quinoline derivatives are accessible by a rather efficient polymer-supported, multi-step synthesis which capitalizes on three sizeable classes of commercially available building blocks. The construction of quinoline libraries comprised of 10^3-10^4 members can now be undertaken. Extensions of our basic strategy to other heterocyclic systems, e.g., tetrahydroiso-quinolines, are under active investigation in these laboratories.

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11. Purchased from Rapp Polymere GmbH, Ernst Simon Str. 9, D-72072 Tübingen, Germany.
12. Physical data for selected compounds are as follows. **2**: mp 26-28°C (ethyl acetate/dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.44 (s, 1H), 8.13 (d, J= 8.9 Hz, 1H), 7.27 (d, J= 2.8 Hz, 1H), 7.12 (dd, J= 8.9 Hz, J= 2.8 Hz, 1H), 4.15-4.08 (m, 4H), 2.38 (t, J= 6.8 Hz, 2H), 1.92-1.75 (m, 4H), 1.24 (t, J= 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 173.2, 163.4, 142.1, 134.3, 127.3, 118.8, 113.7, 68.8, 60.4, 33.7, 28.3, 21.4, 14.2. **3**: mp 70-71°C (acetone/hexane); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.12 (d, J= 9.1 Hz, 1H), 8.01-7.97 (m, 2H), 7.64 (tt, J= 7.4 Hz, J= 1.5 Hz, 1H), 7.54-7.48 (m, 3H), 6.93 (dd, J= 9.1 Hz, J= 2.8 Hz, 1H), 5.98 (dt, J= 9.3 Hz, J= 2.4 Hz, 1H), 4.17-4.09 (m, 4H), 3.87 (d, J= 3.1 Hz, 1H), 3.69 (dd, J= 17.7 Hz, J= 2.0 Hz, 1H), 3.21 (dd, J= 17.7 Hz, J= 9.1 Hz, 1H), 2.40 (t, J= 7.2 Hz, 2H), 1.94-1.78 (m, 4H), 1.26 (t, J= 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 200.1, 173.4, 163.9, 142.8, 140.1, 136.8, 134.0, 129.0, 128.5, 127.9, 114.0, 113.5, 68.7, 66.4, 60.6, 46.9, 34.1, 28.7, 21.8, 14.4. **4**: mp 81-82°C (ethyl acetate/hexane). **5**: mp 89-90°C (ethyl acetate/hexane). **12a**α: mp 147-148°C (dichloromethane/-hexane). **12a**β: mp 141-142°C (acetone/hexane). **12b**β: mp 158-159°C (acetone/hexane). **12c**β: mp 147-148°C (acetone/hexane). **12d**β: mp 116-117°C (acetone/hexane). **12e**β: mp 184-185°C (acetone/hexane). **12f**β: mp 138-139°C (dichloromethane/hexane). **12a**γ: mp 125-126°C (acetone/hexane). **12b**γ: mp 145-146°C (acetone/hexane). **12c**γ: mp 121-122°C (acetone/hexane). **12d**γ: mp 132-134°C (acetone/hexane). **12e**γ: mp 196-197°C (acetone/hexane). **12f**γ: mp 169-170°C (dichloromethane/hexane).

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