Glycosylation of Fluoroquinolones through Direct and Oxygenated Polymethylene Linkages as a Sugar-Mediated Active Transport System for Antimicrobials

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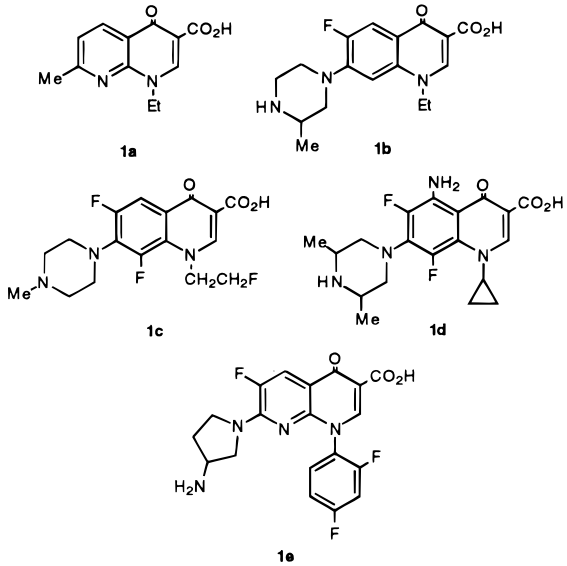
We report herein the synthesis and biological testing of several glycosylated derivatives of some fluoroquinolone antibiotics. In particular, we have prepared several glycosylated derivatives of ciprofloxacin (**2**) in which the carbohydrate units are linked to the free secondary amine of the piperazine unit by: (a) no linker (e.g., a glycosylamine), (b) a β-oxyethyl linker, and (c) a γ-oxypropyl linker. Both glucose and galactose were used as carbohydrates so that six compounds of this type were prepared, e.g., no linker **4a**,**b**, oxyethyl linker **5a**,**b**, and oxypropyl linker **6a**,**b**. In addition the aryl glycosides of glucose and galactose (**7a**,**b**) were prepared from the active 1-(4-hydroxyphenyl)fluoroquinolone (**3**.) The syntheses of the glycosylamines **4a**,**b** involved the direct condensation of glucose and galactose with the hydrochloride salt of ciprofloxacin (**2**). For the oxyalkyl-linked compounds, we first prepared the peracetylated ω-bromoalkyl glycopyranosides **14a**,**b** and **15a**,**b** and then coupled them to the allyl ester of ciprofloxacin (**11**) to give, after saponification to remove all of the esters, the desired fluoroquinolone carbohydrates **5a**,**b** and **6a**,**b**. The final series was prepared from 2,4,5-trifluorobenzoyl chloride (**22**) which gave **3** in four precedented steps. Coupling of **3** with the peracetylated glucosyl and galactosyl halides **12a**,**b** and **26** afforded, after saponification, the desired aryl glycosides **7a**,**b**. Six of these derivatives of ciprofloxacin—**4a**,**b**, **5a**,**b**, and **6a**,**b**—were subjected to microbiological screening. Of the six, compound **6a** showed the highest activity. Since **6a** would give the hydroxypropyl-substituted ciprofloxacin on hydrolysis and its activity is ∼4−8 times less than that of ciprofloxacin (**2**), this implies that compound **6a** is probably being actively transported. Thus preliminary results suggest that some of the compounds are stable in culture conditions and may be differentially transported by multiple resistant organisms. In some cases, the addition of a linker and a carbohydrate to ciprofloxacin lessens, but does not eliminate, antimicrobial activity.

Introduction

The increasing need for inexpensive broad-spectrum antibacterial agents with improved resistance and fewer side effects has prompted renewed interest in fluoroquinolones and their derivatives as potential compounds meeting these requirements. Since the introduction in 1963 of nalidixic acid (**1a**)[1] (Chart 1) for outpatient treatment of urinary tract infections, numerous analogues[2] of this prototype 4-quinolone antibiotic have been synthesized and used as Gram-negative antibacterial agents. The common drawback however to date of all these antibacterials is their rapid development of resistance,[3] requiring intravenous administration of "third-generation" antibiotics for patients with resistant organisms.

In the 1980s quinolones containing fluorine atoms[4] were introduced as a possible alternative. These "second-generation" antibiotics were significantly more potent in vitro, had broader antibacterial spectra than nalidixic acid, and possessed the desirable property of being absorbed after oral administration.[5] Moreover they had relatively long half-lives that allowed for twice-daily dosing, excellent distribution in tissues, and penetration

Chart 1. Structures of Some Members of the Quinolone Antibiotic Class



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into human cells, resulting in antimicrobial activity against intracellular pathogens.[6]

The most recently developed "third generation" of fluoroquinolones[7] retains many of the desirable properties of the second generation with some compounds exhibiting advantageous differences. Lomefloxacin (**1b**)[7a] and fleroxacin (**1c**),[7b] for example, have sufficiently long half-lives to allow only once-daily dosing, while sparfloxacin (**1d**)[7c] and tosufloxacin (**1e**)[7d] have enhanced activities against Gram-positive cocci and anaerobic bacteria. The mechanism of action responsible for the bactericidal activity of fluoroquinolone antibiotics[8] appears to be an inhibition of bacterial DNA gyrase. Fluoroquinolones interfere with the action of the DNA gyrase, preventing closure of the double-stranded nicks produced by the A-subunits.[8e,9] Failure to close these nicks inhibits supercoiling and results in the degradation of chromosomal DNA into fragments by exonucleases,[10] leading to termination of chromosomal replication and interference with cell division and gene expression.[8a,e,9,11]

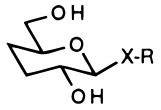
Quinolone inhibitors of the A-subunit of DNA gyrase fall into two major chemical groups: the quinolones and the 1,8-naphthyridones. Extensive SAR studies have been performed on these compounds using as indicators antigyrase activity, generally considered to be a measure of target enzyme inhibition, and/or antibacterial potency which reflects cell penetration and target enzyme inhibition. Hence, certain compounds having good antigyrase activity but poor antibacterial activity[12] are considered to be poor permeants.

Further SAR studies revealed that a fluorine atom at C-6 of the basic 1-alkyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid[12,13] can improve the potency and enhance the activity of an agent as well as broaden its antibacterial spectrum. At C-7 a piperazine ring has also been associated with enhanced potency, although many other substituents impart good activity to the molecule. In another study, Klopman et al.[13a] proposed that cell permeation is controlled by the nature of the C-7 substituent, since for Gram-negative bacteria, a piperazine or an N-substituted piperazine increased activity. Of all the fluoroquinolones, ciprofloxacin (**2**) demonstrated the most potent DNA gyrase-inhibiting activity.

To broaden the spectrum of activity or to intervene against resistance, co-administration of antibacterial agents is occasionally practiced, but incorporation of the molecular features of two different drugs in a single molecule rarely proves effective. Recently, however, one of the more novel attempts involved the successful coupling of a suitable quinolone and certain cephalosporins.[14]

Since the efficacy of a pharmacologic compound is predicated on efficient transport to its target site, we wanted to design actively transported prodrugs of antibacterial agents, where the prodrugs could enhance bacterial uptake of the drug as well as deliver it efficiently into the bacterial metabolism system. Several active transport systems which concentrate nutrients from the environment[15] have evolved, including the sugar-dependent phosphotransferase system (PTS) and the proton-linked system.[16] The most important drug delivery enzymes of the PTS are the glycoside transporters, the best-characterized among them being the

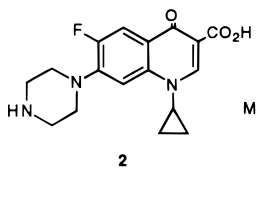
Chart 2



X = O, S, NH R = alkyl, aryl

lactose transporting system of *Staphylcoccus aureus* and the β-glucoside transporting system of enteric Gram-negative organisms.[17] The minimum structural requirement[18] for PTS-mediated transport of glycosides is shown in Chart 2.

Enhancing drug uptake by linkage to other compounds which serve as vehicles has been explored in the pharmaceutical industry for decades. In our study, the glycone would have affinity for the bacterial PTS and thus would serve as the "delivery vehicle", whereas the aglycone would be the fluoroquinolones. Once transported into the bacterial cell, the prodrug would be hydrolyzed to a sugar phosphate and the active antimicrobial at its intracellular target at a concentration 1000-fold higher than by passive transport. Two fluoroquinolones, ciprofloxacin (**2**) and the known fluoroquinolone **3**, were ultimately chosen as target molecules because of their excellent antibacterial activities and structural features. Ciprofloxacin (**2**) has the most



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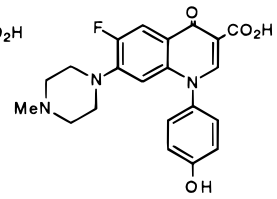
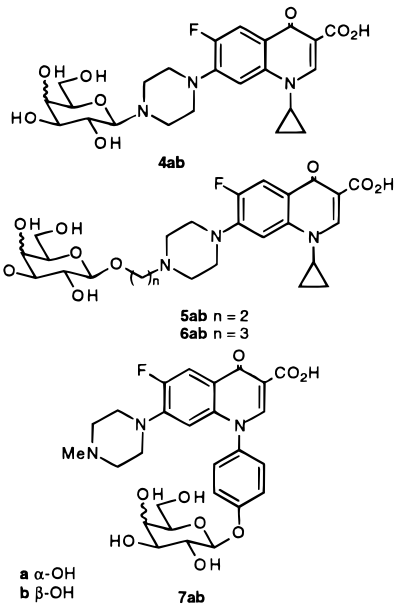


3

potent DNA gyrase-inhibiting activity of any of the fluoroquinolones as well as demonstrated clinical efficacy.[4b] It is the first oral broad-spectrum antimicrobial agent active against *Pseudomonas aeruginosa* and has excellent activity against a wide range of Gram-negative pathogens,[19] including those resistant to third-generation cephalosporins, broad-spectrum penicillins, and newer semisynthetic aminoglycosides. It also has good activity against Gram-positive bacteria. The selection of fluoroquinolone **3** was based on earlier studies[20] showing that methicillin-resistant *S. aureus* (MRSA) could grow on and rapidly hydrolyze aryl glucosides, suggesting that these organisms possessed a similar PTS. The 1-*p*-hydroxyphenyl-substituted compound **3** is the only example of a fluoroquinolone whose antibacterial potency was substantially (e.g., up to 32-fold) increased by the addition of a hydroxyl group.[21]

To minimize any adverse effect on the activity,[22] we decided to link the carbohydrate to the distal nitrogen of the piperazine unit. Several possible linkers, in addition to the absence of a linker unit, were considered: an oxygenated polymethylene chain linker, a carbamate or a urea linker, or a hydroxyamide amino acid linker. As the carbohydrate units, only glucose and galactose derivatives were considered since the best results of bacterial uptake of carbohydrates via the PTS involved these derivatives.[23] Thus we envisioned preparing three classes of prodrugs: **4a**,**b**, **5a**,**b** and **6a**,**b**, and **7a**,**b**.

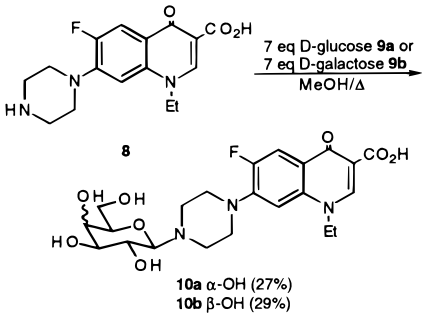


Results and Discussion

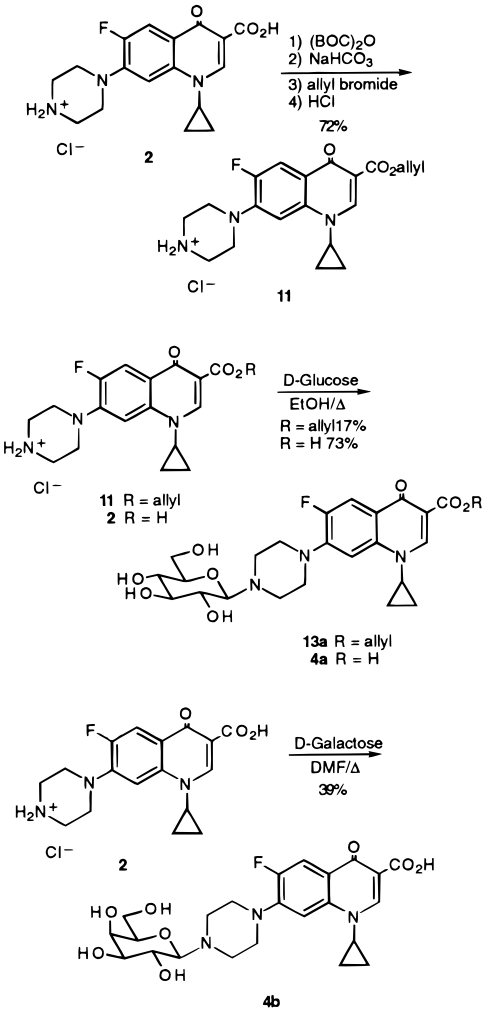
A. Synthesis of the Glycosylated Derivatives of Ciprofloxacin. (1) Synthesis of Directly Attached Carbohydrates (No Linkers). Many literature precedents exist for the preparation of *N*-glycosylamines,[24] including those of Chisholm and Van Vranken[25] who reported the glycosylation of 2,2′-indolylindolines with a variety of sugars. We chose to couple norfloxacin (**8**) directly with the hexoses D-glucose (**9a**) and D-galactose (**9b**) to afford the glycosylated norfloxacins **10a**,**b** in 27% and 29% yield, respectively (Scheme 1). However, we were unable to separate the unreacted D-galactose from the glycosylated product **10b**. After these preliminary results, we explored the synthetic efficiency of coupling sugar moieties with ciprofloxacin (**2**) and the antimicrobial activities of the resulting derivatives.

Ciprofloxacin hydrochloride (**2**)[26] was refluxed with unprotected D-glucose or D-galactose in methanol. After several attempts and prolonging the reaction time, no products were observed, due presumably to the low solubility of the starting materials in methanol. Consequently, a more soluble ester of ciprofloxacin was chosen and reacted with a protected glucose or galactose derivative followed by mild base-catalyzed deprotection of the resulting N-glycosylated ciprofloxacin ester. The allyl ester of ciprofloxacin (**11**) was prepared from **2** in 72% overall yield (Scheme 2) and then refluxed with tetraacetyl D-glucosyl bromide **12a** in dichloroethane in the presence of silver carbonate. Only starting material resulted. Further efforts, involving the use of silver triflate to increase the affinity of silver toward the glycosyl bromide as well as the use of collidine as a base to prevent occurrence of the Amadori rearrangement,[27] failed to give the desired product. However, when the ciprofloxacin ester **11** was reacted in a small-scale experiment with unprotected D-glucose in refluxing ethanol, compound **13a** was obtained in 17% yield. The unprotected ciprofloxacin (**2**) was then reacted with unprotected D-glucose in refluxing ethanol, producing exclusively the *β*-isomer **4a** in 73% yield. The same reaction was applied to the ciprofloxacin−galactose coupling, but no reaction occurred, presumably due to

Scheme 1



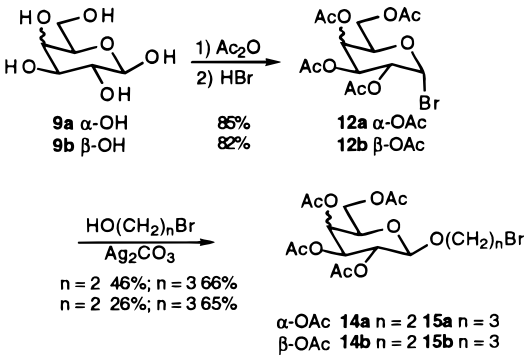
Scheme 2



the low solubility of galactose in ethanol. Refluxing *N*,*N*-dimethylformamide (DMF) eventually effected the desired coupling in 50% yield after 1 day of heating, yielding exclusively the *β*-isomer of the galactose derivative **4b**. The stereochemistry of the products was determined from the coupling constants of the anomeric protons in **4a**,**b** in the high-field ^{1}H NMR spectra, J = 8.8 Hz, in each compound, indicative of a trans-diaxial coupling in a pyranose.

Isolation and purification of the products **4a**,**b** was challenging due to their limited solubilities in most solvents and the lability of the newly formed C−N bond which effectively precluded attempts at crystallization. The only solvent offering any appreciable solubility was dimethyl sulfoxide (DMSO). The glucose derivative **4a**

Scheme 3



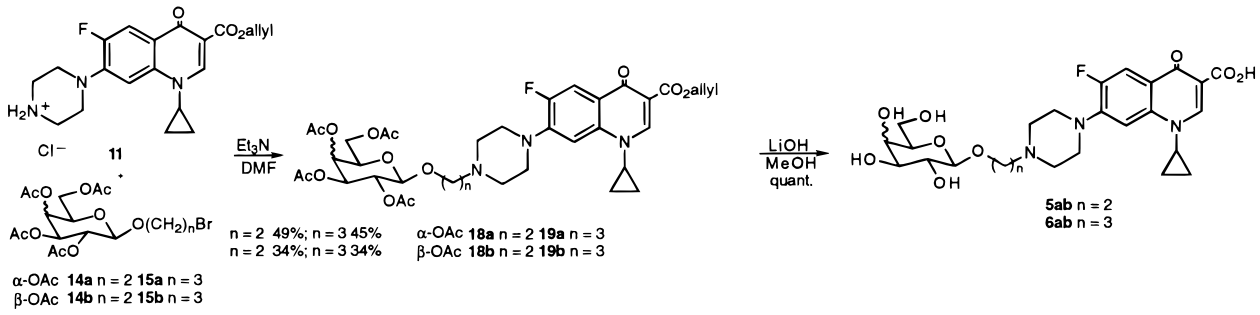
hydrolyzed slowly under fairly mild conditions of silica gel treatment or in water after 20 min, while the galactose derivative **4b** hydrolyzed immediately in water as well as on silica gel. Upon completion of the reaction, the aminoglucoside product **4a** was filtered as a hot suspension to remove excess sugar. After a quick wash with water under a constant stream of nitrogen, the aminoglucoside product **4a** was obtained in high purity by ^{1}H NMR. The crude aminogalactoside product **4b** was dried under vacuum to remove DMF, redissolved in hot methanol, and filtered to remove any insoluble impurities and residual DMF, a process that caused minor hydrolysis of the product. After concentration of the filtrate, hot ethanol was added to the resulting solid to remove the hydrolyzed products. The solution, filtered under nitrogen to avoid moisture, resulted in the purified β-aminogalactoside **4b** in 53% yield.

(2) Synthesis of Oxygenated Polymethylene-Linked Carbohydrates. The synthesis of the two- and three-carbon oxygenated linked derivatives required protection of both the sugar moiety and ciprofloxacin. The sugar derivatives **14a**,**b** and **15a**,**b**, appended to the desired oxygenated polymethylene linkers, were prepared via a Koenigs−Knorr displacement reaction of the corresponding tetraacetyl D-glycosyl bromides **12a**,**b**, formed in 82−85% yields from D-glucose and D-galactose **9a**,**b**, with 2-bromoethanol or 3-bromopropanol to give the bromoethyl glycosides **14a**,**b** in 46% and 26% yield and the bromopropyl compounds **15a**,**b** in 66% and 65% yield, respectively (Scheme 3). Coupling of the ciprofloxacin allyl ester (**11**) with the four bromoalkyl glycosides **14a**,**b** and **15a**,**b** was effected in the presence of triethylamine in hot DMF leading to the desired protected ω-(fluoroquinolonyl)alkyl glycoside tetraacetates **18a**,**b** and **19a**,**b** in 34−49% yields. As in the no linker series, only the β-anomers were isolated, as shown by the coupling constants of the anomeric protons in all four compounds in the high-field ^{1}H NMR spectra (J = 7.9−8.1 Hz). The final deprotection of all of the protecting groups was carried out in a single step, namely treatment with lithium hydroxide in methanol followed by filtration and evaporation to dryness to give the desired products **5a**,**b** and **6a**,**b**, which were purified by precipitation and/or crystallization (Scheme 4). During the synthesis of these oxygenated polymethylene-linked ciprofloxacin−sugar prodrugs, an unusual rearrangement of the sugar moiety under standard coupling conditions was observed. When ciprofloxacin allyl ester (**11**) was first alkylated with 3-bromopropanol and the resulting hydroxypropyl intermediate **20**, formed in 42% yield, was subjected to Koenigs−Knorr reaction with tetraacetyl glucosyl bromide **12a**, the product isolated in 74% yield was surprisingly the rearranged glucofuranoside derivative **21** (Scheme 5) and not the expected glucopyranoside derivative. It should be noted that the Koenigs−Knorr reaction in this instance required heating in dichloroethane for an extended period (since the reaction did not proceed at a lower temperature). This phenomenon would seem to suggest that the glucofuranosides are the more stable products of this equilibration process.[28]

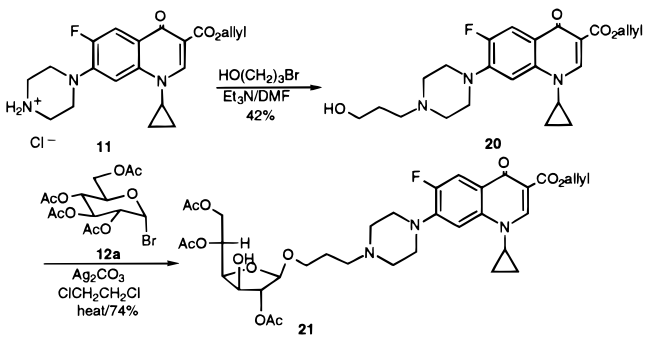
B. Synthesis of Aryl Glycosides of Fluoroquinolones. To prepare the desired hybrids **7a**,**b**, the 1-arylfluoroquinolone precursor **3** had to be made first (Scheme 6). The normal alkylation of a 4-oxoquinoline-3-carboxylate with an alkyl halide could not be used to introduce an aryl group at the 1-position. Consequently, the required 1-aryl derivative **3** was prepared by a 4-step process. Reaction of the acid chloride **22**[26] with the dianion of monoethyl malonate gave the 2,4,5-trifluorobenzoyl acetate in quantitative yield as a mixture of enol and keto tautomers **23a**,**b**. Treatment of this ester mixture with triethyl orthoformate in acetic anhydride gave the ethoxymethylene intermediate, which after evaporation of solvent to dryness, was allowed to react with a slight excess of 4-hydroxyaniline in methylene chloride at room temperature to give the enamino keto ester **24** in 91% yield from **23a**,**b**. Cyclization of **24** with sodium hydride in THF afforded in 96% yield the quinolinecarboxylate **25** which was allowed to react with *N*-methylpiperazine in hot DMF for an extended period to obtain the desired 1-arylfluoroquinolone **3** in 61% yield with 37% recovery of starting material. The overall yield of this 4-step synthesis is 85% (based on recovered starting material in the last step).

Coupling of the fluoroquinolone **3** with the tetraacetyl glucosyl iodide **26**, prepared from the pentaacetyl glycoside by treatment with trimethylsilyl iodide (TMSI),[29]

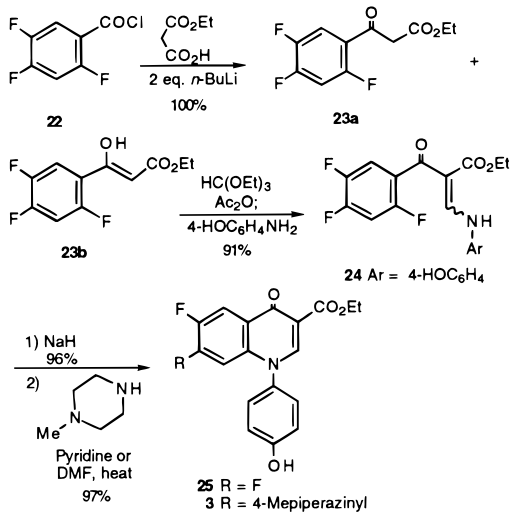
Scheme 4



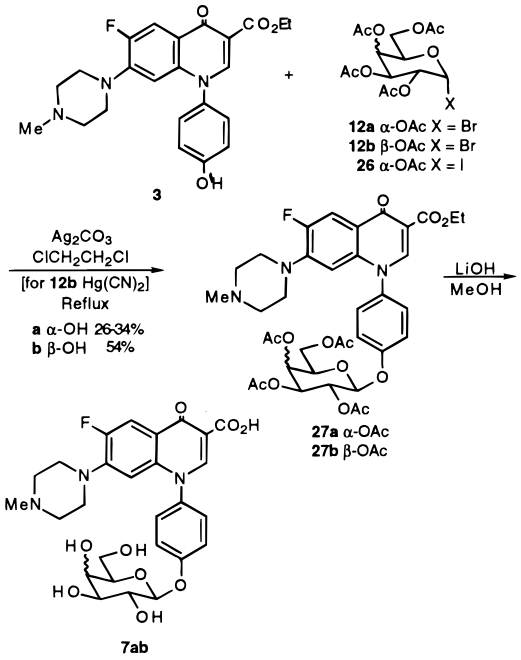
Scheme 5



Scheme 6



Scheme 7



or the corresponding bromides **12a**,**b** in the presence of silver carbonate (and mercuric cyanide in the galactose case) afforded the aryl glycosides of the fluoroquinolone ester **27a**,**b** in 26−34% yields for **27a** and 54% yield for **27b** (Scheme 7). Only the β-anomers were isolated, as shown by the coupling constants of the anomeric protons in the high-field ^{1}H NMR spectra (J = 7.1 and 7.0 Hz, respectively). Final deprotection of all of the protecting groups was carried out by treatment with lithium hydroxide in methanol followed by filtration and evaporation to dryness. After recrystallization from methanol/ethyl acetate, the desired products **7a**,**b** were obtained with a small amount of impurities.

C. Microbiological Testing of the Ciprofloxacin Derivatives. The six sugar conjugates of ciprofloxacin were subjected to microbiological screening along with the parent compound ciprofloxacin (**2**). The tests were performed at the New England Deaconess Hospital in a national reference lab for the microbial susceptibility testing of multiple-resistant bacteria. The compounds were tested against a panel of 32 organisms, including *E. faecalis*, *E. faecium*, *S. aureus*, *P. aeruginosa*, *E. coli*, and others with varying resistance modes. The resistant organisms tested against were vancomycin-resistant (VanA, VanB), cipro-resistant (Cipro-R), multiply resistant *S. aureus* (MRSA), multiply resistant *S. epidermidis* (MRSE), high-level gentamicin resistance (HLGR), and β-lactamase + (BLA+). The nonresistant stock strains from the American Type Culture Collection (ATCC) were also included as controls. Susceptibility testing was performed by the standard agar dilution technique according to NCCLS guidelines. Results were read at 19−24 h of incubation and expressed in terms of minimum inhibition concentrations (MIC) in μg/mL. Table 1 lists the results of microbial susceptibility testing of ciprofloxacin and its sugar conjugates. A less pure sample of the no linker ciprofloxacin−glucose conjugate (labeled as **4a*** in Table 1) was tested along with the pure sample (**4a** in Table 1) and gave comparable results.

Differences in MIC values are considered significant only when the dilution is more than a factor of 2 apart. On this basis, the results indicate that both of the no linker series of glucose or galactose conjugate (**4a**,**b**, respectively) exhibit activities comparable to the parent drug ciprofloxacin (**2**). It is probable that hydrolysis of **4a**,**b** occurred during culture incubation, thereby regenerating ciprofloxacin.

Among the sugar conjugates of ciprofloxacin prepared with direct linkage or with oxyethylene or oxypropylene linkages, **4a**,**b** without a linker were the most active, presumably due to hydrolysis to ciprofloxacin during incubation. The significantly lower activities of the remaining four conjugates with oxyethylene or oxypropylene linkers compared to that of ciprofloxacin suggested that these compounds had sufficient chemical stability in the culture system without liberation of the more active parent compound. Since hydrolysis of **6a** would give *N*-1-hydroxypropyl-substituted ciprofloxacin and its activity is ∼4−8 times less than that of ciprofloxacin (**2**), this implies that compound **6a** is probably being actively transported. The oxypropyleneglucoside **6a** was also more active (4-fold) than the oxypropylenegalactoside **6b** in a number of the organism strains tested, including *E. faecalis* (HLGR, BLA+), *E. faecium* (VanA, VanB), *S. aureus* (MRSA, ATCC), coagulation-negative *S. epidermidis* (MRSE, Cipro-R), *L. monocytogenes*, and *P. aeruginosa*.

Allowing for molecular weight differences, **6a** was perhaps only 2-fold less active than **2** for some resistant enterococci. The difference between **6a** and **6b** indicates

Table 1 [a]

			MIC (μg/mL)								
strain	species	characteristics	**2** (5/11/96)	**2** (8/28/96)	**4a*** (5/11/96)	**4a** (5/11/96)	**4b** (8/28/96)	**5a** (8/28/96)	**5b** (8/28/96)	**6a** (5/11/96)	**6b** (5/11/96)
A0089	*E. faecalis*	HLGR, BLA+	1	2	1	1	2	>32	>32	8	32
A0090	*E. faecalis*	HLGR, BLA+	1	1	1	1	1	32	32	4	16
A0401	*E. faecalis*	VanA	1	2	2	2	2	>32	>32	8	32
A0402	*E. faecalis*	VanA	1	1	1	1	2	32	32	8	32
A1079	*E. faecalis*	VanB	1	1	1	1	1	32	32	8	16
A1081	*E. faecalis*	VanB	0.5	0.5	1	0.5	0.5	16	16	4	16
29212	*E. faecalis*	ATCC	1	1	1	1	1	32	32	8	16
51299	*E. faecalis*	ATCC	1	1	1	1	0.5	16	32	8	16
A1745	*E. faecium*	VanA	>32	>32	>32	>32	>32	>32	>32	>32	>32
A2320	*E. faecium*	VanA	>32	>32	>32	>32	>32	>32	>32	>32	>32
A0803	*E. faecium*	VanB	2	2	4	2	4	>32	>32	16	>32
A1087	*E. faecium*	VanB	4	4	4	4	4	>32	>32	32	>32
19434	*E. faecium*	ATCC	8	8	8	8	8	>32	>32	>32	>32
A2043	*S. aureus*	MRSA, Cipro-R	>32	>32	>32	>32	>32	>32	>32	>32	>32
A2800	*S. aureus*	MRSA, Cipro-R	>32	>32	>32	>32	>32	>32	>32	>32	>32
A0170	*S. aureus*	MRSA	0.5	0.25	0.5	0.5	0.5	4	8	4	8
A0171	*S. aureus*	MRSA	0.5	0.5	0.5	0.5	0.5	8	8	4	16
29213	*S. aureus*	ATCC	0.5	0.5	1	1	0.5	16	8	4	16
A0247	coag.-neg. *Staph.*	MRSE, Cipro-R	>32	>32	>32	>32	>32	>32	>32	>32	>32
A0248	coag.-neg. *Staph.*	MRSE, Cipro-R	>32	>32	>32	>32	>32	>32	>32	>32	>32
A0244	coag.-neg. *Staph.*	MRSE	1	1	1	1	1	32	32	8	32
A0245	coag.-neg. *Staph.*	MRSE	0.5	0.5	0.5	0.5	0.5	16	16	4	8
A0182	*L. monocytogenes*		1	1	2	2	2	>32	>32	8	32
A0183	*L. monocytogenes*		1	1	2	2	2	>32	>32	8	32
28215	*P. aeruginosa*		0.5	0.25	0.5	0.5	0.25	32	16	4	16
28245	*P. aeruginosa*		2	1	4	4	1	>32	>32	32	>32
A3228	*E. coli*	Cipro-R	>32	>32	>32	>32	>32	>32	>32	>32	>32
A3529	*E. coli*	Cipro-R	32	32	32	32	32	>32	>32	>32	>32
AA	*E. coli*	Cipro-R	8	8	8	8	8	>32	>32	>32	>32
25922	*E. coli*	ATCC	<=0.03	<=0.03	<=0.03	<=0.03	<=0.03	2	1	0.12	0.25
AM	*K. pneumoniae*	Cipro-I	2	2	4	2	2	>32	>32	16	>32
A3530	*K. oxytoca*	Cipro-R	8	8	8	8	8	>32	>32	>32	>32

[a] Quality control strains and acceptable limits (as per NCCLS):

25922	*E. coli*	ATCC	0.004−0.015
27853	*P. aeruginosa*	ATCC	0.25−1.0
29213	*S. aureus*	ATCC	0.12−0.5
29212	*E. faecalis*	ATCC	0.25−2.0

either that the compounds have different *gyr*A inhibition or, more likely, that **6a** was transported more efficiently than **6b** or hydrolyzed more rapidly. Confirmatory stability, *gyr*A inhibition, and transport studies will be needed to differentiate these possibilities.

Conclusion

Eight novel fluoroquinolone glycosides were synthesized, and six of them in the ciprofloxacin series were evaluated for antimicrobial susceptibility. Preliminary results suggest that some of the compounds are stable in culture conditions and may be differentially transported by multiple resistant organisms. In some cases, the addition of a linker and a carbohydrate to ciprofloxacin lessens, but does not eliminate, antimicrobial activity.

Experimental Section

General. ^{1}H NMR spectra were recorded at 200z, 360, 400, or 500 MHz and are so indicated. ^{13}C NMR spectra were recorded at 100 MHz. Infrared spectra were recorded on an FT-IR as liquid films (neat), and only significant peaks were recorded. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} 0.2-mm plates. Visualization was done by using ultraviolet light or by using an acid-based stain, prepared from *p*-anisaldehyde (5 mL), concentrated sulfuric acid (5 mL), and glacial acetic acid (0.5 mL) in 95% ethanol (90 mL). Flash chromatography was carried out using E. Merck silica gel 60 (230−400 mesh). Solvent systems are reported as volume percent mixtures. Concentration in vacuo refers to the removal of solvent using a Büchi rotary evaporator and an aspirator pump. All inorganic solutions are aqueous and concentrations are indicated in percent weight, except saturated aqueous sodium chloride (brine). The following solvents and reagents were distilled from the indicated agent under dry nitrogen: dichloroethane from calcium hydride; methanol from magnesium; *N*,*N*-dimethylformamide (DMF) from calcium sulfate under reduced pressure. All other reagents were purified by literature procedures. All reactions were performed under an inert atmosphere of dry argon.

1-Cyclopropyl-1,4-dihydro-6-fluoro-7-[4-(*β*-glucopyranosyl)piperazinyl]-4-oxoquinoline-3-carboxylic Acid, 4a. To a suspension of ciprofloxacin (**2**) (1.0 g, 3.02 mmol) in absolute ethanol (50 mL) was added D-glucose (**9a**) (0.54 g, 3.00 mmol). The mixture was heated to reflux with stirring under an argon atmosphere for 48 h. The milky solution was filtered while it was still hot under a constant stream of nitrogen gas to avoid any moisture. The precipitate was washed with hot methanol (2 × 2 mL) and dried under vacuum, which afforded *β*-glucopyranosyl ciprofloxacin **4a** as a white solid (1.09 g, 73% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 15.18 (1H, s), 8.62 (1H, s), 7.86 (1H, d, J = 13.2 Hz), 7.52 (1H, d, J = 7.4 Hz), 4.91 (1H, d, J = 4.4 Hz), 4.84 (1H, d, J = 4.9 Hz), 4.52 (1H, d, J = 4.0 Hz), 4.34 (1H, t, J = 5.7 Hz), 4.31 (1H, t, J = 5.1 Hz), 3.80 (1H, m), 3.74 (1H, d, J = 8.8 Hz, anomeric), 3.63 (1H, d, J = 10.9 Hz), 3.43−3.36 (2H, m), 3.22 (2H, ddd, J = 3.8, 8.0, 8.0 Hz), 3.14 (2H, dm, J = 3.9 Hz), 3.05−2.97 (4H, m), 2.78−2.75 (2H, m), 1.27 (2H, d, J = 6.4 Hz), 1.15 (2H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 176.8, 166.5, 153.5 (d, J = 248.1 Hz), 148.4, 145.9 (d, J = 9.8 Hz),

139.7, 118.9 (d, J = 7.6 Hz), 111.4 (d, J = 22.7 Hz), 107.1, 106.7, 94.5, 78.9, 78.2, 70.8, 69.6, 61.8, 50.3, 47.0, 36.3, 8.0. HRMS FAB (*m*/*e*) calcd for $C_{23}H_{29}FN_3O_8$ $(M + H)^+$ 494.193869, found 494.192857.

1-Cyclopropyl-1,4-dihydro-6-fluoro-7-[4-(β-galactopyranosyl)piperazinyl]-4-oxoquinoline-3-carboxylic Acid, 4b. To a suspension of ciprofloxacin (**2**) (0.5 g, 1.51 mmol) in dry DMF (15 mL) was added D-galactose (**9b**) (0.27 g, 1.50 mmol). This mixture was heated to 70 °C under an argon atmosphere with stirring for 48 h. After the solvent was removed under vacuum, to the residue was added 25 mL of ethanol and the solution heated to reflux for 30 min. The solution was filtered while it was still hot under a constant stream of nitrogen gas to avoid any moisture. The precipitate was washed with hot methanol (2 × 2 mL) and dried under vacuum, which afforded β-galactopyranosyl ciprofloxacin **4b** as a yellow solid (0.29 g, 39% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 15.13 (1H, s), 8.61 (1H, s), 7.85 (1H, d, J = 13.2 Hz), 7.51 (1H, d, J = 7.1 Hz), 4.71 (1H, d, J = 5.0 Hz), 4.60 (1H, t, J = 5.2 Hz), 4.40 (1H, d, J = 3.4 Hz), 4.30 (1H, d, J = 4.0 Hz), 3.77 (1H, m), 3.68 (1H, d, J = 8.8 Hz, anomeric), 3.62−3.53 (2H, m), 3.50−3.17 (8H, m), 3.02−2.99 (2H, m), 2.75−2.72 (2H, m), 1.27 (2H, d, J = 5.9 Hz), 1.14 (2H, s). HRMS FAB (*m*/*e*) calcd for $C_{23}H_{29}FN_3O_8$ $(M + H)^+$ 494.193869, found 494.194250.

1-Cyclopropyl-1,4-dihydro-6-fluoro-7-[4-(2-[(β-glucopyranosyl)oxy]ethyl)piperazinyl]-4-oxoquinoline-3-carboxylic Acid, 5a. The protected adduct **18a** (43.1 mg, 0.058 mmol) was dissolved in a 3:1 mixture of methanol and water. Lithium hydroxide (24 mg, 0.58 mmol) was added to the solution and the mixture was stirred at room temperature overnight. The mixture was evaporated to dryness and redissolved in a small amount of methanol. The suspension was filtered through a plug of cotton and evaporated to obtain the desired product **5a** as a slightly yellow film (31 mg, 0.058 mmol, 100%). ^{1}H NMR (400 MHz, CD_3OD) δ: 8.75 (1H, s), 7.80 (1H, d, J = 13.7 Hz), 7.42 (1H, d, J = 7.3 Hz), 4.27 (1H, d, J = 7.7 Hz), 4.03−4.09 (1H, m), 3.84 (1H, bd, J = 11.3 Hz), 3.58−3.74 (3H, m), 3.25−3.27 (7H, m), 3.17−3.21 (1H, m), 2.65−2.78 (5H, m), 2.57−2.60 (1H, m), 0.62−0.67 (2H, m), 0.42−0.46 (2H, m). HRMS FAB (*m*/*e*) calcd for $C_{25}H_{33}FN_3O_9$ $(M + H)^+$ 538.220083, found 538.220564.

1-Cyclopropyl-1,4-dihydro-6-fluoro-7-[4-(2-[(β-galactopyranosyl)oxy]ethyl)piperazinyl]-4-oxoquinoline-3-carboxylic Acid, 5b. The protected adduct **18b** (47 mg, 0.064 mmol) was dissolved in a 3:1 mixture of methanol and water. Lithium hydroxide (24 mg, 0.58 mmol) was added to the solution and the mixture was stirred at room temperature overnight. The mixture was evaporated to dryness and redissolved in a small amount of methanol. The suspension was filtered through a plug of cotton and evaporated to obtain the desired product **5b** as a slightly yellow film (34 mg, 0.064 mmol, 100%). ^{1}H NMR (400 MHz, CD_3OD) δ: 8.77 (1H, s), 7.91 (1H, d, J = 13.7 Hz), 7.45 (1H, d, J = 7.5 Hz), 4.22 (1H, d, J = 7.5 Hz), 4.05−4.08 (1H, m), 3.81 (1H, d, J = 2.7 Hz), 3.70−3.75 (3H, m), 3.60−3.62 (1H, m), 3.43−3.55 (3H, m), 3.30−3.33 (4H, m), 2.65−3.05 (6H, m), 1.28−1.34 (2H, m), 1.10−1.14 (2H, m). HRMS FAB (*m*/*e*) calcd for $C_{25}H_{33}FN_3O_9$ $(M + H)^+$ 538.220083, found 538.220685.

1-Cyclopropyl-1,4-dihydro-6-fluoro-7-[4-(3-[(β-glucopyranosyl)oxy]propyl)piperazinyl]-4-oxoquinoline-3-carboxylic Acid, 6a. A solution of **19a** (111 mg, 0.1466 mmol) and lithium hydroxide (61.5 mg, 1.466 mmol) in 6 mL of methanol and water (5:1 ratio of MeOH−water) was stirred at room temperature for 24 h. The solvents were removed in vacuo to give an oily residue. Toluene was added then evaporated in vacuo to remove traces of water to give the desired product **6a** as a white solid (81 mg, 0.147 mmol, 100%). ^{1}H NMR (500 MHz, CD_3OD/CD_3CO_2D) δ: 8.71 (1H, s), 7.85 (1H, d, J = 13.5 Hz), 7.48 (1H, d, J = 7.3 Hz), 4.13 (1H, d, J = 7.7 Hz), 3.81 (1H, m), 3.72 (1H, bm), 3.66 (1H, d, J = 11.5 Hz), 3.51 (1H, dd, J = 11.9, 6.8 Hz), 3.45 (1H, dd, J = 11.9, 5.0 Hz), 3.28 (4H, bs), 3.07 (2H, m), 2.96 (1H, t, J = 8.1 Hz), 2.61 (4H, bs), 2.47 (2H, bt), 1.98 (1H, m), 1.73 (2H, m), 1.29 (2H, m), 1.09 (2H, bs). HRMS FAB (*m*/*e*) calcd for $C_{26}H_{35}FN_3O_9$ $(M + H)^+$ 552.235733, found 552.236157.

1-Cyclopropyl-1,4-dihydro-6-fluoro-7-[4-(3-[(β-galactopyranosyl)oxy]propyl)piperazinyl]-4-oxoquinoline-3-carboxylic Acid, 6b. A solution of **19b** (95.6 mg, 0.1258 mmol) and lithium hydroxide (52.8 mg, 1.258 mmol) in 6 mL of methanol and water (5:1 ratio of MeOH−water) was stirred at room temperature for 23 h. The solvents were removed in vacuo to give an oily residue. Toluene was added to this residue and then evaporated in vacuo to remove traces of water to give the product **6b** as a white solid (70 mg, 0.1269 mmol, 100%). ^{1}H NMR (500 MHz, CD_3OD/CD_3CO_2D) δ: 8.70 (1H, s), 7.87 (1H, d, J = 13.5 Hz), 7.52 (1H, d, J = 7.3 Hz), 4.08 (1H, d, J = 6.6 Hz), 3.81 (1H, m), 3.75 (1H, m), 3.64 (1H, s), 3.55−3.45 (3H, m), 3.32−3.27 (6H, m), 2.60 (4H, m), 2.46 (2H, t, J = 6.9 Hz), 1.98 (1H, m), 1.74 (2H, m), 1.30 (2H, m), 1.12 (2H, m). HRMS FAB (*m*/*e*) calcd for $C_{26}H_{35}FN_3O_9$ $(M + H)^+$ 552.235733, found 552.235987.

1,4-Dihydro-6-fluoro-1-[4-[(β-glucopyranosyl)oxy]phenyl]-7-(4-methylpiperazinyl)-4-oxoquinoline-3-carboxylic Acid, 7a. To a suspension of the fluoroquinolone ester **3** (42.1 mg, 0.1 mmol) and acetoiodoglucose **26** (50 mg, 0.1 mmol) or acetobromogalactose **12a** (90 mg, 0.19 mmol) in dry dichloroethane under an argon atmosphere were added silver carbonate (27.5 mg, 0.1 mmol) and 4 Å molecular sieves (∼20 mg). After the suspension was refluxed for 6 h under an argon atmosphere, the reaction mixture was filtered through Celite and the solution was evaporated. The resulting residue was chromatographed on silica gel (1:10 ethanol/CH_2Cl_2) to yield the acetylated sugar−fluoroquinolone complex **27a** as a white solid. HRMS FAB (*m*/*e*) calcd for $C_{37}H_{43}FN_3O_{13}$ $(M + H)^+$ 756.277992, found 756.277939. This solid was dissolved in methanol (5 mL), and lithium hydroxide (31 mg, 0.75 mmol) was added. After stirring for 2 h at room temperature, the solution was evaporated to give a crude solid. Recrystallization of this solid from ethanol/ethyl acetate yielded the desired compound **7a** (10 mg, 23%). ^{1}H NMR (400 MHz, D_2O) δ: 8.27 (1H, s), 7.79 (1H, d, J = 12.7 Hz), 7.34 (2H, d, J = 8.6 Hz), 7.21 (2H, d, J = 8.6 Hz), 6.44 (1H, d, J = 7.1 Hz), 5.10 (1H, d, J = 7.2 Hz), 3.80 (1H, dd, J = 12.4, 1.9 Hz), 3.60 (1H, dd, J = 12.3, 5.7 Hz), 3.56−3.46 (3H, m), 3.40 (1H, m), 2.88 (4H, bs), 2.42 (4H, bs), 2.09 (3H, s). HRMS FAB (*m*/*e*) calcd for $C_{27}H_{30}FN_3O_9Li$ $(M - H + Li)^+$ 566.2126, found 566.2135; calcd for $C_{27}H_{29}FN_3O_9Li_2$ $(M - 2H + 2Li)^+$ 572.2208, found 572.2224.

1,4-Dihydro-6-fluoro-1-[4-[(β-galactopyranosyl)oxy]-phenyl]-7-(4-methylpiperazinyl)-4-oxoquinoline-3-carboxylic Acid, 7b. To a suspension of the fluoroquinolone ester **3** (83 mg, 0.19 mmol) and acetobromogalactose **12b** (90 mg, 0.19 mmol) in dry dichloroethane an argon atmosphere were added silver carbonate (55 mg, 0.19 mmol), mercuric(II) cyanide (50 mg, 0.19 mmol), and 4 Å molecular sieves (∼20 mg). After the suspension was refluxed for 6 h under an argon atmosphere, the reaction mixture was filtered through Celite and the solution was evaporated. The resulting residue was chromatographed on silica gel (1:10 ethanol/CH_2Cl_2) to yield the acetylated sugar−fluoroquinolone complex **27b** as a white solid. HRMS FAB (*m*/*e*) calcd for $C_{37}H_{43}FN_3O_{13}$ $(M + H)^+$ 756.277992, found 756.277939. This solid was dissolved in 5:1 methanol/H_2O (10 mL), and lithium hydroxide (42 mg, 0.99 mmol) was added. After stirring for 5 min at room temperature, the solution was evaporated to give a crude solid. Recrystallization of this solid from methanol/ethyl acetate yielded the desired compound **7b** (52 mg, 47%). ^{1}H NMR (400 MHz, D_2O) δ: 8.26 (1H, s), 7.82 (1H, d, J = 13.1 Hz), 7.36 (2H, d, J = 8.6 Hz), 7.21 (2H, d, J = 8.6 Hz), 6.48 (1H, d, J = 7.0 Hz), 5.04 (1H, d, J = 7.6 Hz), 3.89 (1H, d, J = 3.12 Hz), 3.81−3.63 (5H, m), 2.91 (4H, bs), 2.44 (4H, bs), 2.10 (3H, s). HRMS FAB (*m*/*e*) calcd for $C_{27}H_{30}FN_3O_9Li$ $(M - H + Li)^+$ 566.2126, found 566.2141; calcd for $C_{27}H_{29}FN_3O_9Li_2$ $(M - 2H + 2Li)^+$ 572.2208, found 572.2227.

2-Propenyl 1-Cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-piperazinylquinoline-3-carboxylate Hydrochloride, 11. A solution of ciprofloxacin (**2**) (5.01 g, 15.1 mmol), di-*tert*-butyl dicarbonate (4.025 g, 18.4 mmol), and sodium bicarbonate (6.27

g, 74.6 mmol) in 100 mL of anhydrous DMF was stirred at room temperature for 2.5 h under an argon atmosphere. Allyl bromide (6 mL, 69.5 mmol, freshly distilled) was added and the reaction mixture was heated at 90−100 °C for 24 h. After the mixture was cooled to room temperature, the solvent was removed in vacuo to give a white residue. This was taken up in 100 mL of chloroform and 50 mL of dichloromethane. The mixture was washed with water (2 × 100 mL) and brine (1 × 100 mL) and dried over sodium sulfate. After evaporation of the solvents in vacuo, 7.08 g of a white solid was obtained. It was then dissolved in 130 mL of ethyl acetate in a 500-mL Erlenmeyer flask. Concentrated HCl (∼20 mL) was added dropwise and the solution turned a yellow color. The solvent was removed in vacuo to give 4.00 g (72% yield) of the desired protected ciprofloxacin **11** as a yellow solid. ^{1}H NMR (200 MHz, CD_3OD) δ: 9.40 (2H, bs), 8.43 (1H, s), 7.73 (1H, d, J = 13.2 Hz), 7.40 (1H, d, J = 7.1 Hz), 5.95 (1H, m), 5.50−5.10 (2H, m), 4.67 (2H, d, J = 5.0 Hz), 4.00−3.20 (9H, m), 1.26 (2H, bm), 1.07 (2H, bm).

Acetobromoglucose, 12a. This compound was prepared in 85% yield on a 10-g scale by treatment of D-glucose with acetic anhydride and catalytic sulfuric acid followed by treatment of the intermediate product with acetic anhydride and HBr according to the procedure reported by Redemann.[31] ^{1}H NMR (360 MHz, $CDCl_3$) δ: 6.61 (1H, d, J = 4.0 Hz), 5.59 (1H, t, J = 9.7 Hz), 5.16 (1H, t, J = 9.8 Hz), 4.83 (1H, dd, J = 9.9, 4.0 Hz), 4.35−4.28 (2H, m), 4.13 (1H, dd, J = 12.5, 1.9 Hz), 2.10 (3H, s), 2.09 (3H, s), 2.05 (3H, s), 2.04 (3H, s).

Acetobromogalactose, 12b. This compound was prepared in 82% yield on an 8-g scale by treatment of D-galactose with acetic anhydride and catalytic sulfuric acid followed by treatment of the intermediate product with acetic anhydride and HBr according to the procedure reported by Redemann.[30] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.70 (1H, d, J = 3.9 Hz), 5.52 (1H, dd, J = 3.3, 1.3 Hz), 5.40 (1H, dd, J = 10.6, 3.3 Hz), 5.05 (1H, dd, J = 10.6, 3.9 Hz), 4.48 (1H, t, J = 6.7 Hz), 4.19 (1H, dd, J = 11.4, 6.7 Hz), 4.11 (1H, dd, J = 11.4, 6.7 Hz), 2.15 (3H, s), 2.05 (3H, s), 2.04 (3H, s), 2.01 (3H, s).

2-Bromoethyl β-Glucopyranoside Tetraacetate, 14a. To a solution of acetobromoglucose **12a** (100 mg, 0.24 mmol) and 2-bromoethanol (32 mg, 0.24 mmol) in anhydrous dichloroethane were added silver carbonate (66.18 mg, 0.24 mmol) and crushed 4 Å molecular sieves (∼50 mg). After the reaction mixture stirred for 2 h under an argon atmosphere, TLC indicated that all starting material had been consumed. The reaction mixture was filtered through Celite and the solution evaporated in vacuo. The residue was chromatographed on silica gel (hexane/ethyl acetate, 2:1) to obtain the desired product **14a** as a colorless oil (50 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.20 (1H, app t, J = 9.4 Hz), 5.07 (1H, app t, J = 9.6 Hz), 5.00 (1H, dd, J = 9.6, 8.0 Hz), 4.56 (1H, d, J = 7.9 Hz), 4.24 (1H, dd, J = 12.3, 4.8 Hz), 4.11−4.17 (2H, m), 3.77−3.83 (1H, m), 3.70 (1H, ddd, J = 10.0, 4.8, 2.4 Hz), 3.43−3.46 (2H, m), 2.08 (3H, s), 2.05 (3H, s), 2.01 (3H, s), 1.99 (3H, s).

2-Bromoethyl β-Galactopyranoside Tetraacetate, 14b. To a solution of acetobromogalactose **12b** (478 mg, 1.16 mmol) and 2-bromoethanol (305 mg, 2.32 mmol) in anhydrous dichloroethane were added silver carbonate (320 mg, 0.24 mmol) and crushed 4 Å molecular sieves (∼50 mg). After the reaction mixture stirred for 2 h under an argon atmosphere, TLC indicated that all starting material had been consumed. The reaction mixture was filtered through Celite and the solution evaporated. The residue was chromatographed on silica gel (1:2 ethyl acetate/hexane) to obtain the desired product **14b** as a colorless oil (137 mg, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.35 (1H, dd, J = 1.0, 3.4 Hz), 5.19 (1H, dd, J = 10.5, 7.9 Hz), 4.99 (1H, dd, J = 10.5, 3.4 Hz), 4.51 (1H, d, J = 7.9 Hz), 4.17−4.05 (3H, m), 3.89 (1H, td, J = 6.6, 1.1 Hz), 3.75−3.82 (1H, m), 3.41−3.48 (2H, m), 2.11 (3H, s), 2.05 (3H, s), 2.02 (3H, s), 1.95 (3H, s).

3-Bromopropyl β-Glucopyranoside Tetraacetate, 15a. To a solution of acetobromoglucose **12a** (700 mg, 1.702 mmol) in 1,2-dichloroethane (8.5 mL, 0.2 M) were added 3-bromopropanol (308 mL, 3.405 mmol), 4 Å molecular sieves (∼50 mg), and silver carbonate (258.1 mg, 0.936 mmol). The reaction mixture was stirred under an argon atmosphere for 12 h at room temperature in the dark. The solids were filtered and the filtrate was concentrated in vacuo to give a crude residue. Flash column chromatography (30−35% ethyl acetate−hexane) of the crude residue gave 672.8 mg (66% yield) of the desired product **15a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.20 (1H, t, J = 9.5 Hz), 5.06 (1H, t, J = 9.9 Hz), 4.97 (1H, dd, J = 9.6, 8.0 Hz), 4.49 (1H, d, J = 8.0 Hz), 4.25 (1H, dd, J = 12.3, 4.8 Hz), 4.12 (1H, dd, J = 12.3, 2.4 Hz), 3.97 (1H, m), 3.69 (2H, m), 3.45 (2H, m), 2.15 (2H, m), 2.08 (3H, s), 2.05 (3H, s), 2.01 (3H, s), 1.99 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.56, 170.14, 169.30 (x2), 100.93, 72.59, 71.68, 71.12, 68.24, 67.23, 61.78, 32.10, 30.00, 20.64, 20.59, 20.50, 20.49. IR (neat): 2961, 1755, 1435, 1370, 1223, 1171, 1040 cm^{-1}.

3-Bromopropyl β-Galactopyranoside Tetraacetate, 15b. To a solution of acetobromogalactose **12b** (1.2867 g, 3.129 mmol) in 1,2-dichloroethane (15 mL, 0.2 M) were added 3-bromopropanol (566 mL, 6.258 mmol), 4 Å molecular sieves (∼50 mg), and silver carbonate (474.6 mg, 1.721 mmol). The reaction mixture was stirred under an argon atmosphere for 48 h at room temperature in the dark. The solids were filtered and the filtrate was concentrated in vacuo to give a crude residue. Flash column chromatography on silica gel (1:3 ethyl acetate/hexane) of the crude residue gave 961.2 mg (65% yield) of the desired product **14b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.36 (1H, dd, J = 3.4, 0.9 Hz), 5.15 (1H, dd, J = 10.5, 7.9 Hz), 4.99 (1H, dd, J = 10.5, 3.4 Hz), 4.45 (1H, d, J = 7.9 Hz), 4.12 (2H, m), 3.96 (1H, m), 3.89 (1H, dt, J = 0.9, 6.7 Hz), 3.66 (1H, m), 3.44 (2H, m), 2.13 (2H, m), 2.12 (3H, s), 2.05 (3H, s), 2.03 (3H, s), 1.95 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.30, 170.15, 170.04, 169.46, 101.40, 70.69, 70.50, 68.70, 67.19, 66.87, 61.15, 32.07, 30.08, 20.70, 20.57, 20.54, 20.47. IR (neat): 2942, 1752, 1435, 1372, 1223, 1055 cm^{-1}.

Propenyl 1-Cyclopropyl-1,4-dihydro-6-fluoro-7-[4-(2-[(β-glucopyranosyl)oxy]ethyl)piperazinyl]-4-oxoquinoline-3-carboxylate Tetraacetate, 18a. The 2-bromoethyl β-glucopyranoside tetraacetate (**14a**) (48.6 mg, 0.11 mmol) and ciprofloxacin allyl ester hydrochloride (**11**) (22.4 mg, 0.055 mmol) were dissolved in dry DMF (1 mL). The reaction mixture was heated at 100 °C under an argon atmosphere for 20 h. The solution was evaporated and the residue was chromatographed on silica gel (chloroform:methanol gradient elution 98:2 to 90:10) to obtain the desired product **18a** as a slightly yellow film (20 mg, 49%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.54 (1H, s), 8.01 (1H, d, J = 13.3 Hz), 7.27 (1H, d, J = 7.1 Hz), 6.08 (1H, ddt, J = 17.2, 10.5, 5.5 Hz), 5.50 (1H, ddd, J = 17.2, 3.1, 1.5 Hz), 5.30 (1H, ddd, J = 10.5, 2.6, 1.2 Hz), 5.24 (1H, app t, J = 9.5 Hz), 5.12 (1H, dd, J = 9.8, 9.6 Hz), 5.04 (1H, dd, J = 9.6, 8.0 Hz), 4.84 (2H, dt, J = 5.5, 1.3 Hz), 4.61 (1H, d, J = 8.0 Hz, anomeric), 4.29 (1H, dd, J = 12.3, 4.7 Hz), 4.18 (1H, dd, J = 12.3, 2.4 Hz), 4.04 (1H, ddd, J = 10.4, 5.6, 5.6 Hz), 3.71−3.78 (2H, m), 3.46 (1H, ddd, J = 10.6, 7.1, 3.9 Hz), 3.28 (4H, m), 2.69−2.79 (6H, m), 2.11 (3H, s), 2.08 (3H, s), 2.05 (3H, s), 2.03 (3H, s), 1.32−1.38 (2H, m), 1.13−1.17 (2H, m). HRMS FAB (*m*/*e*) calcd for $C_{36}H_{45}FN_3O_{13}$ $(M + H)^+$ 746.293642, found 746.294032.

Propenyl 1-Cyclopropyl-1,4-dihydro-6-fluoro-7-[4-(2-[(β-galactopyranosyl)oxy]ethyl)piperazinyl]-4-oxoquinoline-3-carboxylate Tetraacetate, 18b. The 2-bromoethyl β-galactopyranoside tetraacetate (**14b**) (118 mg, 0.26 mmol) and ciprofloxacin allyl ester hydrochloride (**11**) (54.2 mg, 0.13 mmol) were dissolved in dry DMF (1 mL). The reaction mixture was heated at 100 °C under an argon atmosphere for 20 h. The solution was evaporated and the residue was chromatographed on silica gel (chloroform/MeOH gradient elution 98:2 to 90:10) to obtain the desired product **18b** as a slightly yellow film (33 mg, 34%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.50 (1H, s), 7.98 (1H, d, J = 13.3 Hz), 7.24 (1H, d, J = 7.1 Hz), 6.03 (1H, ddt, J = 17.2, 10.5, 5.5 Hz), 5.45 (1H, d, J = 17.2, 1.5 Hz), 5.38 (1H, d, J = 3.4 Hz), 5.23 (2H, m), 5.01 (1H, dd, J = 10.4, 3.4 Hz), 4.80 (2H, dt, J = 5.5, 1.2 Hz), 4.53 (1H, d, J = 8.0 Hz, anomeric), 4.18 (1H, dd, J = 12.1, 6.5 Hz), 4.11 (1H, dd, J = 11.2, 6.9 Hz), 4.01 (1H, ddd, J = 5.4, 5.4, 10.4 Hz), 3.91 (1H,

app t, $J = 7.4$ Hz), 3.70−3.74 (1H, m), 3.39−3.43 (1H, m), 3.25 (4H, app t, $J = 4.5$ Hz), 2.65−2.67 (6H, m), 2.14 (3H, s), 2.05 (3H, s), 2.03 (3H, s), 1.97 (3H, s), 1.27−1.32 (2H, m), 0.09−1.13 (2H, m). HRMS FAB (*m*/*e*) calcd for $C_{36}H_{45}FN_3O_{13}$ $(M + H)^+$ 746.293642, found 746.294192.

2-Propenyl 1-Cyclopropyl-1,4-dihydro-6-fluoro-7-[4-(3-[(*β*-glucopyranosyl)oxy]propyl)piperazinyl]-4-oxoquinoline-3-carboxylate, 19a. To a solution of the bromide **15a** (253.1 mg, 0.5393 mmol) and ciprofloxacin allyl ester hydrochloride (**11**) (200 mg, 0.4903 mmol) in 5 mL of dry DMF was added triethylamine (410 mL, 2.9418 mmol). The reaction mixture was heated at 90−100 °C for 24 h under an argon atmosphere. The solvent was then removed in vacuo to give an oily residue. Flash column chromatography (silica gel, 4% MeOH−chloroform) of this crude residue gave 184.6 mg (45% yield) of the desired product **19a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (1H, s), 7.98 (1H, d, $J = 13.2$ Hz), 7.24 (1H, d, $J = 7.1$ Hz), 6.03 (1H, ddt, $J = 17.2$, 10.4, 5.4 Hz), 5.46 (1H, d, $J = 17.2$ Hz), 5.25 (1H, d, $J = 10.4$ Hz), 5.20 (1H, t, $J = 9.5$ Hz), 5.08 (1H, t, $J = 9.7$ Hz), 4.99 (1H, t, $J = 8.1$ Hz), 4.80 (2H, d, $J = 5.4$ Hz), 4.50 (1H, d, $J = 7.9$ Hz, anomeric), 4.25 (1H, dd, $J = 12.3$, 4.6 Hz), 4.13 (1H, dd, $J = 12.2$, 2.2 Hz), 3.94 (1H, m), 3.69 (1H, m), 3.58 (1H, m), 3.42 (1H, bm), 3.27 (4H, m), 2.63 (4H, bm), 2.46 (2H, bm), 2.08 (3H, s), 2.05 (3H, s), 2.01 (3H, s), 2.00 (3H, s), 1.81 (2H, m), 1.30 (2H, m), 1.12 (2H, m). HRMS FAB (*m*/*e*) calcd for $C_{37}H_{47}FN_3O_{13}$ $(M + H)^+$ 760.309292, found 760.310322.

2-Propenyl 1-Cyclopropyl-1,4-dihydro-6-fluoro-7-[4-(3-[(*β*-galactopyranosyl)oxy]propyl)piperazinyl]-4-oxoquinoline-3-carboxylate, 19b. To a solution of the bromide **15b** (281 mg, 0.598 mmol) and ciprofloxacin allyl ester hydrochloride (**11**) (222 mg, 0.5442 mmol) in 6 mL of dry DMF was added triethylamine (455 mL, 3.2654 mmol). The reaction mixture was heated at 90−100 °C for 23 h under an argon atmosphere. The solvent was then removed in vacuo to give an oily residue. Flash column chromatography (silica gel, 4−5% MeOH−chloroform) of this crude residue gave 155.9 mg (34% yield) of the desired product **19b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (1H, s), 7.96 (1H, d, $J = 13.3$ Hz), 7.23 (1H, d, $J = 7.1$ Hz), 6.04 (1H, ddt, $J = 17.1$, 10.4, 5.5 Hz), 5.45 (1H, dd, $J = 17.1$, 1.4 Hz), 5.37 (1H, d, $J = 3.0$ Hz), 5.25 (1H, dd, $J = 10.5$, 1.2 Hz), 5.18 (1H, dd, $J = 10.4$, 8.0 Hz), 5.00 (1H, dd, $J = 10.5$, 3.4 Hz), 4.79 (2H, d, $J = 5.5$ Hz), 4.46 (1H, d, $J = 7.9$ Hz, anomeric), 4.17 (1H, dd, $J = 11.2$, 6.4 Hz), 4.09 (1H, dd, $J = 11.2$, 7.1 Hz), 3.95 (1H, m), 3.89 (1H, t, $J = 6.8$ Hz), 3.57 (1H, m), 3.41 (1H, m), 3.26 (4H, m), 2.63 (4H, m), 2.47 (2H, t, $J = 6.3$ Hz), 2.14 (3H, s), 2.05 (3H, s), 2.03 (3H, s), 1.97 (3H, s), 1.80 (2H, m), 1.28 (2H, m), 1.11 (2H, m). HRMS FAB (*m*/*e*) calcd for $C_{37}H_{47}FN_3O_{13}$ $(M + H)^+$ 760.309292, found 760.310437.

2-Propenyl 1-Cyclopropyl-1,4-dihydro-6-fluoro-7-[4-(3-hydroxypropyl)piperazinyl]-4-oxoquinoline-3-carboxylate, 20. A solution of ciprofloxacin allyl ester hydrochloride (**11**) (500 mg, 1.22 mmol), 3-bromopropanol (200 mg, 1.41 mmol), and triethylamine (1.0 mL, 7.2 mmol) in 3.0 mL of dry DMF was heated at 100−110 °C for 15 h under an argon atmosphere. After the reaction mixture was cooled to room temperature, the solids were filtered off and rinsed with ∼5 mL of DMF. The DMF was removed under vacuum on a rotary evaporator to give an oily residue. Flash column chromatography (90:10 chloroform−methanol) of this crude residue provided the desired *N*-(3-hydroxypropyl) product **20** as a white solid (222 mg, 42%). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 8.47 (1H, s), 7.92 (1H, d, $J = 13.2$ Hz), 7.21 (1H, d, $J = 7.0$ Hz), 6.03 (1H, ddt, $J = 17.1$, 10.7, 5.2 Hz), 5.44 (1H, d, $J = 17.3$ Hz), 5.25 (1H, d, $J = 10.4$ Hz), 4.78 (2H, d, $J = 5.3$ Hz), 3.82 (2H, bt, $J = 5.0$ Hz), 3.40 (1H, bm), 3.24 (4H, bm), 2.74 (6H, bm), 2.50 (1H, bt, $J = 5.0$ Hz), 1.77 (2H, bt, $J = 5.2$ Hz), 1.27 (2H, bm), 1.11 (2H, bm). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 172.87, 165.13, 153.23 (d, $J = 247$ Hz), 148.15, 144.19 (d, $J = 11$ Hz), 137.80, 132.27, 122.93 (d, $J = 7$ Hz), 118.05, 113.00 (d, $J = 23$ Hz), 109.80, 104.86, 65.26, 64.34, 58.52, 52.90, 49.81, 34.44, 26.96, 8.01. HRMS FAB (*m*/*e*) calcd for $C_{23}H_{29}FN_3O_4$ $(M + H)^+$ 430.214210, found 430.214416.

2-Propenyl 1-Cyclopropyl-1,4-dihydro-6-fluoro-7-[4-(3-[(*β*-glucofuranosyl)oxy]propyl)piperazinyl]-4-oxoquinoline-3-carboxylate 2′,5′,6′-Triacetate, 21. To a solution of acetobromoglucose **12a** (452 mg, 1.1 mmol) in 1,2-dichloroethane (5.0 mL, 0.2 M) were added the 3-hydroxypropyl ciprofloxacin allyl ester (**20**) (430 mg, 1.0 mmol), 4 Å molecular sieves (∼30 mg), and silver carbonate (303.3 mg, 1.1 mmol). The reaction mixture was heated at 50−60 °C under an argon atmosphere for 12 h in the dark. The solids were filtered off and the filtrate was concentrated in vacuo to give a crude residue. Flash column chromatography (95:5 chloroform−methanol) of this crude residue gave the unexpected glucofuranose product **21** (561 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (1H, s), 8.01 (1H, d, $J = 13.3$ Hz), 7.25 (1H, d, $J = 6.6$ Hz), 6.05 (1H, ddt, $J = 17.1$, 10.5, 5.1 Hz), 5.71 (1H, d, $J = 5.2$ Hz), 5.46 (1H, dd, $J = 17.2$, 1.4 Hz), 5.26 (1H, dd, $J = 10.4$, 1.3 Hz), 5.19 (1H, t, $J = 2.8$ Hz), 4.89 (1H, dd, $J = 9.6$, 2.2 Hz), 4.82 (2H, d, $J = 5.5$ Hz), 4.32 (1H, dd, $J = 4.5$, 3.2 Hz), 4.20 (2H, bm), 3.95 (1H, m), 3.56 (2H, t, $J = 6.3$ Hz), 3.42 (1H, m), 3.27 (4H, m), 2.65 (4H, m), 2.48 (2H, bt, $J = 7.2$ Hz), 2.10 (3H, s), 2.09 (3H, s), 2.08 (3H, s), 1.81 (1H, bs), 1.77 (2H, m), 1.31 (2H, bm), 1.12 (2H, bm). HRMS FAB (*m*/*e*) calcd for $C_{35}H_{45}FN_3O_{12}$ $(M + H)^+$ 718.298728, found 718.299275.

Ethyl 2,4,5-Trifluoro-α-oxobenzenepropanoate, 23a, and Ethyl 3-Hydroxy-3-(2,4,5-trifluorophenyl)-2-propenoate, 23b. To a solution of the monoethyl malonate (1.0 g, 7.58 mmol) and triphenylmethane (∼3 mg) in 30 mL of THF under an argon atmosphere was slowly added *n*-butyllithium (2.5 M in THF) until the solution turned orange. The solution was then cooled to −50 °C and to it was added the solution of the acid chloride **22** (0.5 g, 2.53 mmol) in 8 mL of THF dropwise. After the addition, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. After it was diluted with ether, the reaction mixture was washed with 10% HCl solution, saturated sodium bicarbonate solution, and brine. The organic layer was dried over $MgSO_4$ and evaporated to yield the crude trifluorobenzoyl acetates **23a**,**b** (0.63 g, 100%) as a yellow oil, which exist as a mixture of enol and keto tautomers. Compound **23a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.71 (1H, s), 7.74 (1H, m), 7.00 (1H, m), 5.84 (1H, s), 4.26 (2H, q, $J = 7.2$ Hz), 1.34 (3H, t, $J = 7.2$ Hz). Compound **23b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82 (1H, m), 7.02 (1H, m), 4.21 (2H, q, $J = 7.2$ Hz), 4.26 (3H, t, $J = 7.2$ Hz), 3.94 (2H, d, $J = 3.8$ Hz).

Ethyl 2,4,5-Trifluoro-*β*-([(4-hydroxyphenyl)amino]-methylene)-α-oxobenzenepropanoate, 24. A solution of the esters **23a**,**b** (1 g, 4.06 mmol) in ethyl orthoformate (0.71 g, 6.13 mmol) and acetic anhydride (5.30 g, 52 mmol) was heated at 130 °C under an argon atmosphere for 2 h with removal of the ethyl acetate formed during the reaction. The solution was evaporated under reduced pressure to give an oil that was dissolved in dichloromethane (40 mL). 4-Hydroxyaniline (0.50 g, 4.5 mmol) was added to the solution. After stirring at room temperature for 1 h, the solution was evaporated to dryness and a light yellow solid was obtained. The solid was washed with hexane, filtered, and dried under vacuum to give the phenol **24** (1.357 g, 91%) as a creamy white solid as a mixture of *E* and *Z* isomers. *Z* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 13.4 (1H, bd, $J = 13.7$ Hz), 8.48 (1H, d, $J = 13.7$ Hz), 7.30 (1H, m), 7.13 (2H, d, $J = 8.8$ Hz), 6.92−6.78 (3H, m), 5.50 (1H, bs), 4.11 (2H, q, $J = 7.1$ Hz), 1.10 (3H, t, $J = 7.1$ Hz). *E* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 14.3 (1H, bd, $J = 14.3$ Hz), 8.42 (1H, d, $J = 14.2$ Hz), 7.30 (1H, m), 7.08 (2H, d, $J = 8.8$ Hz), 6.92−6.78 (3H, m), 5.50 (1H, bs), 4.09 (2H, q, $J = 7.1$ Hz), 0.98 (3H, t, $J = 7.1$ Hz).

Ethyl 6,7-Difluoro-1,4-dihydro-1-(4-hydroxyphenyl)-4-oxoquinoline-3-carboxylate, 25. Sodium hydride (60% suspension in oil, 0.162 g, 4.06 mmol) was added slowly to a cold solution of the benzoylacrylate **24** (1.35 g, 3.7 mmol) in THF (30 mL). The mixture was heated to reflux for 3 h under an argon atmosphere and cooled to room temperature. Water was added, and the precipitate was filtered, washed with water, and dried under vacuum, yielding the quinolone **25** (1.23 g, 96%) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.11 (1H, bs), 8.35 (1H, s), 8.04 (1H, m), 7.41 (2H, d, $J = 8.3$

Hz), 6.94 (2H, d, J = 8.3 Hz), 6.89 (1H, m), 4.15 (2H, q, J = 7.0 Hz), 1.20 (3H, t, J = 7.0 Hz).

Ethyl 1,4-Dihydro-6-fluoro-1-(4-hydroxyphenyl)-7-(4-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylate, 3. *N*-Methylpiperazine (3.19 g, 31.8 mmol) was added to a solution of the fluoroquinolone **25** (1.1 g, 3.18 mmol) in pyridine (20 mL) at 115 °C. After heating at 115 °C for 24 h under an argon atmosphere, the solvent was removed under vacuum. The residue was chromatographed on silica gel (ethanol/$CHCl_3$) to recover the starting material (0.41 g, 37%) and to obtain the desired product **3** (0.81 g, 61%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.28 (1H, s), 8.29 (1H, s), 7.77 (1H, d, J = 13.4 Hz), 7.38 (2H, d, J = 8.6 Hz), 6.98 (2H, d, J = 8.6 Hz), 6.31 (1H, d, J = 7.1 Hz), 4.15 (2H, q, J = 7.0 Hz), 2.95 (4H, bs), 2.37 (4H, bs), 2.14 (3H, s), 1.20 (3H, t, J = 7.1 Hz).

Acetoiodoglucose, 26. Glucose pentaacetate was added into a solution of trimethylsilyl iodide (0.256 g, 1.28 mmol) in 20 mL of dichloromethane under an argon atmosphere at room temperature. The reaction mixture was stirred at room temperature for 2.5 h. Removal of the solvent in vacuo and purification by flash chromatography on silica gel (1:2 ethyl acetate/hexane) yielded the glucosyl iodide **26** (0.5368 g, 0.83%) as a light brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.98 (1H, d, J = 4.3 Hz), 5.45 (1H, dd, J = 10.2, 9.5 Hz), 5.16 (1H, dd, J = 10.2, 9.5 Hz), 4.32 (1H, dd, J = 12.7, 4.1 Hz), 4.19 (1H, dd, J = 9.9, 4.3 Hz), 4.07 (1H, m), 4.04 (1H, m), 2.08 (3H, s), 2.07 (3H, s), 2.04 (3H, s), 2.02 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.5, 169.8, 169.6, 169.5, 74.9, 72.9, 71.7, 70.3, 66.9, 60.8, 20.8, 20.7, 20.6, 20.5.

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