ChemInform Abstract: Diversity-Oriented Synthesis of Quinolines via Friedlaender Annulation Reaction under Mild Catalytic Conditions

4 AUTHORS, INCLUDING:

Subhas Bose
Indian Institute of Chemical Technology
82 PUBLICATIONS **1,837** CITATIONS

Idrees Mohammed
New York University Abu Dhabi
13 PUBLICATIONS **233** CITATIONS

Janapala Venkateswara Rao
Indian Institute of Chemical Technology
154 PUBLICATIONS **1,796** CITATIONS

Diversity-Oriented Synthesis of Quinolines via Friedländer Annulation Reaction under Mild Catalytic Conditions

D. Subhas Bose,*,[†] Mohd. Idrees,[†] N. M. Jakka,[‡] and J. Venkateswara Rao[‡]

Organic Chemistry Division-III, Fine Chemicals Laboratory, and Biology Division, Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500 607, India

An efficient and practical method has been manifested for the diversity-oriented synthesis of quinolines via Friedländer annulation reaction for the generation of a wide range of structurally interesting and pharmacologically significant compounds by using ceric ammonium nitrate as a catalyst (10 mol %) at ambient temperature in 45 min. A variety of functional groups are introduced at various positions of the quinoline moiety, and further the diversity of the core skeleton was expanded at R_1 and R_2 positions by the synthesis of various hybrids. Initial screening of the compounds for cytotoxicity against a series of cancer cell lines showed promising results.

Introduction

In the postgenomic era, the rapid identification of small-molecules having efficacy to perturb the macromolecular receptors is a major challenge for understanding the complex biological events of life and hence diseases.[1] In this direction, the recent trend showed a drastic shift of the focus from natural products to the combinatorial chemistry and diversity-oriented synthesis (DOS). This shift is evident by the recent successes of DOS[2] and further supported by a chemoinformatics data mining study which revealed that, on average, natural products have higher molecular weights, less nitrogen atoms but more oxygen atoms, and are more complex with large number of rings and chiral centers than the corresponding members from combinatorial libraries.[3] Unlike target-oriented synthesis of natural products and their analogues, the goal of DOS is the facile generation of small molecules of structurally diverse nature from simple starting materials. DOS involves deliberate, simultaneous, rapid, and efficient synthesis of more than one target compound for lead identification and optimization.[4] As molecular structure is the intrinsic requirement for a biological function, privileged structures represent an ideal source of basic scaffolds for lead generation and are defined as "a single molecular framework able to provide ligands for diverse receptors".[5] Diversity-oriented syntheses around privileged structures has been called as "*rational DOS*".[6]

As a privileged fragment, quinoline is a common structural motif found in many natural products with remarkable pharmacological properties. Members of this family have wide applications in medicinal chemistry, being used as antimalarial (chloroquine and mefloquine), anti-inflammatory, antiasthmatic, antibacterial, and antihypersensitive activities,[7,8] cytotoxic agents (e.g., benzo[5,6]pyrrolizino[1,2-*b*]quino-

lines), natural topoisomerase I inhibitors lutonin A and camptothecin and tyrosine kinase PDGF-RTK inhibitor[9] (Figure 1), hence continues to spur synthetic efforts regarding their acquisition.[10] In addition to this, quinolines are valuable synthons used for the preparation of nanostructures and polymers that combine enhanced electronic, optoelectronic, or non-linear optical properties with excellent mechanical properties.[11] In light of the broad array of biological activity,
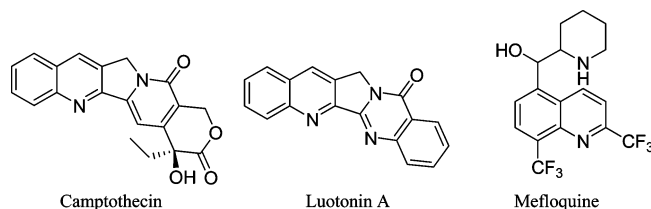

Figure 1. Some biologically active quinolines.

several methods for the construction of this heterocyclic nucleus have been reported. Although methods such as the Skraup, Doebner von Miller, and Combes procedures have been reported in the literature,[12,13] the Friedländer annulation is a staple reaction of organic synthesis to produce poly substituted quinolines. The reaction involves an acid or base catalyzed annulation reaction between 2-aminoaryl ketone and a carbonyl compound possessing a reactive α-methylene group. Classically, the Friedländer reaction is carried out either by refluxing an aqueous or alcoholic solution of reactants in the presence of base or by heating at high temperature ranging from 150−220 °C in the absence of catalyst.[14] Recently, improved protocols, new catalysts, and ionic liquids have been reported for this reaction that avoid the use of strongly basic conditions.[15] Subsequent work showed that acid catalysts are more effective than base catalysts for the Friedländer annulation. Several acid catalysts have been used in the Friedländer reaction including $ZnCl_2$, phosphoric acid, sodium fluoride, silver phosphotungstate, and $AuCl_3 \cdot 3H_2O$ among others.[16] Unfortunately, many of these approaches have significant drawbacks such as low

---

* To whom correspondence should be addressed. E-mail: dsb@iict.res.in, bose_iict@yahoo.co.in. Fax: +91-40-27160387.
  † Organic Chemistry Division-III, Fine Chemicals Laboratory.
  ‡ Biology Division.

Table 1. CAN Catalyzed Synthesis of Substituted Quinolines[a,b,c]

entry	o-aminoketone (1)	ketone (2)	time (min)	quinoline (3)	yield (%)[b]
1.			45	3a	96,[20] 65[c]
2.			60	3b	92
3.			45	3c	90[21]
4.			60	3d	89
5.			45	3e	92
6.			45	3f	94
7.			180	3g	78
8.			45	3h	92
9.			45	3i	90
10.			120	3j	75

[a] Reaction conditions: o-aminoarylketone (10 mmol), α-methyleneketone (10 mmol), CAN (10 mol %) MeOH (10 mL), RT; all products were characterized by mp, IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. [b] Yields refer to pure isolated products after chromatography. [c] Conc. H_2SO_4 used instead of CAN.

yields of the products, prolonged reaction times, harsh conditions, stoichiometric quantities of reagents, difficult to handle especially on large scale, and often do not allow for adequate diversity on the quinoline ring system. Moreover, the potential application of this reaction in the DOS for the generation of biologically active quinolines is yet to be explored. Herein, we describe an efficient utilization of ceric ammonium nitrate (CAN) catalyzed Friedlander annulation reaction for the DOS of a wide range of structurally interesting and biologically active quinolines.

Results and Discussion

Among the various cerium(IV) complexes, cerium(IV) ammonium nitrate (CAN) is one of the most important oxidants in organic synthesis. It is non-toxic, sufficiently stable in different solvents including water, and it is commercially available.[17] Owing to its unique catalytic properties, it has been extensively used for a plethora of organic transformations such as carbon−carbon bond formation, halogenation, protection/

deprotection sequences, oxidation, oxidative free-radical reactions in green media such as water, and ionic liquids via single-electron transfer mechanism or by Lewis acid catalysis. As a part of one of the ongoing investigations in our laboratory toward the development of new protocols for the expeditious synthesis of biologically relevant heterocycles through transition metal catalyzed tandem reactions,[18] we observed the high efficiency of CAN catalysis in sequential condensation/annulation reactions of o-aminoaryl carbonyls **1** and ketones containing an active methylene group **2** for the synthesis of substituted quinolines **3**. It is remarkable to note that the reaction proceeds efficiently in high yields at ambient conditions within a few minutes with low catalyst concentration (5−10 mol %). To the best of our knowledge there have been no reports on the utilization of cerium(IV) complexes for DOS of quinolines via Friedländer annulation reaction.[19]

In an attempt to find the optimum reaction conditions, a systematic study was carried out on a representative case by varying the concentration of the catalyst, solvent, and the

reaction temperature. In screening a set of solvents, we observed a direct correlation between polarity and yield (MeOH >EtOH > CH$_3$CN > THF > CH$_2$Cl$_2$ > toluene). Thus, the high yields were obtained in polar solvents particularly MeOH, whereas cyclohexane proved to be the least effective (for details see the Supporting Information).

As depicted in Table 1, various 1,3-dicarbonyl compounds including alkyl acetoacetates and acetyl acetone, cyclic β-diketones and acyclic ketones reacted with 2-aminoaryl ketones to give the corresponding substituted quinolines without any side products. Interestingly, cyclic ketones such as 4-*tert*-butylcyclohexanone and dimedone reacted with 2-aminoaryl ketones to afford the respective tricyclic quinolines in good yields. To improve the yields, we performed the reactions using different catalyst concentrations. The optimum results were obtained with a 0.1:1:1 ratio of CAN, *o*- aminoaryl ketone, α-methylene ketone or β-diketones in methanol solvent. However, condensation of 2-aminobenzophenone with benzoylacetonitrile requires a higher molar ratio of catalyst, longer reaction time, and gives relatively low yield (Table 1, entry 7). Furthermore, the condensation of *o*-aminobenzophenone with ethyl acetoacetate in the presence of conc. H$_2$SO$_4$ afforded the quinoline product in only 65% yield (Table 1, entry 1). It is also interesting to note here that when 1,1,1-trifluoroacetylacetone was used as 1,3-dicarbonyl compound, a regioselective condensation reaction at the acetyl group led to β-enaminone **4** as the major reaction product (70%) (Scheme 1). The sequential condensation/annulation reaction to form **3k** was accomplished by heating the reaction mixture at 75 °C for 8 h. It may be presumed that the strong electro-withdrawing trifluoroacetyl group affects the annulation step (Scheme 1).

Scheme 1
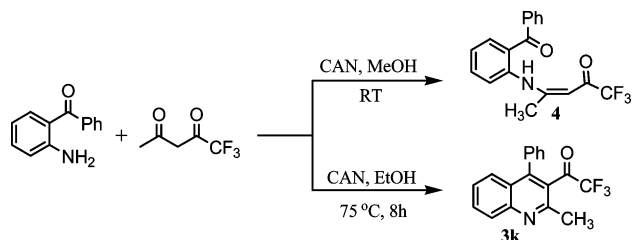
Having established the mild catalytic route for the expeditious generation of quinoline scaffolds, we then proceeded to further expand the scope of this reaction. A vast array of quinolines with maximum structural diversity was synthesized as an effort for the generation of drug-like compounds with broad spectrum of biological activities particularly anticancer ones. The diversity of this core skeleton (Figure 2) was expanded by following three major forward synthetic strategies, (a) diversification at R$_1$, (b) substitutions at R$_2$ diversity point, and (c) generation of quinoline and pyrrol-5-one fused heterocyclic systems involving both R$_1$ and R$_2$ diversity points.
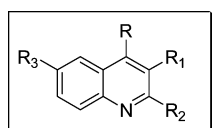

Figure 2. Diversity points.

Diversification at R$_1$. Initially, a series of 1,3-dicarbonyl compounds (**6a−d**) was synthesized by heating a mixture of selected nucleophiles (e.g., morpholine, piperidine, *R*-phenethylamine, and (-)-menthol) and *tert*-butylacetoacetate (TBAA, **5**) in dry xylene for 5 min in 95−98% yields (Scheme 2).[22] The ^{1}H NMR of the intermediate 1,3-dicarbonyl compounds (**6a**, **6b**, and **6d**) showed that keto and enol forms are in the ratio of 3:1 in deuterated chloroform (Table 2). Compound **6c** did not show any significant enol peaks in ^{1}H NMR.

Scheme 2. Synthesis of Quinolines **7a−d**[a,b]
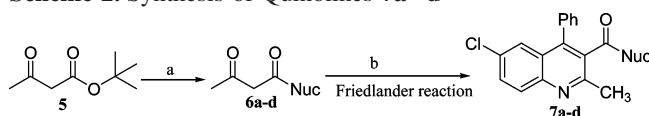
[a] Reagents and conditions: (a) Nuc[b], xylene, Δ, 95−98%(b) 2-amino-5-chlorobenzophenone, MeOH, cerric ammonium nitrate 10 mol %, RT, 45 min, 90−95%. [b] Nuc = morpholine, piperidine, *R*-phenethylamine, and (-)-menthol.

These 1,3-dicarbonyl compounds (**6a−d**) were then reacted with 2-amino-5-chlorobenzophenone and CAN 10 mol % using MeOH at room temperature (RT) for a period of 45 min to obtain a series of novel quinoline amides and esters in 90−95% yields (**7a−d**) mentioned in Table 2.

Table 2. Structures of Intermediates **6a−d** and Quinolines **7a−d**[a]

[a] ^{1}H-NMR (in CDCl$_3$) of the compounds (**6a−d**) showed keto−enol tautomeric forms in 3:1 ratio.

Second, making use of TBAA (**5**) and cyclization of thioformanilides by Dess-Martin periodinane (DMP) to generate benzothiazole ring system,[23] we synthesized a novel quinoline-benzothiazole hybrid molecule (Compound **9** in Scheme 3). This scheme was started by heating a mixture of *tert*-butylacetoacetate and *p*-toluidine in dry xylene for a period of 5 min to afford a 1,3-dicarbonyl compound (**6e**) in 95% yield. Interestingly, this compound **6e** did not show any tautomeric peaks in ^{1}H NMR. Compound **6e** upon treatment with 2-amino-5-chlorobenzophenone and CAN 10 mol % using MeOH at RT for 45 min gave the quinoline amide **7e** in 90% yield. Quinoline amide **7e** was then treated with Lawesson's reagent in dry toluene for a period of 1−2 h to afford quinoline thioamide **8** in 80% yield. Compound **8** was finally cyclized by reacting it

Scheme 3. Synthetic Route of Quinoline-Benzothiazole Hybrid Molecule **9**[a,b]
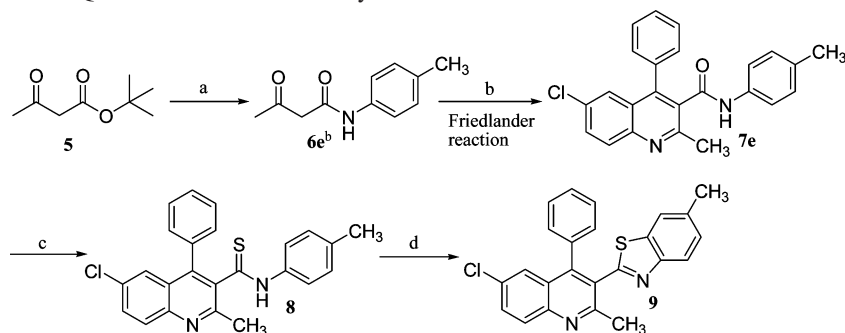
[a] Reagents and conditions: (a) p-toluidine, xylene, Δ, 5 min, 95% (b) 2-amino-5-chlorobenzophenone, MeOH, cerric ammonium nitrate 10 mol %, RT, 45 min, 90% (c) Lawesson's reagent, dry toluene, reflux, 1−2 h, 80% (d) DMP, CH$_2$Cl$_2$, 15 min, RT, 85%. [b] ^{1}H-NMR (in CDCl$_3$) of the compound **6e** did not showed keto−enol tautomerism significantly.

with DMP in CH$_2$Cl$_2$ solvent at RT for a period of 15 min to give quinoline-benzothiazole hybrid molecule **9** in 85% yield after column purification.

Substitutions at R$_2$ Diversity Point. Substitution reactions at R$_2$ diversity point generated a diverse array of quinoline scaffolds. In this direction initially we prepared ethyl 6-chloro-2-(chloromethyl)-4-phenylquinoline-3-carboxylate[24] (**10**) by the treatment of 2-amino-5-chlorobenzophenone with 4-chloroethylacetoacetate in MeOH using CAN 10 mol % as catalyst at RT for a period of 45 min to afford the compound **10** in 95% yield (Scheme 4).

**Scheme 4.** Formation of Quinoline **10**
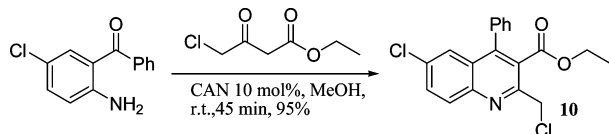
Compound **10** was highly reactive toward nucleophilic substitution reactions because of the presence of active

chloromethyl group at second position of the quinoline ring system. Nucleophiles such as S-prolinol, N-boc-piperizine, and morpholine were substituted on the methylene group present at second position to afford compounds (**11**, **12**, and **13**). Similarly, to incorporate interesting thiourea pharmacophore (frequently found in anti-HIV, and antitumor drug designing reports)[25] in between two quinoline moieties, we synthesized the C$_2$ symmetric quinoline dimer molecule **14** in 75% yield by reacting 2.0 equiv of the compound **10** with 1.0 equiv of thiourea in dry acetonitrile using NaH at 80−82 °C for a period of 5−6 h (Scheme 5).

Further, we substituted the active chloro functionality of compound **10** with D-glucose diacetonide to obtain quinoline 1,2:5,6-diisopropylidene-D-glucose ester **15** (Scheme 6). This was synthesized in 85% yield by treating a mixture of D-glucose diacetonide and NaH in dry tetrahydrofuran (THF) with compound **10** at 0 °C followed by stirring at RT for 5−6 h until the TLC showed completion of the reaction. Compound **15** was then treated with 0.8% H$_2$SO$_4$ in MeOH and stirred for 12 h to afford quinoline 1,2-isopropylidene-

Scheme 5. Diversification of Compound **10**[a]
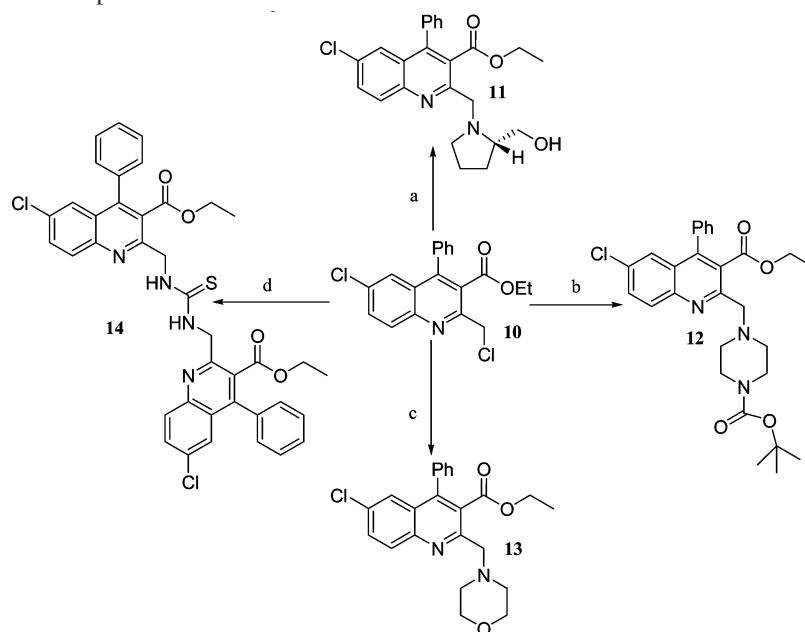
[a] Reagents and conditions: (a) S-prolinol, pyridine, CH$_3$CN, cat. DMAP, RT, 5−6 h, 75% (b) N-Boc-piperizine, pyridine, CH$_3$CN, cat. DMAP, RT, 5−6 h, 85% (c) morpholine, CH$_3$CN, cat. DMAP, RT, 5−6 h, 85% (d) thiourea, NaH, CH$_3$CN, reflux, 5−6 h, 75%.

Scheme 6. Synthesis of Quinoline-Glucose Hybrid[a]
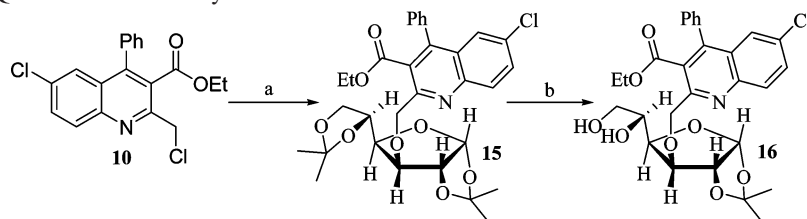
[a] Reagents and conditions: (a) D-glucose diacetonide, NaH, dry THF, 0 °C−RT, 5−6 h, 85% yield (b) 0.8% H_2SO_4, MeOH, RT, 12 h, 65% yield.
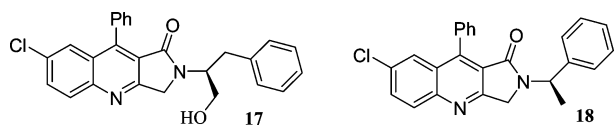
Figure 3. Novel quinolin-pyrrolone fused compounds.

D-glucose ester **16** in 65% yield. We rationalized the synthesis of quinoline-D-glucose hybrid molecule **16** by keeping in view that leaving the fifth and sixth positions free in the hybrid molecule would lead to its entry in the cytoplasm of the targeted cell by the natural enzymatic process called phosphorylation at sixth position. After the phosphorylation step it would get accumulated in the cytoplasm without being metabolized further as positions first, second, and third are blocked. Now the quinoline fragment may act on the biological system within the cell to give the required biological activity, and the accumulated modified glucose fragment may in turn inhibit the phosphorylation step. This approach of utilizing carbohydrates especially D-glucose in the design of antitumor compounds is reported in the literature with successful results as tumor cells rely more on glycolysis rather than oxidative phosphorylation (Warburg effect).[26,27]

Generation of Quinoline and Pyrrol-5-one Fused Heterocyclic Systems. Finally it is interesting to report here two novel 2,3-dihydropyrrolo[3,4-*b*]quinolin-1-ones (**17** and **18**, Figure 3) synthesized, structurally related to the DNA topoisomerase I inhibiting cytotoxic quinoline alkaloids such as camptothecin,[28] luotonin A, and isoluotonin A.[29]

Compound **17** was synthesized by treating compound **10** with *S*-phenylalaninol and pyridine in acetonitrile for 2−3 h at RT to give an intermediate ester **17a**, which upon further stirring for 12 h at 40−45 °C afforded compound **17** in 80% yield (Scheme 7). Similarly, compound **10** was reacted with *R*-phenethylamine and pyridine in acetonitrile for a period of 2−3 h at RT to obtain an intermediate ester **18a**, which upon stirring at 40−45 °C gave compound **18** in 75% yield. Conversion of **18a** to the cyclized form **18** was nicely detected by ^{1}H NMR spectrum.

Cytotoxicity Evaluation

The cytotoxic activities of the compounds **7a−e**, **8**, **9**, and **11−18** were evaluated in vitro against four tumor cell lines: THP-1 (human acute monocytic leukemia), U-937 (human histiocytic lymphoma), HL-60 (human promyelocytic leukemia), and Jurkat (Human T-cell leukemia). In all the

Scheme 7
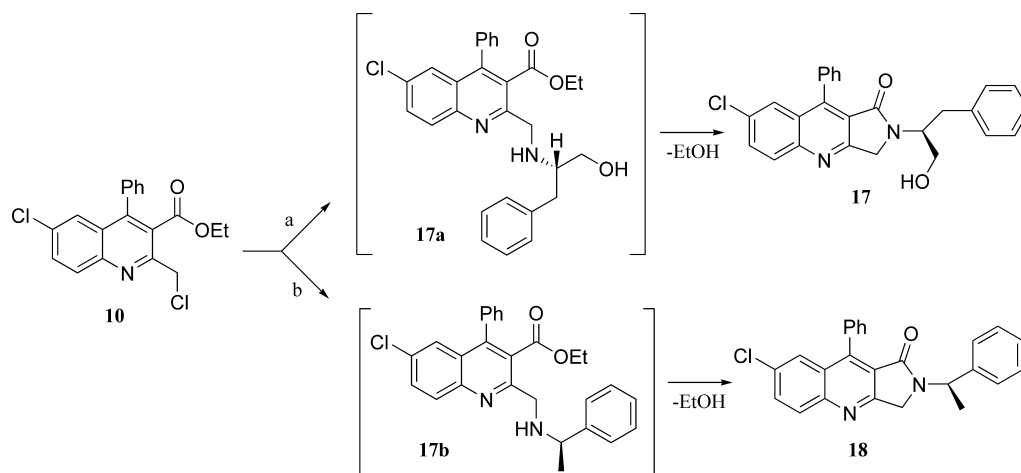
Table 3. In Vitro Cytotoxicity Data of Substituted Quinolines on THP-1,U-937, HL-60, and Jurkat Tumor Cell Lines

compound	IC$_{50}$ (μM) ± SE			
	THP-1	U-937	HL-60	Jurkat
14	22.45 ± 3.97	45.51 ± 5.57	20.20 ± 4.96	18.74 ± 2.72
15	6.02 ± 0.68	3.79 ± 0.41	4.20 ± 0.55	2.59 ± 0.40
16	9.02 ± 0.77	5.89 ± 0.67	5.65 ± 0.89	3.45 ± 0.52
18	3.51 ± 0.42	5.02 ± 0.56	2.51 ± 0.40	5.18 ± 0.28
camptothecin	0.071 ± 0.0053	1.980 ± 0.11	0.600 ± 0.03	0.026 ± 0.002
etoposide	2.16 ± 0.15	17.94 ± 1.19	1.83 ± 0.20	5.35 ± 0.63

experiments, the cell lines were seeded at a final density of 2×10^4 cells per well in 96 well microtiter plates. All leukemia cell lines (THP-1, U-937, HL-60, and Jurkat) were cultured in RPMI-1640. The media were supplemented with 10% heat inactivated FCS, 1 mM NaHCO$_3$, 2 mM L-glutamine, and penicillin-streptomycin in a humidified atmosphere of 95%, 5% CO$_2$ at 37 °C. Cytotoxicity was measured using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrasolium bromide) as described by Mosmann.[30] The stock solutions of the testing compounds were prepared by dissolving 8 mg of each compound in 1 mL of dimethylsulfoxide (DMSO) and further diluted to obtain required experimental stock solutions from 0.5 to 50 ppm. The cells were treated with different concentrations of the test compounds, and their cytotoxicities were compared with the activity of positive controls, camptothecin and etoposide, at identical conditions with five replicates each. The tumor cells (2×10^4) were seeded in each well containing 0.1 mL of RPMI medium in 96 well plates. After 24 h different test concentrations were added, and cell viability was assessed after 48 h by adding 10 μL of MTT (5 mg/mL) per well. The plates were incubated at 37 °C for additional 4 h. The rate of color production was measured at 570 nm in a spectrophotometer (Spectra Max Plux; supported by SOFT-max PRO-3.0).

Among 15 compounds tested in this series, compounds **14**, **15**, **16**, and **18** showed significant cytotoxic activities (the remaining compounds showed IC$_{50}$ values more than 100 ppm). On the basis of the regression equation, IC$_{50}$ values (average concentration of the drug required to produce 50% cell growth inhibition) of the selected potent compounds were calculated, and the results are presented in Table 3. As evident from the table, all the compounds (except compound **14** which showed moderate activity) showed potent cytotoxicity against the four tumor cell lines. Compounds **15**, **16**, and **18** showed IC$_{50}$ values in the range of 2.59 to 9.02 μM, which are comparable with camptothecin and in some cases better than the marketed anticancer drug Etoposide.

Conclusion

In summary, an efficient DOS of privileged quinoline scaffolds has been described by using Friedlander annulation reaction using CAN catalysis at ambient temperature in a short period of time. This approach has led to the generation of a diverse array of functionalized quinoline scaffolds of considerable relevance for chemistry-driven drug discovery. Moreover, in the preliminary studies, compounds **14**, **16**, **17**, and **18** have shown promising activities against a series of cancer cell lines. We anticipate that the protocol of quinoline synthesis and the DOS strategies described in the manuscript could be explored further to have interesting implications in the fields of combinatorial chemistry and chemistry-driven drug discovery.

Experimental Section

Typical Procedure for the Synthesis of Methyl 6-Chloro-2-(2-methoxy-2-oxoethyl)-4-phenyl-3-quinolinecarboxylate (3f). A mixture of 2-amino-5-chlorobenzophenone (2.31 g, 10.0 mmol), dimethyl 1,3-acetonedicarboxylate (1.74 g,

10.0 mmol), and CAN (0.548 g, 1 mmol, 10 mol %) in methanol (10 mL) was stirred at RT for 45 min. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with EtOAc (30 mL), and washed with water (15 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography using EtOAc: petroleum ether (1:10) to afford the pure product **3f** (3.48 g, 94%). mp 110−120 °C. ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 3.47 (s, 3H, CH$_3$), 3.71 (s, 3H, CH$_3$), 4.18 (s, 2H, ArCH$_2$), 7.31−7.35 (m, 2H, ArH), 7.47−7.55 (m, 4H, ArH), 7.64−7.69 (dd, 1H, J_1 = 9.06, J_2 =2.26 Hz, ArH), 8.02−8.06 (d, 1H, J = 9.06 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 43.1, 52.2, 125.4, 126.5, 127.2, 128.4, 128.5, 128.8, 129.0, 129.1, 131.0, 131.5, 133.2, 135.3, 146.2, 147.1, 151.6, 168.2, 170.3. HRMS (ESI) calcd for C$_{20}$H$_{16}$NO$_4$Cl 370.0846 [M+H]$^+$, found 370.0837. This procedure was followed for the preparation of all the substituted quinolines (**3a−j**) mentioned in Table 1.

Ethyl 2-Methyl-4-phenyl-3-quinolinecarboxylate (3a). mp 99−102 °C (Lit. m.p.[20] 99−100 °C). ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 0.89−0.96 (t, 3H, J = 7.55 Hz, CH$_3$), 2.76 (s, 3H, ArCH$_3$), 3.98−4.06 (q, 2H, J = 7.55 Hz, CH$_2$), 7.32−7.56 (m, 7H, ArH), 7.65−7.71 (m, 1H, ArH), 8.02−8.06 (d, 1H, J = 8.31 Hz, ArH). MS (EI): m/z (%) = 291 (M$^+$, 95), 246 (100), 218 (50), 176 (20), 85 (20), 71 (40), 57 (80), 43 (70).

Methyl 2-Ethyl-4-phenyl-3-quinolinecarboxylate (3b). mp 105−106 °C. ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 1.38−1.47 (t, 3H, J = 7.43 Hz, CH$_3$), 2.95−3.08 (q, 2H, J = 7.43 Hz, ArCH$_2$), 3.53 (s, 3H, CO$_2$CH$_3$), 7.31−7.58 (m, 7H, ArH), 7.64−7.73 (m, 1H, ArH), 8.05−8.11 (d, 1H, J = 8.18 Hz, ArH). MS (EI): m/z (%) = 291 (M$^+$, 100), 276 (95), 260 (10), 232 (40), 204 (45), 177 (10), 71 (10), 57 (30), 43 (25).

1-(2-Methyl-4-phenyl-3-quinolyl)ethanone (3c). mp 111−112 °C (Lit. m.p.[21] 113−114 °C). ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 1.96 (s, 3H, COCH$_3$), 2.67 (s, 3H, ArCH$_3$), 7.32−7.73 (m, 8H, ArH), 8.01−8.07 (d, 1H, J = 8.17 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 23.7, 31.7, 124.9, 126.0, 126.3, 128.5, 128.7, 129.9, 134.7, 135.1, 143.7, 147.4, 153.3, 205.4. MS (EI): m/z (%) = 261 (M$^+$, 50), 246 (100), 218 (55), 176 (25), 57 (10), 43 (25).

2-(*tert*-Butyl)-7-chloro-9-phenyl-1,2,3,4-tetrahydroacridine (3d). mp 148−150 °C. ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 0.87 (s, 9H, 3 × CH$_3$), 1.41−1.62 (m, 2H, CH$_2$), 2.10−2.18 (m, 1H, CH), 2.22−2.34 (m, 1H, ArCH), 2.59−2.68 (m, 1H, ArCH), 3.00−3.15 (m, 1H, ArCH), 3.22−3.33 (m, 1H, ArCH), 7.18−7.23 (m, 3H, ArH), 7.46−7.58 (m, 4H, ArH), 7.89−7.92 (d, 1H, J = 8.87 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 24.1, 27.1, 29.4, 32.5, 34.8, 44.6, 124.5, 127.4, 128.1, 128.7, 128.8, 128.9, 129.2, 129.8, 130.0, 131.1, 136.3, 144.6, 145.9, 159.7. HRMS (ESI) calcd for C$_{23}$H$_{24}$NCl 350.1675 [M + H]$^+$, found 350.1680.

7-Chloro-3,3-dimethyl-9-phenyl-1,2,3,4-tetrahydro-1-acridinone (3e). mp 219−220 °C. ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 1.17 (s, 6H, 2 × CH$_3$), 2.52 (s, 2H, COCH$_2$), 3.23 (s, 2H, ArCH$_2$), 7.11−7.15 (m, 2H, ArH), 7.36−7.37 (m, 1H, ArH), 7.48−7.53 (m, 3H, ArH), 7.64−7.69 (dd, 1H, J_1 = 9.06, J_2 =2.26 Hz, ArH), 7.95−7.99 (d, 1H, J = 9.06

Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 28.3, 32.2, 48.2, 54.1, 123.2, 126.7,127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 130.1, 132.4, 136.7, 147.3, 150.0, 161.4, 197.6. MS (ESI) *m/z* 336 ([M + H]$^+$, 100). HRMS (ESI) calcd for C$_{21}$H$_{18}$NOCl 336.1155 [M + H]$^+$, found 336.1146.

6-Chloro-3-cyano-2,4-diphenylquinoline (3g). mp 192−194 °C.^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 7.46−7.72 (m, 9H, ArH), 7.75−7.81 (dd, 1H, J_1 = 9.63, J_2 =3.02 Hz, ArH), 7.96−8.02 (m, 2H, ArH), 8.15 (d, 1H, J = 8.87 Hz, ArH).^{13}C NMR (75 MHz, CDCl$_3$): δ 116.8, 128.6, 129.0, 129.1, 129.2, 129.3, 129.6, 130.0, 130.1, 130.8, 131.7, 133.4, 133.9, 133.8, 137.7, 147.0, 155.5, 158.7. EIMS: *m/z* (%) 343 (M^{+2}, 25), 341 (72), 157 (12), 117 (15), 101 (45), 79 (100). Anal. Calcd for C$_{22}$H$_{13}$N$_2$Cl: C, 77.53, H, 3.84, N, 8.22. Found: C, 77.38, H, 3.76, N, 8.17. IR (KBr): 2219 cm^{-1}.

Ethyl 6-Chloro-2-(2-phthalimidoethoxy)methyl-4-phenylquinoline-3-carboxylate (3h). mp 165−166 °C.^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 0.92 (t, 3H, J = 7.55 Hz, CH$_3$), 3.68−3.74 (t, 2H, J = 6.04 Hz, OCH$_2$), 3.81−3.87 (t, 2H, J = 6.04 Hz, NCH$_2$), 4.00−4.08 (q, 2H, J = 7.55 Hz, CO$_2$CH$_2$), 4.91 (s, 2H, ArCH$_2$), 7.29−7.34 (m, 2H, ArH), 7.45−7.51 (m, 4H, ArH), 7.61−7.73 (m, 3H, ArH), 7.77−7.83 (m, 2H, ArH), 7.80−8.02 (d, 1H, J = 9.06 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.5, 37.4, 61.4, 67.6, 73.5, 123.2, 123.3, 125.3, 127.0, 127.1, 128.3, 128.5, 128.7, 129.3, 131.0, 131.2, 132.1, 133.2, 133.8, 134.9, 145.5, 146.4, 155.0, 167.5, 168.1. HRMS (ESI) calcd for C$_{29}$H$_{23}$N$_2$O$_5$Cl 515.1373 [M + H]$^+$, found 515.1359.

***tert*-Butyl 6-chloro-2-methyl-4-phenyl-3-quinolinecarboxylate (3i).** mp 141−143 °C.^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 1.21 (s, 9H, 3 × CH$_3$), 2.73 (s, 3H, ArCH$_3$), 7.22 (tt, 2H, J = 8.6, 2.1 Hz, ArH), 7.32−7.37 (m, 2H, ArH), 7.42−7.44 (d, 1H, J = 2.26 Hz, ArH), 7.47−7.54 (m, 3H, ArH), 7.58−7.63 (dd, 1H, J_1 = 9.06, J_2 =2.26 Hz, ArH), 7.96−8.00 (d, 1H, J = 9.06 Hz, ArH).^{13}C NMR (75 MHz, CDCl$_3$): δ 23.5, 27.5, 82.6, 125.1, 126.1, 128.3, 128.6, 129.5, 130.4, 130.8, 132.1, 135.0, 144.5, 145.8, 154.8, 167.0. MS (ESI) *m/z* (%) 354 (M + H, 100). HRMS (ESI) calcd for C$_{21}$H$_{21}$NO$_2$Cl 354.1260 [M + H]$^+$, found 354.1246.

3,3-Dimethyl-9-methyl-1,2,3,4-tetrahydro-1-acridinone (3j). mp 104−106 °C.^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 1.12 (s, 6H, 2 × CH$_3$), 2.66 (s, 2H, ArCH$_3$), 3.06 (s, 2H, COCH$_2$), 3.18 (s, 2H, ArCH$_2$), 7.55 (ddd, 1H, J = 8.2, 6.8, 1.2 Hz, ArH), 7.75 (ddd, 1H, J = 8.2, 6.8, 1.2 Hz, ArH), 8.02 (d, 1H, J = 8.2 Hz, ArH), 8.21 (d, 1H, J = 8.2 Hz, ArH).^{13}C NMR (75 MHz, CDCl$_3$): δ 15.6, 28.2, 31.2, 47.9, 54.7, 124.1, 125.5, 126.3, 127.5, 129.1, 130.7, 148.1, 150.0, 160.6, 200.2. HRMS (ESI) calcd for C$_{16}$H$_{17}$NO 239.1310 [M + H]$^+$, found 239.1304.

(Z)-4-(2-Benzoylphenylamino)-1,1,1-trifluoropent-3-en-2-one (4). ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 2.05 (s, 3H, CH$_3$), 5.42 (s, 1H, =CH), 7.26−7.69 (m. 9H, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 20.3, 91.5, 114.5 (q, J = 218 Hz), 127.1, 127.3, 128.5, 129.4, 130.3, 130.7, 131.7, 133.5, 134. 4, 137.6, 176.6 (q, J = 34 Hz), 195.3. MS (ESI) *m/z* (%) 334 (M + H, 100).

2,2,2-Trifluoro-1-(2-methyl-4-phenylquinolin-3-yl)ethanone (3k). mp 82−84 °C (Lit.^{16c} mp 80−81 °C). ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 2.61 (s, 3H, ArCH$_3$), 7.36−7.41

(m, 2H, ArH), 7.57−7.68 (m, 5H, ArH), 7.92 (m, 1H, ArH), 8.12 (d, J = 8.4 Hz, 1H, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 23.8, 115.6 (q, J = 308 Hz), 126.1, 127.1, 127.6, 128.5, 129.1, 129.4, 130.3, 131.3, 131.6, 147.5, 148.3, 153.3, 189.2 (q, J = 38 Hz). MS (ESI) *m/z* (%) 316 (M + H, 100).

Typical Procedure for the Preparation of (6-Chloro-2-methyl-4-phenyl-3-quinolyl)(morpholino)methanone (7a). A mixture of 2-amino-5-chlorobenzophenone (1.155 g, 5.0 mmol), 1-morpholino-1,3-butanedione, **6a** (0.855 g, 5.0 mmol), and CAN (0.274 g, 0.5 mmol, 10 mol %) in methanol (5 mL) was stirred at RT for 60 min. After completion of the reaction (monitored by TLC), the mixture was diluted with ethyl acetate (30 mL), and washed with water (15 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography using EtOAc: petroleum ether (1:10) to afford the pure product **7a** (1.65 g, 90%). mp 187−189 °C; ^{1}H NMR (200 MHz, CDCl$_3$, TMS) δ 2.68 (s, 3H, ArCH$_3$), 2.75−2.91 (m, 2H, CH$_2$), 2.97−3.22 (m, 2H, CH$_2$), 3.27−3.40 (m, 2H, CH$_2$), 3.45−3.63 (m, 2H, CH$_2$), 7.23−7.33 (m, 1H, ArH), 7.46−7.68 (m, 6H, ArH), 7.95−8.03 (d, 1H, J = 9.14 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 23.4, 41.36, 46.4, 66.3, 124.9, 125.7, 128.1, 129.0, 129.1, 129.3, 130.1, 130.5, 130.9, 132.4, 134.2, 143.2, 146.1, 155.1, 167.0. MS (ESI): *m/z* (%) = 367 (M+H, 100). This procedure was followed for the preparation of the compounds **7b−d.**

(6-Chloro-2-methyl-4-phenyl-3-quinolyl)(piperidino)methanone (7b). m.p.170−171 °C; ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 1.15−1.58 (m, 6H, 3 × CH$_2$), 2.71 (s, 3H, ArCH$_3$), 2.76−2.86 (m, 1H, CH), 3.00−3.09 (m, 1H, CH), 3.33−3.42 (m, 1H, CH), 3.48−3.59 (m, 1H, CH), 7.29−7.35 (m, 1H, ArH), 7.46−7.67 (m, 6H, ArH), 7.98−8.03 (d, 1H, J = 8.30 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 23.4, 24.0, 25.1, 25.9, 124.9, 125.9, 127.7, 128.8, 129.0, 129.4, 130.0, 130.4, 130.5, 132.2, 134.3, 142.9, 145.9, 155.3, 166.6. MS (ESI): *m/z* (%) = 365 (M + H, 100).

N3-[(1R)-1-Phenylethyl]-6-chloro-2-methyl-4-phenyl-3-quinolinecarboxamide (7c). mp 225−227 °C; ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 1.13−1.91 (d, 3H, J = 6.80 Hz, CH$_3$), 2.77 (s, 3H, ArCH$_3$), 4.99−5.10 (q, 1H, J_1 = 6.80 Hz, J_2 = 7.55 Hz, CH), 5,48−5.58 (broad doublet, 1H, J = 7.55 Hz, CONH), 6.91−7.00 (m, 2H, ArH), 7.19−7.29 (m, 4H, ArH), 7.34−7.43 (m, 2H, ArH), 7.47−7.56 (m, 3H, ArH), 7.61−7.66 (dd, 1H, J_1 = 9.06 Hz, J_2 = 2.26 Hz, ArH), 7.97−8.02 (d, 1H, J = 9.06 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 20.4, 23.5, 48.6, 125.1, 126.0, 127.3, 128.7, 128.8, 129.3, 129.4, 130.5, 130.7, 130.8, 132.2, 134.7, 141.8, 144.0, 145.9, 155.8, 166.7. MS (ESI): *m/z* (%) = 401 (M + H, 100).

(1R,2R,5R)-2-Isopropyl-5-methylcyclohexyl-6-chloro-2-methyl-4-phenyl-3-quinolinecarboxylate (7d). [α]$_D$ −68.93° (c 1.03, CHCl$_3$, 20 °C). m.p.146−147 °C; ^{1}H NMR (200 MHz, CDCl$_3$, TMS) δ 0.55−0.63 (d, 1H, J = 7.03 Hz, CH), 0.69−0.89 (dd, 6H, J_1 = 15.62 Hz, J_2 = 7.03 Hz, 2 × CH$_3$), 0.90−1.28 (m, 3H, CH$_3$), 1.29−1.69 (m, 7H, 3 × CH$_2$ + CH), 2.73 (s, 3H, ArCH$_3$), 4.57−4.72 (dt, 1H, J_1 = 10.94 Hz, J_2 = 4.68 Hz, OCH), 7.27−7.67 (m, 7H, ArH), 7.94−8.03 (d, 1H, J = 8.59 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 15.8, 20.9, 22.0, 22.9, 23.8, 25.6, 31.4, 39.9, 46.7, 75.9, 125.2, 126.2, 128.6, 128.9, 129.6, 129.9, 130.0, 132.4,

134.8, 144.7, 146.1, 154.8, 167.9. MS (ESI): *m/z* (%) = 436 (M + H, 100).

N1-(4-Methylphenyl)-3-oxobutanamide (6e). A mixture of *tert*-butyl acetoacetate (1.58 g, 10.0 mmol), and *p*-toluidine (1,07 g, 10.0 mmol), in 10 mL of dry xylene was heated in a 50 mL beaker for a period of 5 min until colorless vapors of *tert*-butanol came out. TLC (EtOAc: petroleum ether, 1:2), showed the completion of the reaction. The reaction mixture was cooled and washed with hexane. Upon flash chromatography of this crude solid resulted in a pure cream colored solid **6e** (1.81 g, 95% yield). mp 92−93 °C; ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 2.30 (s, 3H, COCH$_3$), 2.31 (s, 3H, ArCH$_3$), 3.51 (s, 2H, COCH$_2$CO), 7.04−7.10 (d, 1H, *J* = 8.31 Hz, ArH), 7.36−7.41 (d, 1H, *J* = 8.31 Hz, ArH), 9.09 (broad singlet, 1H, CONH). MS (ESI): *m/z* (%) = 192 (M + H, 100), 214 (M + Na$^+$, 20).

N3-(4-Methylphenyl)-6-chloro-2-methyl-4-phenyl-3-quinolinecarboxamide (7e). A mixture of 2-amino-5-chlorobenzophenone (1.155 g, 5.0 mmol), N1-(4-methylphenyl)-3-oxobutanamide, **6e** (0.955 g, 5.0 mmol), and CAN (0.274 g, 0.5 mmol, 10 mol %) in methanol (5 mL) was stirred at RT for 60 min. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate (30 mL), and washed with water (15 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography using EtOAc: petroleum ether (1:1) to afford the pure product **7e** (1.74 g, 90%). mp 227−229 °C; ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 2.29 (s, 3H, ArCH$_3$), 2.83 (s, 3H, ArCH$_3$), 6.80 (s, 1H, CONH), 6.93−7.01 (m, 4H, ArH), 7.40−7.55 (m, 6H, ArH), 7.62−7.67 (dd, 1H, J_1 = 9.06 Hz, J_2 = 2.66 Hz, ArH), 7.97−8.01 (d, 1H, *J* = 9.06 Hz, ArH). MS (ESI): *m/z* (%) = 387.20 (M + H, 100).

N3-(4-Methylphenyl)-6-chloro-2-methyl-4-phenyl-3-quinolinecarbothioamide (8). Lawesson's reagent (0.404 g, 1.0 mmol) was added to the stirred solution of quinoline amide **7f** (0.774 g, 2.0 mmol) in dry toluene 5 mL at 60 °C. The reaction mixture was refluxed for 1−2 h, and after the completion of the reaction (monitored by TLC) toluene was removed by vacuo distillation. Sodium hypochlorite was added to the residue to quench the reaction. Ice-cubes were added to get a dark yellow crude solid which was filtered through a Buchner funnel. Recrystallization using acetone: water afforded pure pale yellow prisms of compound **8** (0.645 g) in 80% yield. mp 179−180 °C; ^{1}H NMR (200 MHz, CDCl$_3$, TMS) δ 2.35 (s, 3H, ArCH$_3$), 2.75 (s, 3H, ArCH$_3$), 6.34 (s, 1H, CSNH), 7.05−7.17 (d, 1H, *J* = 8.53 Hz, ArH), 7.29−7.63 (m, 9H, ArH), 7.98−8.05 (d, 1H, *J* = 9.30 Hz, ArH). MS (ESI): *m/z* (%) = 403 (M + H, 100).

2-(6-Chloro-2-methyl-4-phenyl-3-quinolyl)-6-methyl-1,3-benzothiazole (9). DMP (0.424 g, 1.1 mmol) was added to a stirred solution of quinoline thioformanilide, **8** (0.403 g, 1.0 mmol) in CH$_2$Cl$_2$ (5 mL) at RT. The progress of the reaction was monitored with TLC. After completion, it was quenched with H$_2$O (2 × 5 mL) and extracted with CH$_2$Cl$_2$ (2 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford the crude product which was purified by column chromatography on silica gel using EtOAc:petroleum

ether (1:3) as eluent to give compound **9** as a light yellow solid (0.341 g) in 85% yield. m.p.185−187 °C; ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 2.47 (s, 3H, ArCH$_3$), 2.65 (s, 3H, ArCH$_3$), 7.23−7.33 (m, 6H, ArH), 7.50−7.52 (m, 2H, ArH), 7.64−7.69 (m, 1H, ArH), 7.88−7.92 (d, 1H, *J* = 8.50 Hz, ArH), 8.03−8.07 (d, 1H, *J* = 9.06 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 21.5, 24.7, 121.1, 122.9, 126.4, 127.5, 127.7, 128.2, 128.4, 130.0, 130.6, 131.2, 132.2, 134.8, 135.5, 136.6, 146.3, 147.8, 151.0, 157.7, 163.6. MS (ESI): *m/z* (%) = 401 (M + H, 100).

Ethyl 6-Chloro-2-(chloromethyl)-4-phenyl-3-quinolinecarboxylate (10). A mixture of 2-amino-5-chlorobenzophenone (2.31 g, 10.0 mmol), ethyl 4-chloroacetoacetate (2.07 g, 10 mmol), and CAN (0.548 g, 1 mmol, 10 mol %) in methanol (15 mL) was stirred at RT for 60 min. After completion of the reaction (monitored by TLC), the mixture was diluted with ethyl acetate (40 mL), and washed with water (25 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography using petroleum ether to afford the pure product **10** (3.41 g, 95%). mp 105−106 °C; Lit. 106−108 °C.[24] ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 0.87−0.93 (t, 3H, *J* = 7.55 Hz, CH$_3$), 3.97−4.05 (q, 2H, *J* = 7.55 Hz, CO$_2$CH$_2$), 4.97 (s, 2H, ArCH$_2$), 7.32−7.36 (m, 2H, ArH), 7.48−7.55 (m, 4H, ArH), 7.66−7.70 (dd, 1H, J_1 = 9.06 Hz, J_2 = 2.66 Hz, ArH), 8.04−8.08 (d, 1H, *J* = 9.06 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.1, 45.5, 61.4, 124.7, 126.3, 126.6, 128.5, 128.9, 129.0, 131.4, 131.8, 132.9, 134.1, 145.1, 146.9, 153.0, 166.2. MS (FAB): *m/z* (%) = 360 (M$^+$, 45), 362 (M+2, 28), 363 (M+3, 4), 364 (M+4, 4).

Ethyl 6-Chloro-2-[(2S)-2-(hydroxymethyl)tetrahydro-1H-1-pyrrolyl]methyl-4-phenyl-3-quinolinecarboxylate (11). A (0.718 g, 2) mmol portion of compound **10** was dissolved in CH$_3$CN followed by the addition of Et$_3$N (1 mL) and catalytic DMAP. Stirring was continued for a period of 30 min at RT followed by the addition of *S*-prolinol (0.202 g, 2 mmol). Reaction was continued until complete disappearance of the starting material was observed with TLC. CH$_3$CN was removed in vacuo, quenched with cold water, and extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford the crude product. Column chromatography of the crude product gave a dark red color solid compound **11** (0.637 g, 75% yield). [α]$_D$ −21.20° (c 1.02, CHCl$_3$, 20 °C). mp 172−174 °C; ^{1}H NMR (200 MHz, CDCl$_3$, TMS) δ 0.76−0.86 (t, 3H, *J* = 7.35 Hz, CH$_3$), 1.49−1.90 (m, 4H, 2 × CH$_2$), 2.33 (m, 1H, CH), 2.62−2.74 (m, 1H, CH), 2.85−2.97 (m, 1H, asymmetric CH), 3.24−3.36 (m, 1H, OCH), 3.48−3.58 (m, 1H, OCH), 3.80−4.03 (m, 3H, CO$_2$CH$_2$ + ArCH), 4.35−4.45 (m, 1H, ArCH), 7.26−7.41 (m, 2H, ArH), 7.45−7.57 (m, 4H, ArH), 7.61−7.69 (dd, 1H, J_1 = 8.81 Hz, J_2 = 2.20 Hz, ArH), 7.99−8.05 (d, 1H, *J* = 8.81 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.3, 23.8, 26.7, 55.1, 57.8, 62.0, 61.5, 68.3, 125.4, 126.8, 129.0, 129.0, 129.2, 131.0, 131.9, 133.8, 134.7, 145.4, 147.4, 167.7. MS (ESI): *m/z* (%) = 425 (M + H, 100). This procedure was followed for the synthesis of the compounds **12** and **13**.

Ethyl 2-[4-(*tert*-Butoxycarbonyl)piperazino]methyl-6-chloro-4-phenyl-3-quinolinecarboxylate (12). mp 169−171 °C; ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 0.79−0.84 (t, 3H, J = 7.55 Hz, CH$_3$), 1.43 (s, 9H, 3 × CH$_3$), 2.40−2.48 (m, 4H, 2 × CH$_2$), 3.26−3.33 (m, 4H, 2 × CH$_2$), 3.88−3.96 (m, 4H, CO$_2$CH$_2$ + ArCH$_2$), 7.31−7.36 (m, 2H, ArH), 7.47−7.54 (m, 4H, ArH), 7.62−7.67 (dd, 1H, J_1 = 9.06 Hz, J_2 = 2.26 Hz, ArH), 7.99−8.03 (d, 1H, J = 9.06 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.4, 28.3, 43.7, 52.4, 60.8, 63.6, 79.6, 125.2, 127.0, 127.5, 128.3, 128.6, 129.2, 130.8, 131.0, 132.8, 135.0, 145.4, 146.2, 154.6, 156.5, 167.8. MS (ESI): *m/z* (%) = 510 (M + H, 100).

Ethyl 6-Chloro-2-(morpholinomethyl)-4-phenyl-3-quinolinecarboxylate (13). mp 162−164 °C; ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 0.82−0.91 (t, 3H, J = 7.34 Hz, CH$_3$), 2.45−2.53 (t, 4H, J = 5.14 Hz, 2 × CH$_2$), 3.56−3.64 (t, 4H, J = 5.14 Hz, 2 × CH$_2$), 3.92−4.05 (m, 4H, CO$_2$CH$_2$ + ArCH$_2$), 7.31−7.39 (m, 2H, ArH), 7.46−7.58 (m, 4H, ArH), 7.63−7.70 (dd, 1H, J_1 = 8.81 Hz, J_2 = 2.20 Hz, ArH), 8.01−8.08 (d, 1H, J = 9.55 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.5, 53.1, 60.9, 64.0, 66.9, 125.3, 127.0, 127.6, 128.3, 128.6, 129.3, 130.8, 131.0, 132.8, 135.1, 145.4, 146.1, 156.5, 167.8. MS (ESI): *m/z* (%) = 411 (M + H, 100).

Ethyl 6-Chloro-2-([([6-chloro-3-(ethoxycarbonyl)-4-phenyl-2-quinolyl]methylamino) carbothioyl]aminomethyl)-4-phenyl-3-quinolinecarboxylate (14). To a solution of thiourea (0.152 g, 2 mmol), in dry CH$_3$CN was added NaH, 60% w/w (0.177 g, 4.4 mmol), in portions at 0 °C. After stirring for 30 min compound **10** (1.436 g, 4.0 mmol) was added, and the reaction mixture was refluxed for 5−6 h until TLC showed complete disappearance of the starting materials. CH$_3$CN was removed in vacuo, and the reaction was quenched with cold water (5 mL). Ethyl acetate (2 × 5 mL) was used for extraction, which was washed simultaneously with brine and dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Column chromatography on silica gel (EtOAc: petroleum ether 1:3) gave a pale yellow solid compound **14** (1.084 g, 75% yield). ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 0.79−0.86 (t, 6H, J = 6.80 Hz, 2 × CH$_3$), 1.85 (s, 2 × NH), 3.90−3.98 (q, 4H, J = 7.55 Hz, 2 × CH$_2$), 4.28 (s, 4H, 2 × ArCH$_2$), 7.12−7.19 (m, 2H, ArH), 7.42−7.51 (m, 4H, ArH), 7.60−7.66 (dd, 1H, J_1 = 9.06 Hz, J_2 = 2.26 Hz, ArH), 7.81−7.86 (d, 1H, J = 9.06 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.4, 37.6, 61.3, 125.2, 126.4, 126.9, 128.3, 128.6, 129.1, 131.0, 131.1, 132.8, 135.3, 145.5, 146.6, 155.7, 167.5. MS (ESI): *m/z* (%) = 724 (M + H, 100).

Ethyl 2-[((3a*S*,5*S*,6*S*,6a*S*)-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethylperhydrofuro[2,3-*d*][1,3]dioxol-6-yloxy)methyl]-6-chloro-4-phenyl-3-quinolinecarboxylate (15). To a solution of D-glucose diacetonide (1.30 g, 5 mmol), in dry THF was added NaH, 60% w/w (0.200 g, 5.5 mmol), in portions at 0 °C. After stirring for 30 min compound **10** (1.795 g, 5 mmol) was added and stirring was continued for further 2−4 h at RT until TLC showed complete disappearance of the starting materials. CH$_3$CN was removed in vacuo, and the reaction was quenched with cold water (5 mL) and extracted with ethyl acetate (2 × 5 mL). The combined extracts were washed with brine and dried

(Na$_2$SO$_4$) and concentrated under reduced pressure to afford a solid residue, which was purified by silica gel column chromatography (EtOAc: petroleum ether 2:5) gave a gummy compound **15** (2.482 g, 85% yield). [α]$_D$ −28.481° (c 1.58, CHCl$_3$, 20 °C). ^{1}H NMR (200 MHz, CDCl$_3$, TMS) δ 0.77−0.86 (t, 3H, J = 7.41 Hz, CH$_3$), 1.24−1.49 (m, 12H, 4 × CH$_3$), 3.86−4.08 (m, 6H, CO$_2$CH$_2$ + OCH$_2$ + 2 × CH), 4.18−4.30 (m, 1H, CH), 4.59−4.63 (d, 1H, J = 3.70 Hz, CH), 4.98−5.05 (d, 2H, J = 5.92 Hz, ArCH$_2$), 5.76−5.81 (d, 1H, J = 3.70 Hz, CH), 7.25−7.39 (m, 2H, ArH), 7.45−7.55 (m, 4H, ArH), 7.63−7.71 (dd, 1H, J_1 = 8.89 Hz, J_2 = 2.22 Hz, ArH), 8.02−8.09 (d, 1H, J = 8.89 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.3, 25.4, 26.2, 26.8, 61.3, 67.0, 72.4, 73.2, 81.0, 82.0, 83.0, 105.2, 108.9, 111.7, 125.3, 126.9, 127.0, 128.3, 128.8, 129.0, 129.3, 131.1, 131.4, 133.4, 135.0, 145.6, 146.6, 154.3, 167.6. MS (ESI): *m/z* (%) = 584 (M + H, 100).

Ethyl 2-[((3a*S*,5*R*,6*S*,6a*S*)-5-[(1*S*)-1,2-dihydroxyethyl]-2,2-dimethylperhydrofuro[2,3-*d*][1,3]dioxol-6-yloxy)methyl]-6-chloro-4-phenyl-3-quinolinecarboxylate (16). To a stirred solution of compound **15** (1.168 g, 2 mmol) in MeOH (15 mL), was added aqueous 0.8% H$_2$SO$_4$ solution and stirred for overnight. TLC (ethyl acetate: hexane, 1:1) showed the completion of the reaction. Methanol was removed in vacuo, and the residue was treated with saturated solution of NaHCO$_3$ and extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), filtered, and the solvent was removed in vacuo. Purification by column chromatography using EtOAc:petroleum ether (1:2) afforded a colorless solid compound **16** (0.707 g, 65% yield). [α]$_D$ −40.19° (c 1.02, CHCl$_3$, 20 °C). [α]$_D$ −40.19° (c 1.02, CHCl$_3$, 20 °C). mp 104−106 °C; ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 0.80−0.90 (t, 3H, J = 7.55 Hz, CH$_3$), 1.22−1.33 (m, 6H, 2 × CH$_3$), 2.03 (s, 1H, OH), 2.07 (s, 1H, OH), 3.70−3.77 (m, 1H, CH), 3.89−4.15 (m, 5H, CO$_2$CH$_2$, + OCH$_2$ + CH), 4.22−4.30 (m, 1H, CH), 4.62−4.66 (d, 1H, J = 3.77 Hz, CH), 4.86−4.94 (d, 1H, J = 16.61 Hz, ArCH), 5.12−5.20 (d, 1H, J = 16.61 Hz, ArCH), 5.93−5.97 (d, 1H, J = 3.77 Hz, CH), 7.27−7.34 (m, 2H, ArH), 7.49−7.56 (m, 4H, ArH), 7.69−7.74 (dd, 1H, J_1 = 9.06 Hz, J_2 = 2.26 Hz, ArH), 8.18−8.23 (d, 1H, J = 9.06 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.4, 26.3, 26.8, 61.9, 64.7, 68.12, 69.1, 80.4, 81.9, 82.9, 105.8, 111.8, 125.4, 126.8, 128.5, 129.0, 130.0, 133.6, 132.1, 134.6, 145.2, 147.6, 153.9, 166.8. MS (ESI): *m/z* (%) = 545 (M + H, 100).

2-[(1*S*)-1-Benzyl-2-hydroxyethyl]-7-chloro-9-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (17). To a mixture of compound **10** (0.718 g, 2 mmol), and Et$_3$N (1 mL) in CH$_3$CN (5 mL) was added *S*-phenylalaninol (0.302 g, 2 mmol). The stirring was continued for a period of 2−3 h at RT. TLC showed the appearance of a new spot corresponding to the intermediate ester **17a**. The reaction mixture was further stirred at 40−45 °C for a period of 12 h, until the TLC showed the complete disappearance of the intermediate **17a**. CH$_3$CN was removed in vacuo, quenched with cold water (5 mL), and extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), filtered, and the solvent was removed

in vacuo. Column chromatography of the crude product gave a light red color compound **17** (0.686 g, 80 [α]$_D$ −91.000° (c 1.00, CHCl$_3$, 20 °C). mp 80−82 °C; ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 2.71 (broad singlet, 1H, OH), 3.00−3.07 (d, 2H, J = 7.55 Hz, ArCH$_2$), 3.72−3.85 (m, 2H, CH$_2$), 4.42−4.53 (m, 3H, CH$_2$-pyrrolone + asymmetric CH), 7.08−7.39 (m, 7H, ArH), 7.50−7.56 (m, 3H, ArH), 7.65−7.72 (m, 2H, ArH), 7.98−8.04 (d, 1H, J = 9.06 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): 35.1, 49.3, 56.0, 62.7, 120.7, 126.0, 126.5, 127.8, 128.0, 128.5, 128.7, 129.0, 129.7, 130.4, 131.8, 132.7, 137.4, 146.7, 147.7, 160.9, 166.3. MS (ESI): *m/z* (%) = 430 (M + H, 30), 380 (35), 366 (100). This procedure was followed for the preparation of the compound **18**.

7-Chloro-9-phenyl-2-[(1R)-1-phenylethyl]-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (18). [α]$_D$ 266.05° (c 1.09, CHCl$_3$, 20 °C). mp 125−127 °C; ^{1}H NMR (300 MHz, CDCl$_3$, TMS) δ 1.68−1.73 (d, 3H, J = 7.55 Hz, CH$_3$), 4.10−4.17 (d, 1H, J = 16.61 Hz, CH-pyrrolone), 4.43−4.50 (d, 1H, J = 16.61 Hz, CH-pyrrolone), 5.75−5.83 (q, 1H, J = 7.55 Hz, asymmetric CH), 7.21−7.39 (m, 5H, ArH), 7.41−7.47 (m, 2H, ArH), 7.54−7.62 (m, 3H, ArH), 7.66−7.70 (dd, 1H, J_1 = 9.06 Hz, J_2 = 2.26 Hz, ArH), 7.74−7.76 (d, 1H, J = 2.26 Hz, ArH), 8.00−8.04 (d, 1H, J = 9.06 Hz, ArH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 17.0, 46.4, 49.1, 120.9, 126.1, 127.2, 127.8, 128.1, 128.7, 129.0, 129.8, 129.9, 130.6, 131.8, 132.0, 132.7, 139.9, 146.9, 148.0, 160.9, 165.0. MS (ESI): *m/z* (%) = 399 (M + H, 15).

Supporting Information Available. General experimental information, experimental procedures, characterization data and copies of ^{1}H, ^{13}C NMR and mass spectra of the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.

(2) For example:(a) Lee, D.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709–712. (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G. -Q.; Roecker, A. J.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953. (c) Arya, P.; Chou, D. T. H.; Baek, M.-G. *Angew. Chem., Int. Ed.* **2001**, *40*, 339–346. (d) Pelish, H. E.; Westwood, N. J.; Feng, Y.; Kirchhausen, T.; Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 6740–6741. (e) Schmidt, D. R.; Kwon, O.; Schreiber, S. L. *J. Comb. Chem.* **2004**, *6*, 286–292. (f) Robinson, A.; Thomas, G. L.; Spandl, R. L.; Welch, M.; Spring, D. R. *Org. Biomol. Chem.* **2008**, *6*, 2978–2981. (g) Galloway, W. R. J. D.; Diáz-Gavilán, M.; Isidro-Llobet, A.; Spring, D. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1194–1196.

(3) (a) Feher, M.; Schmidt, J. M. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 218–227. (b) Hotha, S.; Tripathi, A. *J. Comb. Chem.* **2005**, *7*, 968–976.

(4) Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem.* **2008**, *6*, 1149–1158.

(5) (a) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235–2246. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.

(6) Reayi, A.; Arya, P. *Curr. Opin. Chem. Biol.* **2005**, *9*, 240–247.

(7) (a) Larsen, R. D.; Corley, E. G.; King, A. O.; Carrol, J. D.; Davis, P.; Verhoeven, T. R.; Reider, P. J.; Labelle, M.; Gauthier, J. Y.; Xiang, Y. B.; Zamboni, R. J. *J. Org. Chem.* **1996**, *61*, 3398–3405. (b) Chen, Y. L.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. *J. Med. Chem.* **2001**, *44*, 2374–2378. (c) Roma, G.; Braccio, M. D.; Grossi, G.; Mattioli, F.; Ghia, M. *Eur. J. Med. Chem.* **2000**, *35*, 1021–1026.

(8) (a) Kalluraya, B.; Sreenivasa, S. *Farmaco* **1998**, *53*, 399–404. (b) Dube, D.; Blouin, M.; Brideau, C.; Chan, C.-C.; Desmarais, S.; Ethier, D.; Falgueyret, J. P.; Friesen, R. W.; Girard, M.; Girard, Y.; Guay, J.; Riendeau, D.; Tagari, P.; Young, R. N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1255–1260.

(9) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166–187, and reviews of this series. (b) Maguire, M. P.; Sheets, K. R.; McVety, K.; Spada, A. P.; Zilberstein, A. *J. Med. Chem.* **1994**, *37*, 2129–2137. (c) Bilker, O.; Lindo, V.; Panico, M.; Etiene, A. E.; Paxton, T.; Dell, A.; Rogers, M.; Sinden, R. E.; Morris, H. R. *Nature* **1998**, *392*, 289–292.

(10) (a) Marco-Contelles, J.; Pérez-Mayoral, E.; Samadi, A.; Carmo Carreiras, M.; Soriano, E. *Chem. Rev.* **2009**, *109*, 2652–2671. (b) Kim, J. N.; Chung, Y. M.; Im, Y. J. *Tetrahedron Lett.* **2002**, *43*, 6209–6211. (c) Legros, J.-Y.; Primault, G.; Fiaud, J.-C. *Tetrahedron* **2001**, *57*, 2507–2514.

(11) (a) Agrawal, A. K.; Jenekhe, S. A. *Chem. Mater.* **1996**, *8*, 579–589. (b) Jenekhe, S. A.; Lu, L.; Alam, M. M. *Macromolecules* **2001**, *34*, 7315–7324. (c) Jegou, G.; Jenekhe, S. A. *Macromolecules* **2001**, *34*, 7926–7928.

(12) (a) Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1996; Vol. 5, p 167. (b) Cho, C. S.; Oh, B. H.; Kim, T. J.; Kim, T. J.; Shim, S. C. *Chem. Commun.* **2000**, 1885–1886. (c) Jiang, B.; Si, Y. G. *J. Org. Chem.* **2002**, *67*, 9449–9451.

(13) (a) Skraup, H. *Chem. Ber.* **1880**, *13*, 2086–2087. (b) Friedländer, P. *Ber.* **1882**, *15*, 2572–2575. (c) Mansake, R. H.; Kulka, M. *Org. React.* **1953**, *7*, 59–98. (d) Linderman, R. J.; Kirollos, K. S. *Tetrahedron Lett.* **1990**, *31*, 2689–2693. (e) Theoclitou, M. E.; Robinson, L. A. *Tetrahedron Lett.* **2002**, *43*, 3907–3910.

(14) (a) Cheng, C.-C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37–201. (b) Thummel, R. P. *Synlett* **1992**, 1–12. (c) Eckert, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 208–210. (d) Gladiali, S.; Chelucci, G.; Mudadu, M. S.; Gastaut, M. A.; Thummel, R. P. *J. Org. Chem.* **2001**, *66*, 400–405.

(15) (a) Bose, D. S.; Kumar, R. K. *Tetrahedron. Lett.* **2006**, *47*, 813–816. (b) Wu, J.; Xia, H.-G.; Gao, K. *Org. Biomol. Chem* **2006**, *4*, 126–129. (c) Bose, D. S.; Kumar, R. K. *Heterocycles* **2006**, *68*, 549–559. (d) Zhou, T.; Lin, J.-L.; Chen, Z.-C. *Lett. Org. Chem.* **2008**, *5*, 47. (e) Niknam, K.; Zolfigol, M. A.; Dehghani, A. *Heterocycles* **2008**, *75*, 2513–2521. (f) Jiang, B.; Dong, J.-J.; Jin, Y.; Du, X.-L.; Xu, M. *Eur. J. Org. Chem.* **2008**, 2693–2696. (g) Palimkar, S. S.; Siddiqui, S. A.; Daniel, T; Lahoti, R. J.; Srinivasan, K. V. *J. Org. Chem.* **2003**, *68*, 9371–9378.

(16) (a) Strekowski, L.; Czarny, A.; Lee, H. *J. Fluorine Chem.* **2000**, *104*, 281–284. (b) Hu, Y. Z.; Zhang, G.; Thummel, R. P. *Org. Lett.* **2003**, *5*, 2251–2253. (c) Arcadi, A.; Chiarini, M.; Giuseppe, S. D.; Marinelli, F. *Synlett* **2003**, 203–206. (d) Yadav, J. S.; Reddy, B. V. S.; Premalatha, K. *Synlett* **2004**, 963–966. (e) McNaughton, B. R.; Miller, B. L. *Org. Lett.* **2003**, *5*, 4257–4259. (f) Walser, A.; Flynn, T.; Fryer, R. I. *J. Heterocycl. Chem.* **1975**, *12*, 737–741. (g) Sik, C. C.; Jin, S. H.; Chul, S. S. *J. Heterocycl. Chem.* **2005**, *42*, 1219–1222.

(17) (a) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68. (b) Nair, V.; Balagopal, L.; Rajan, R.; Mathew, J. *Acc. Chem. Res.* **2004**, *37*, 21–30. (c) Dhakshinamoorthy, A. *Synlett* **2005**, 3014–3015.

(18) (a) Bose, D. S.; Sudharshan, S.; Chavhan, S. W. *ARKIVOC* **2005**, (iii), 228–236. (b) Bose, D. S.; Fatima, L.; Mereyala,

H. B. *J. Org. Chem.* **2003**, *68*, 587–590. (c) Bose, D. S.; Rudradas, A. P.; Mereyala, H. B. *Tetrahedron Lett.* **2002**, *43*, 9195–9197.

(19) While preparing the manuscript a report has appeared which describes the utilization of CAN for the synthesis of quinolines in refluxing conditions for several hours. Sridharan, V.; Ribelles, P.; Ramos, M. T.; Menendez, J. C. *J. Org. Chem.* **2009**, *74*, 5715–5718.

(20) Fehnel, E. A. *J. Heterocycl. Chem.* **1967**, *4*, 565–570.

(21) Fehnel, E. A.; Cohn, D. E. *J. Org. Chem.* **1966**, *31*, 3852.

(22) Nottingham, D. W.; Witzeman, S. J. *J. Org. Chem.* **1991**, *56*, 1713–1718.

(23) Bose, D. S.; Idrees, M. *J. Org. Chem.* **2006**, *71*, 8261–8263.

(24) Muscia, G. C.; Bollini, M.; Carnevale, J. P.; Bruno, A. M.; Asís, S. E. *Tetrahedron Lett.* **2006**, *47*, 8811–8815.

(25) (a) Xiong, X.; Liu, H.; Fu, L.; Li, L.; Li, J.; Luo, X.; Mei, C. *Chemotherapy* **2008**, *54*, 463–474. (b) Vig, R.; Mao, C.; Venkatachalam, T. K.; Tuel-Ahlgren, L.; Sudbeck, E. A.;

Uckun, F. M. *Bioorg. Med. Chem.* **1998**, *6*, 1789–1797. (c) Nair, P. C.; Sobhia, M. E. *Eur. J. Med. Chem.* **2008**, *43*, 293–299.

(26) Meutermans, W.; Le, G. T.; Becker, B. *ChemMedChem* **2006**, *1*, 1164–1194.

(27) (a) Aft, R. L.; Zhang, F. W.; Gius, D. *Br. J. Cancer* **2002**, *87*, 805–812. (b) Suzuki, H.; Aly, N. S. M.; Wataya, Y.; Kim, H.-S.; Tamai, I.; Kita, M.; Uemura, D. *Chem. Pharm. Bull.* **2007**, *55*, 821–824.

(28) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888–3890.

(29) Cagir, A.; Eisenhauer, B. M.; Gao, R.; Thomas, S. J.; Hecht, S. M. *Bioorg. Med. Chem.* **2004**, *12*, 6287–6299.

(30) Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55–63.