arations were washed, and after 1 h, the second cumulative contractions of aortic strips by 5-HT were observed in the presence of test drugs. The anti-5-HT_2 activity of the drug was calculated from the dose–response curve and expressed as a pA_2 value if its blockade was competitive.

To test the anti-α_1 activity, phenylephrine (0.01–10 μM) was given to the preparations instead of 5-HT.

5-HT_2 or α_1 Antagonistic Activity in Rats in Vivo. A male SD rat was anesthetized with urethane (1 g/kg, ip) and alpha-chloralose (80 mg/kg, ip). A catheter, connected to a pressure transducer, was inserted into the carotid artery to measure blood pressure, and a venous catheter was cannulated for drug injection. After 1 h of oral administration of a test drug or vehicle, 5-HT (300 μg/kg, iv) was injected, and the change of the hypertensive phase, immediately after a transient hypotensive phase, was measured. The anti-5-HT_2 activity was expressed as an inhibition percentage.

To test anti-α_1 activity, phenylephrine (30 μg/kg, iv) was injected into rats instead of 5-HT and the change in the blood pressure was measured.

Inhibition of Head-Twitch Response in Mice. A test drug was orally given to mice 1 h before administration of 5-hydroxytryptophan (5-HTP: 100 mg/kg, ip). Numbers of head-twitch responses were counted for 5 min (or 8 min) at 30 min after injection of 5-HTP. Inhibitory activities were expressed as percentages versus control values.

Registry No. **4a**, 116056-07-6; **4b**, 118801-67-5; **4c**, 27182-43-0; **4d**, 133365-36-3; **4e**, 133365-38-5; **4f**, 133365-37-4; **4g**, 6969-71-7; **5a**, 133365-54-5; **5b**, 133365-52-3; **5c**, 133365-53-4; **5d**, 134951-50-1; **5e**, 134951-51-2; **5f**, 133365-55-6; **5g**, 137540-94-4; **6b**, 133365-56-7; **6c**, 133365-61-4; **7a**, 133364-92-8; **7a**·HCl, 133364-93-9; **7b**, 133364-85-9; **7b**·HCl, 133364-84-8; **7c**, 133372-09-5; **7c**·HCl, 133364-87-1; **7d**, 133364-94-0; **7d**·HCl, 133364-95-1; **7e**, 133364-98-4; **7e**·HCl, 133364-99-5; **7f**, 133364-96-2; **7f**·HCl, 133364-97-3; **7g**, 137540-95-5; **7g**·HCl, 133364-91-7; **8c**, 133364-88-2; **8c**·HCl, 133364-89-3; **9c**, 137540-96-6; **9c**·HCl, 133364-90-6; **10b**, 137540-97-7; **10b**·HCl, 133365-00-1; **11b**, 137540-98-8; **12a**, 137540-99-9; **12a**·HCl, 133365-11-4; **12b**, 133365-03-4; **12b**·HCl, 133365-04-5; **12c**, 133365-07-8; **12c**·HCl, 133365-08-9; **12d**, 133365-13-6; **12d**·HCl, 133365-14-7; **13b**, 133365-27-2; **13b**·HCl, 133365-28-3; **14b**, 133365-15-8; **14b**·HCl, 133365-16-9; **14c**, 133365-17-0; **14c**·HCl, 133365-18-1; **15b**, 133365-25-0; **15b**·HCl, 133365-26-1; **16b**, 133365-19-2; **16b**·maleate (1:1), 133365-20-5; **17b**, 133365-05-6; **17b**·HCl, 133365-06-7; **17c**, 133365-09-0; **17c**·HCl, 133365-10-3; **18b**, 16011-96-4; **19b**, 133365-43-2; **20a**, 133364-77-9; **20a**·2HCl, 133364-78-0; **20b**, 133365-29-4; **20b**·2HCl, 133364-76-8; **20h**, 137541-00-5; **20h**·HCl, 133364-79-1; **21a**, 133405-29-5; **21a**·HCl, 133364-64-4; **21b**, 133364-61-1; **21b**·HCl, 133364-62-2; **21c**, 133364-65-5; **21c**·2HCl, 133364-66-6; **21g**, 137541-01-6; **21g**·2HCl, 137541-02-7; **21h**, 133364-74-6; **21h**·HCl, 133364-75-7; **22b**, 133364-67-7; **22b**·maleate (1:1), 133364-68-8; **23b**, 133364-69-9; **23b**·2HCl, 133364-70-2; 1-bromo-2-chloroethane, 107-04-0; 4-[bis(4-fluorophenyl)methylene]piperidine, 58113-36-3; phenoxycarbonyl isocyanate, 5843-43-6; 2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethanol, 106088-85-1.

Communications to the Editor

Synthesis, Stability, and Biological Evaluation of Water-Soluble Prodrugs of a New Echinocandin Lipopeptide. Discovery of a Potential Clinical Agent for the Treatment of Systemic Candidiasis and *Pneumocystis carinii* Pneumonia (PCP)

The development of more efficacious agents against opportunistic infections is critical due to the growing population of immunocompromised individuals.[1] Mycoses are common among AIDS, organ transplant, and cancer chemotherapy patients.[2] It has been shown that 1,3-β-glucan synthesis inhibitors are effective antifungal agents against *Candida* species, especially *Candida albicans*.[3] These inhibitors were believed to be of very narrow spectrum; however, it appears that a broader range of organisms is susceptible.[4,8a] Of particular importance was the discovery that the cell wall of the cyst form of *Pneumocystis carinii* contained 1,3-β-glucans.[5a] *P. carinii*, whose phylogeny has been the subject of recent controversy,[5] is an opportunistic organism responsible for an often fatal pneumonitis among HIV patients and other

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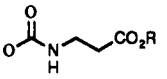
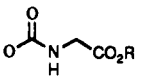
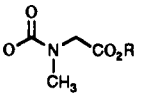
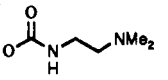
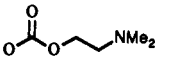
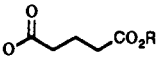
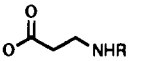
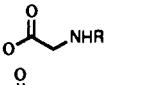
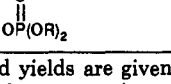
immunocompromised hosts.[6] Although it remains a rare condition among the general population, there have been recent reports of PCP among otherwise normal patients with unexplained T-cell deficiencies.[7] Subsequently, it was demonstrated that glucan synthesis inhibitors reduced the pulmonary alveolar cyst load in a rat model of PCP.[8] Although several structural classes of glucan synthesis inhibitors are known,[9] the class to which the most attention has been given is a group of cyclic hexapeptides related to echinocandin B.[10] These lipopeptides exhibit poor oral absorption and thus require parenteral administration.

Table I. Structure and Yields of Acylated Derivatives of Lipopeptide 4[a]

compd	4, OR′ =	7 (% yield)	8 (% yield)
a		R = Bz (40)	R = H (70)
b		R = Bz (25)	R = H (86)
c		–	R = H (18)
d		–	TFA salt (47)
e		–	TFA salt (22)
f		R = Bz (18)	R = H (70)
g		R = CBZ (59)	R = H HCl salt (77)
h		R = CBZ (45)	R = H HCl salt (82)
i		R = Bz (58)	R = H, Na (60)

[a] Isolated yields are given in parentheses and are unoptimized. See ref 23 for preparation.

Previous SAR studies were successful in maintaining potency and eliminating potential toxic effects due to red blood cell hemolysis.[11] Cilofungin 2 was identified as a promising new antifungal agent.[12] Although this semisynthetic agent proved effective against candidiasis in humans,[13] there was toxicity associated with the vehicle in which cilofungin was administered.[14] Lipopeptide 3

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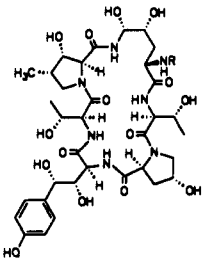
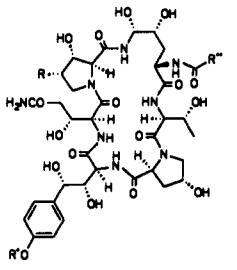
(L-671,329)[15] and the related analogue 4 (L-688,786)[16] are fermentation products obtained from *Zalerion arboricola* that show no appreciable red blood cell hemolysis (MLC >400 μg/mL). These compounds differ from echinocandin B by one or two amino acid residues and the fatty amide side chain. However, like 2 and the other echinocandins, lipopeptide 4 lacks appreciable water solubility (<0.1 mg/mL).[17] As a solution to this problem, we investigated potential prodrugs[18] of 4, linked through the phenolic hydroxyl of the homotyrosine, that would possess a formal charge at physiological pH and render the lipopeptide water soluble.

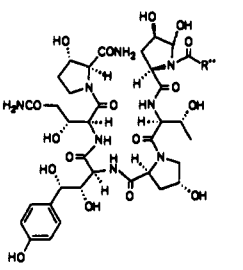
The echinocandins that bear a hemiaminal hydroxyl group at C5 of the ornithine are unstable at pH >7 and undergo a facile base-catalyzed ring opening and rearrangement to the 5-membered ring hemiaminal isomer 5.[16a] Initial efforts to functionalize the phenolic hydroxyl group directly using a weak base such as pyridine led to a mixture of acylation products, or, when a stronger base such as DMAP was employed, led to acylation products derived from the ring-opened compound 5. Although the base-sensitive hemiaminal could be protected as a benzyl ether,[19] it was desirable to avoid the extra steps that this would entail. It was envisioned that the stoichiometric generation of the phenoxide, in an aprotic medium, would minimize the base-catalyzed decomposition pathway. While a number of methods failed or gave inferior results,[20]



1 Echinocandin B R=Linoleoyl

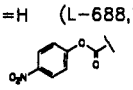
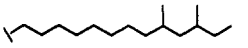
2 Cilofungin R=p-Octyloxybenzoyl





3 R=CH_3 R'=H (L-671,329) **5**

4 R=H R'=H (L-688,786)

6 R=H R'=  R'' = 

solid $LiOH \cdot H_2O$ in DMF in the presence of the acylating agent gave the desired products with little or no side products. The success of the reaction depended upon the selective generation of phenoxide while avoiding hydrolysis of the acylating agent or base-catalyzed decomposition of the lipopeptide.[21] The use of solid NaOH in DMF gave a greater amount of hydrolysis of the acylating agent. The yields given in Table I reflect either incomplete reaction and/or mass loss upon purification by reverse-phase HPLC. Evidence that acylation occurred at the phenol and not at one of the other eight hydroxyl groups in the molecule was as follows. The 400-MHz ^1H NMR spectrum (CD_3OD) of 4 exhibited an AB system for the aromatic protons at δ 7.13 (d, J = 8.5 Hz) and 6.75 (d, J = 8.5 Hz) and had a UV absorption λ^{MeOH} at 276 nm ($\epsilon^{1\%}$ = 15). The acylated compounds showed a downfield shift for the aromatic resonances of approximately 0.25 and 0.35 ppm, respectively, while the UV absorption at 276 nm diminished. Mass spectral measurements confirmed the molecular formulas.

The choice of acylating agent was crucial to the success of the reaction. The use of reactive acid chlorides led mainly to recovered starting material, presumably due to preferential reaction with water present in the starting lipopeptide.[22] Use of the less reactive pentafluorophenyl and *p*-nitrophenyl ester derivatives displayed higher selectivity for acylation of the phenoxide.

This method enabled the preparation of the acyl prodrug

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(17) Estimated by preparing a saturated aqueous solution at 20 °C, filtering through a 0.2-μm filter, and measuring a UV absorbance at 273 nm of 0.127. A standard solution of 4 in methanol (0.40 mg/mL) had an absorbance of 0.750.

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(19) This compound was prepared by suspending L-688,786 (20.0 g, 18.8 mmol) in 800 mL of THF and adding benzyl alcohol (200 mL, 1930 mmol). To the resultant solution was added camphorsulfonic acid (4.00 g, 17.2 mmol). After 17 h, the acid was neutralized with aqueous $NaHCO_3$. The filtrate was concentrated, and the product was precipitated by pouring into 2 L of acetonitrile. Purification by flash chromatography (ethyl acetate 75%/methanol 25%) gave 12.4 g (57%) of the desired compound as a white powder.

(20) Other conditions for acylation/alkylation gave inferior results: Cs_2CO_3/DMF; NaHMDS/DMF; LiHMDS/DMF; DMAP/pyridine; DOWEX, OH^- form; NaOH/DMF.

(21) Solid $LiOH \cdot H_2O$ dissolved very slowly in the DMF reaction medium. Therefore, the phenoxide at the homotyrosine is present in only small amounts in the presence of a large pool of acylating or phosphorylating agent. The low levels of base presumably account for the observed chemoselectivity of the derivatization.

(22) Compound 4 typically contained 7–10 wt % of water by KF assay.

Table II. Evaluation of Cilofungin 2, Lipopeptide 4, and Prodrug Derivatives

compd	solubility[a] (mg/mL)	solution stability[c] $T_{1/2}$, h	glucan synthesis inhibition:[d] IC_{50} (μM)	minimum lytic concn,[e] (μg/mL)	minimum fungicidal concentration (μg/mL)[f]					in vivo assay results[i]	
					C. albicans		*C. trop.*	*C. parap.*	*C. pseudo.*[g]	TOKA[j] MED_{99} MPK	PCP[k] MED_{90} MPK
					MY 1055	MY 1028	MY 1012	MY 1010	MY 1100		
2	ND	NA[l]	1.0	>400	0.5 (11)	0.5 (10)	0.25 (11)	16 (11)	ND[h]	3	>2.5
4	<0.1	NA	0.07	>400	0.25 (17)	0.125 (18)	0.06 (18)	4 (17)	2 (10)	3	0.15
8a	>50	≫100[m]	>10	>400	128	128	128	>128	ND	>6	>0.60
8b	>50	≫100[m]	>10	>400	4	4	8	ND	32	>6	>0.30
8c	>40[b]	≫100[m]	>1	25	2	2	1	ND	8	>6	>0.60
8d	>28	82 ± 6	1.0	25	1	1	1	ND	64	6	0.60
8e	>40	0.31 ± 0.09	0.1	50	0.25	0.125	0.125	2	1	6	0.60
8f	>60[b]	19 ± 6[n]	1.0	>400	0.5	0.5	0.5	ND	2	6	0.60
8g	>50	23 ± 6	0.2	100	1	1	0.5	16	ND	6	0.15
8h	>20	1.4 ± 0.1	0.05	100	0.5	1	≤0.06	ND	2	3	0.60
8i	>42	≫100[o]	>10	>400	2	4	4	32	ND	3	0.15

[a] Solubility in distilled water. [b] Solubility in pH 7 phosphate buffer. [c] Measured at 20 °C in 50% acetonitrile/pH 7.0 phosphate buffer. Mean ± SD. [d] See ref 9b. [e] In whole human blood. [f] Duplicate det's except 2 and 4 show the median (no. of duplicate det's). [g] *Candida albicans, tropicalis, parapsilosis,* and *pseudotropicalis.* [h] ND = not done. [i] 5 animals/group. [j] Target organ kidney assay. See ref 3b. MED_{99} is the minimum effective dose to lower number of viable colony forming units by 99%. ip administration. [k] *Pneumocystis carinii* pneumonia assay. See ref 8a. MED_{90} is the minimum dose required to reduce the alveolor cyst load by 90%. Subcutaneous administration. [l] NA = not applicable. [m] <1.5% hydrolysis after 100 h. [n] Mean ± standard error. [o] <0.1% hydrolysis after 100 h.

derivatives **8a–i** listed in Table I.[23] The carboxylate esters **7f–h** were prepared from the reaction of the corresponding activated pentafluorophenyl esters with compound **4**. Although the corresponding *p*-nitrophenyl esters gave transesterification, reaction times were longer than with the pentafluorophenyl analogues and the products were difficult to separate from the remaining starting materials. The carbamates and carbonate were prepared via the *p*-nitrophenyl carbonate **6**. The lithium phenoxide of **4** was treated with bis(*p*-nitrophenyl) carbonate. The intermediate could be isolated in 35% yield, but it was more convenient to add the secondary nucleophile directly. The benzyl-protected esters **7a** and **7b** were formed by the addition of the corresponding amino esters; however, it was found that the protecting group was unnecessary as **8c** was prepared by the direct addition of sarcosine. Likewise, compounds **8d** and **8e** were formed directly. The phosphate **8i** was prepared by dibenzylphosphorylation with tetrabenzylpyrophosphate.[24] Hydrogenolytic deblocking of the benzyl and CBZ protecting groups of **7a**, **7b**, and **7f–i** gave the desired prodrugs. The monosodium salt **8i** was prepared from the acid (R = H, H) by careful neutralization to pH 5 with NaOAc. The amine-bearing prodrugs **8d**, **8e**, **8g**, and **8h** were substantially more stable as a salt of a strong acid such as TFA or HCl. All intermediates 7 and final compounds 8 required purification by reverse-phase HPLC except **8f**, **8g**, and **8h**.

Table II contains the physical properties and biological assay results for cilofungin **2**, lipopeptide **4**, and the prodrug derivatives of **4**. All prodrugs were soluble in water, or pH 7 phosphate buffer, which was a major criterion for the development of these derivatives. We also required that these compounds possess substantial solution stability at pH 7. Compounds were dissolved in 50% acetonitrile/50% pH 7.0 aqueous phosphate buffer at 20 °C, and the disappearance of prodrug was monitored by HPLC. The determinations were carried out in triplicate. In this fashion, the solution half-lives were determined for the various prodrugs. The carbamates **8a–c** were very stable, showing <1.5% decomposition after 100 h. The phosphate ester **8i** was even more stable, showing <0.1% decomposition after 100 h. The other derivatives displayed varying degrees of stability. Of particular note was the relatively rapid rate of hydrolysis of the dimethylamino carbamate **8d** and carbonate **8e**. This was presumably due to participation of the dimethylamino group in the hydrolysis since acidic solutions of these compounds were considerably more stable.

Compounds were tested for their hemolytic potential against human red blood cells, a potential source of toxicity. The minimum lytic concentrations were determined by successively diluting the compounds in water containing 10% DMSO and adding the solution to whole human

(23) A general procedure for the preparation of **7a**, **7b**, and **8c–e** is as follows: Enough L-688,786 **4** was dissolved in DMF to produce a 0.1 M solution. Bis(*p*-nitrophenyl) carbonate (1.4 equiv) was added followed by solid $LiOH·H_2O$ (1.1 equiv). After several hours at room temperature, the reaction was judged complete by reverse-phase HPLC analysis (C8 Zorbax, 50% water/50% acetonitrile, 2 mL/min, 30 °C). Although this intermediate **6** could be isolated in 35% yield, it was more convenient to perform the subsequent displacement in situ. The nucleophile (amine or alcohol) was added and stirring was continued until **6** was consumed as determined by HPLC. The mixture was quenched with a small amount of acetic acid and the solvent was removed in vacuo. Purification of the residue by reverse-phase HPLC with UV detection (λ = 210,277 nm) gave the desired product. For **7a** and **7b**, the benzyl protecting groups were removed by hydrogenolysis at atmospheric pressure with 50 wt % of 10% Pd–C as catalyst in ethanol–water. Removal of the catalyst by filtration and purification as necessary by HPLC gave the final products **8a** and **8b**. Preparation of **7f–i**: Compound **4** was dissolved in DMF (~0.1 M), and the acylating agent (pentafluorophenyl ester or tetrabenzyl pyrophosphate) was added (1.4 equiv) followed by $LiOH·H_2O$ (1.1 equiv). Stirring was continued for 18–24 h, and the mixture was quenched with a small amount of acetic acid. After purification by reverse-phase HPLC the desired products were isolated as lyophilizates. The benzyl protecting groups were removed by hydrogenolysis at atmospheric pressure with 50–100 wt % of 10% Pd–C as catalyst in ethanol–water. Removal of the catalyst by filtration and purification as necessary by HPLC gave the final products **8f–i**. The phosphate **8i** was transformed to the monosodium salt before lyophilization by the careful addition of 1.0 equiv of NaOAc to the combined HPLC fractions. All compounds were isolated as lyophilizates. All products had satisfactory 400-MHz ^1H NMR (CD_3OD), UV, and high- and/or low-resolution mass spectra. The purity of all isolated compounds was ≥93% by HPLC analysis (4.6 × 250 mm C8 Zorbax, 45% H_2O/55% CH_3CN 0.1% TFA, 1.5 mL/min, 40° C, λ = 210 nm).

(24) Khorana, H. G.; Todd, A. R. Studies on Phosphorylation. Part XI. The Reaction between Carbodi-imides and Acid Esters of Phosphoric Acid. A New Method for the Preparation of Pyrophosphates. *J. Chem. Soc.* **1953**, 2257–2260.

blood. The wells were incubated at 37 °C for 2 h and examined visually for red blood cell lysis. The prodrugs that were expected to be anionic at pH 7 were not lytic up to concentrations of 400 μg/mL. However, the amine-bearing, cationic derivatives were substantially more lytic than the other prodrugs or 4.

The minimum fungicidal concentrations (MFC's) were determined against a panel of *Candida* sp. pathogens.[3b] Wells containing 150 μL of yeast nitrogen base with 1% dextrose were inoculated with approximately 5×10^3 CFU of yeast. These cultures were clinical isolates that are maintained in the Merck collection. Growth was allowed for 24 h at 35 °C in wells containing a range, by 2-fold serial dilution, from 128 to 0.06 μg/mL of drug to determine minimum inhibitory concentrations (MIC's). Subsequently, 1.5-μL aliquots were used to inoculate Sabouraud dextrose agar (SDA) plates, and these were incubated at 35 °C for 24 h. The MFC was defined as the minimum concentration of drug showing less than five colonies per spot. Control plates showed a substantial amount of growth. The hydrolytically stable derivatives were notably less active against *Candida* sp. than the parent 4. This result was also reflected in the glucan synthesis inhibition assay.[9b] These results suggested that the phenolic hydroxyl is important for antifungal activity.

Compounds 2, 4, and 8a–i were evaluated in vivo in the target organ kidney assay (TOKA).[25] DBA/2 mice (5 per dosage level) were challenged, by tail vein injection, with 5×10^4 cells of *C. albicans* (MY 1055) suspended in sterile saline. Mice were dosed intraperitoneally with a vehicle sham or drug at 1.5, 3.0, and 6.0 mg/kg (MPK) twice daily for 4 days. Seven days postinfection, the animals were sacrificed and their kidneys were removed, prepared, and cultured on SDA plates at 35 °C for 24 h. The number of colony forming units per gram of kidney (CFU/g) was determined. The minimum effective dose (MED_{99}) was the dose required to reduce the CFU/g by at least 99% over the vehicle sham control. Control groups typically gave 10^6–10^7 CFU of *C. albicans* per gram of kidney. The hydrolytically stable carbamate prodrugs were ineffective while the more easily hydrolyzed compounds 8d–h produced MED_{99}'s of 3 or 6 MPK. The phosphate 8i, although it was very resistant to hydrolysis, was as effective as 4, giving an MED_{99} of 3 MPK. When dosed intravenously via the tail vein, 8i produced an MED_{99} of 2.5 MPK.

The compounds were evaluated in a rat PCP model.[8a] Immunosuppressed Sprague–Dawley rats (5 per dosage level) with a confirmed *P. carinii* infection were dosed subcutaneously at 0.15 and 0.60 mg/kg (MPK) twice daily for 4 days. Compound 2 was dosed at several levels up to 2.5 MPK. On the fifth day, the rats were sacrificed and the lungs were removed and prepared. The number of cysts per lung was determined by microscopic examination of a known amount of lung homogenizate. The minimum effective dose (MED_{90}) was the dose required to reduce the number of cysts by at least 90% over the vehicle sham controls. Control groups typically ranged from 10^7 to 10^8 cysts per lung. The relative activity of compounds 8a–i correlated roughly with the ease of solution hydrolysis as was seen in the TOKA except for the phosphate ester. Cilofungin 2 was at least 15 times less potent than 4 or the phosphate ester 8i in this PCP model.

Although several compounds showed acceptable efficacy in vivo in both PCP and TOKA assays, only the phosphate prodrug 8i (L-693,989) showed high activity in both assays and additionally possessed superior solution stability. The observation that 8i was hydrolytically stable and yet had in vivo activity comparable to the parent 4 suggested that the phosphate ester underwent rapid enzymatic hydrolysis. Preliminary pharmacokinetic data in primates (rhesus and chimpanzee) showed that prodrug 8i was efficiently converted to parent drug 4 and produced a more sustained therapeutic level of 4 than direct iv administration of 4 itself.[26] Because of the favorable overall profile, the phosphate ester was chosen for further evaluation as a potential clinical agent for the treatment of PCP and candidiasis.

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Supplementary Material Available: NMR spectra for 6, 7a,b,f–i, and 8a–i (16 pages). Ordering information is given on any current masthead page.

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Potent Non-6-Fluoro-Substituted Quinolone Antibacterials: Synthesis and Biological Activity

The fluoroquinolone antibacterials[1] represented generically by 1 (Table I) have generated much excitement after the discovery that a fluorine atom at C-6 enhances antibacterial activity. Norfloxacin is generally considered to be the first derivative noted for a significant increase in activity. However, flumequine was the first to demonstrate the advantage of a C-6 fluorine atom. The next entries into this class of antibacterials were ofloxacin, ciprofloxacin, and more recently tosufloxacin, all of which contain a piperazinyl or aminopyrrolidinyl moiety for R_7 and diverse groups for R_1.

Structure–activity studies have demonstrated that the optimum substituent at the C-6 position was a fluorine atom[2] in both the quinolone and naphthyridone series, and

(1) For a recent review on the new generation of quinolones see: Wentland, M. P. Structure–activity relationships of fluoroquinolones. In *New generation of quinolones*; Siporin, C., Heifetz, C. L., Domagala, J. M., Eds.; Marcel Dekker, Inc.: New York, 1990; pp 1–43.

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