Inhibitors of Cholesterol Biosynthesis. 4. *trans*-6-[2-(Substituted-quinolinyl)ethenyl/ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-ones, a Novel Series of HMG-CoA Reductase Inhibitors[1]

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Received June 8, 1990

A series of substituted quinoline mevalonolactones were prepared and evaluated for their ability to inhibit the enzyme HMG-CoA reductase both in vitro and (cholesterol biosynthesis) in vivo. Since previous studies suggested that the 4-(4-fluorophenyl) and 2-(1-methylethyl) substituents afforded optimum potency, attention was focused on variations at position 6 of the quinoline ring. Biological evaluation of a small number of analogues bearing a variety of 6-substituents showed that modification at this position had little effect on potency. Several compounds (**8b**, **8e**, and **11**) were identified that showed comparable potency to compactin and mevinolin in both the in vitro and in vivo assays.

We have previously described two series of novel HMG-CoA reductase inhibitors. In each series the structurally complex hexahydronaphthalene ring system common to the naturally occurring fungal metabolites compactin and mevinolin was replaced by a five-membered monocyclic heteroaromatic system, such as the nonbasic pyrrole[2] and pyrazole[3] ring systems. Inhibitors containing basic six-membered monocyclic heteroaromatic[4] and nonbasic[5,6] heteroaromatic ring systems have been reported.

This report describes the synthesis and biological activity of a series of quinoline mevalonolactones, the first HMG-CoA reductase inhibitors to contain a basic bicyclic heteroaromatic ring system.

In addition, many of the compounds described herein exhibit improved in vitro potency when compared to both the pyrrole and pyrazole mevalonolactones previously reported.

Chemistry

Most potent inhibitors of HMG-CoA reductase have the 4-hydroxy-2*H*-pyran-2-one moiety flanked by a bulky lipophilic group and an alkyl group, where both of these groups are anchored in the correct spatial arrangement by various carbocyclic and heterocyclic structures.[7]

We initially investigated the synthesis of quinoline-containing mevalonolactones in which the lactone moiety was connected to position 3 of the quinoline nucleus via a two-carbon spacer and was flanked at positions 2 and 4 by an alkyl group and a 4-fluorophenyl group, respectively.[2,3] By attaching the lactone moiety at position 4 of the quinoline nucleus and employing an alkyl flanking group at position 3 we were able to investigate whether the "benzenoid" ring of the quinoline nucleus could replace the 4-fluorophenyl flanking group and give a compound which retained biological activity. Our general synthetic strategy to the quinolin-3-ylmevalonolactones employed the Friedlander reaction between a suitably substituted benzophenone derivative and an active methylene compound to construct the target quinoline nucleus (Scheme I).

Acid-catalyzed condensation of the requisite 2-aminobenzophenones[8] with various β-keto esters produced esters **1a–e**. Reduction to alcohols **2a–e** followed by Swern oxidation afforded the corresponding aldehydes **3a–e**, which were converted, with >95% *E* selectivity, to α,β-unsaturated esters **4a–e** by reaction with carbomethoxymethylenetriphenylphosphorane. DIBAL-H reduction afforded alcohols **5a–e**, which were oxidized to aldehydes **6a–e** by employing either MnO_2 or the Swern procedure. Condensation with the dianion of ethyl acetoacetate[9] then gave δ-hydroxy-β-keto esters **7a–e**. Stereoselective reduction employing the boron-chelation method of Narasaka and Pai[10] gave, after hydrolysis, a mixture of *erythro*- and *threo*-1,3-dihydroxy acids (>12:1) which were lactonized by refluxing in toluene with azeotropic removal of water. Generally, the lactones were crystalline, such that the small amount of the cis stereoisomer present was easily removed by recrystallization, providing almost exclusively the racemic trans stereoisomers **8a–e**.

Compounds containing a saturated bridging unit were readily available from **4** via catalytic hydrogenation to give **9**. The same sequence of steps utilized for the synthesis of lactones **8a–e** was then employed to convert **9** to lactone **10**.

Treatment of lactone **8d** with *m*-chloroperbenzoic acid in refluxing dichloromethane produced *N*-oxide **11**, which was expected to exhibit very different physicochemical properties than the parent quinoline (vide supra).

Lactone **8d** was also synthesized as the pure, biologically active 3*R*,5*S* stereoisomer employing Heathcock's β-ketophosphonate lactone synthon[11] (Scheme II). Thus, β-ketophosphonates **12** and **13** (prepared as an 8:1 mixture of diastereomers employing the literature procedure[12]) were

(1) A preliminary report of this work was presented at the 198th Meeting of the ACS, Miami, FL, September 10–15, 1989, MEDI 73. Following this report workers at Bayer AG presented data on a similar series of compounds at the 10th International Symposium on Drugs Affecting Lipid Metabolism, Houston, TX, November 8–11, 1989, Abstracts 510, 511.
(2) Roth, B. D.; Ortwine, D. F.; Stratton, C. D.; Sliskovic, D. R.; Wilson, M. W.; Newton, R. S. *J. Med. Chem.* **1990**, *33*, 21 and references contained therein.
(3) Sliskovic, D. R.; Roth, B. D.; Wilson, M. W.; Hoefle, M. L.; Newton, R. S. *J. Med. Chem.* **1990**, *33*, 31.
(4) Beck, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Bergmann, E.; Granzer, H.; Jendralla, B.; v. Kerekjarto, B.; Krause, R.; Paulus, E.; Schubert, W.; Wess, G. *J. Med. Chem.* **1990**, *33*, 52.
(5) Coppola, G. M.; Scallen, T. J.; DelPrete, A.; Montano, R. *Heterocycles* **1989**, *29*, 1497.
(6) Kathawala, F. G.; Scallen, T. J.; Engstom, R. G.; Weinstein, D. B.; Schuster, H.; Stabler, R. *Abstracts of Papers*, 194th National Meeting of the American Chemical Society, New Orleans, August 30–September 4, 1987; American Chemical Society: Washington, DC, 1987; MEDI 79.
(7) Roth, B. D.; Sliskovic, D. R.; Trivedi, B. K. *Annu. Rep. Med. Chem.* **1989**, *24*, 147.
(8) Walsh, D. A. *Synthesis* **1980**, 677 and references contained therein.
(9) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1981**, *96*, 1082.
(10) (a) Narasaka, K.; Pai, H. C. *Chem. Lett.* **1980**, 1415. (b) Ibid. *Tetrahedron* **1984**, *40*, 2233.
(11) Heathcock, C. H.; Hadley, C. R.; Rosen, T.; Theisen, P. D.; Hecker, S. J. *J. Med. Chem.* **1987**, *30*, 1858.

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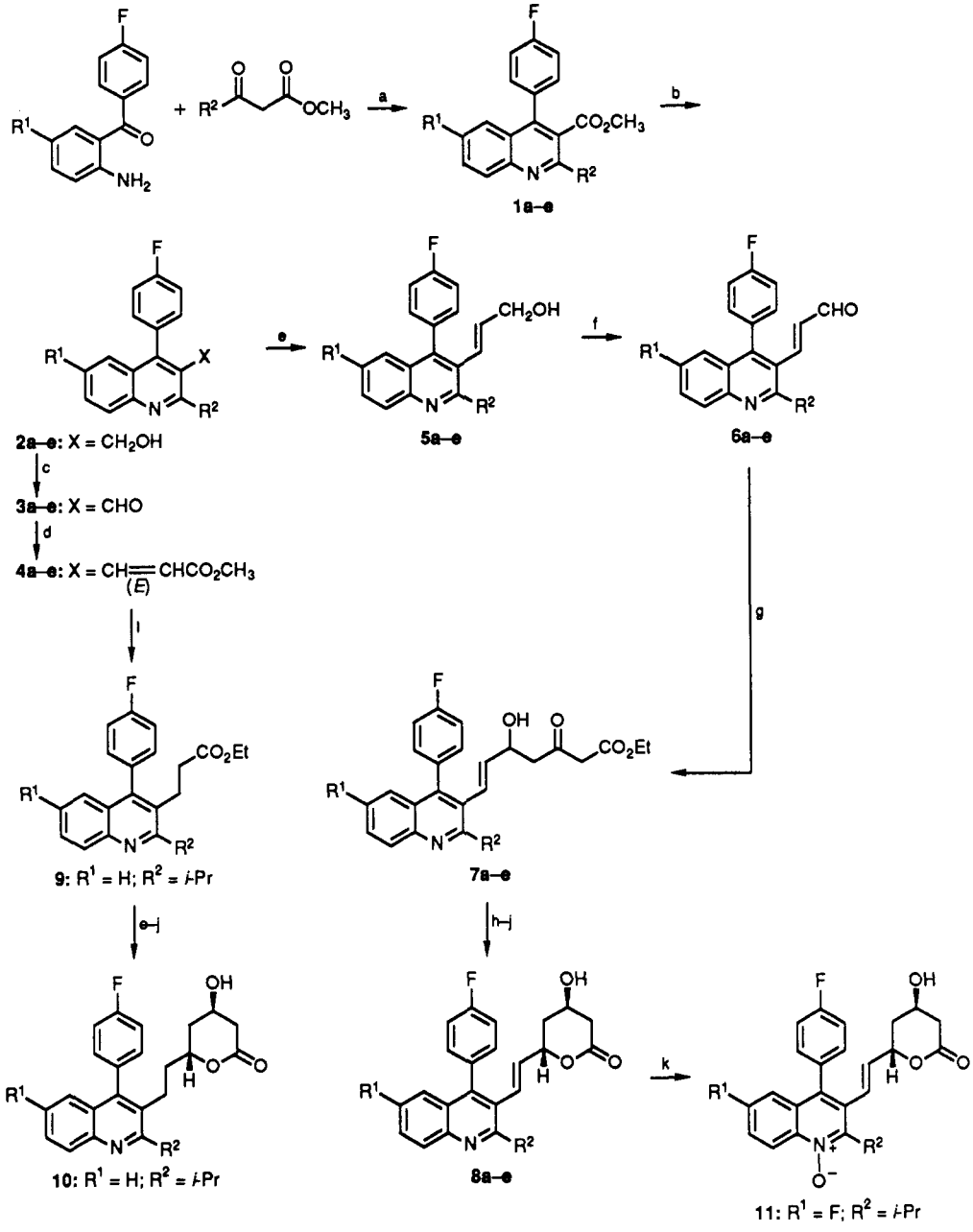
Scheme I[a]



[a] (a) pTSA, toluene, Δ; (b) DIBAL-H, CH_2Cl_2, −78 °C; (c) $(COCl)_2$, DMSO, TEA, −78 °C; (d) $Ph_3P{=}CHCO_2CH_3$; (e) DIBAL-H, CH_2Cl_2, −78 °C; (f) Swern or MnO_2, toluene, Δ; (g) $^-CH_2CO^-CHCO_2Et$; (h) $B(Et)_3$, $NaBH_4$, $(CH_3)_3CCO_2H$ then H_2O_2; (i) NaOH then HCl; (j) toluene, Δ; (k) *m*CPBA, CH_2Cl_2, Δ; (l) 10% Pd/C, H_2, MeOH.

coupled with aldehyde **3**, employing the conditions developed by Roush and Masamune[13] (LiCl, DBU, CH_2Cl_2), in 64% yield. This yield represents the best achieved.[14] The resulting enones (**14** and **15**) were deprotected and stereoselectively reduced (Et_3B, $NaBH_4$) to give a mixture of *erythro*- (**16**) and *threo*-1,3-dihydroxy esters. Saponification followed by lactonization and chromatography gave predominantly *trans*-lactone (+)-**17** (trans:cis = 26:1). HPLC analysis of the corresponding (*R*)-(+)-α-methylbenzamide derivatives indicated an enantiomeric purity of 89% ee.

In an attempt to increase the aqueous solubility of these compounds (and thereby improve absorption in vivo), a dimethylamino group was incorporated into position 2 of the quinoline ring in place of the isopropyl group (Scheme III).

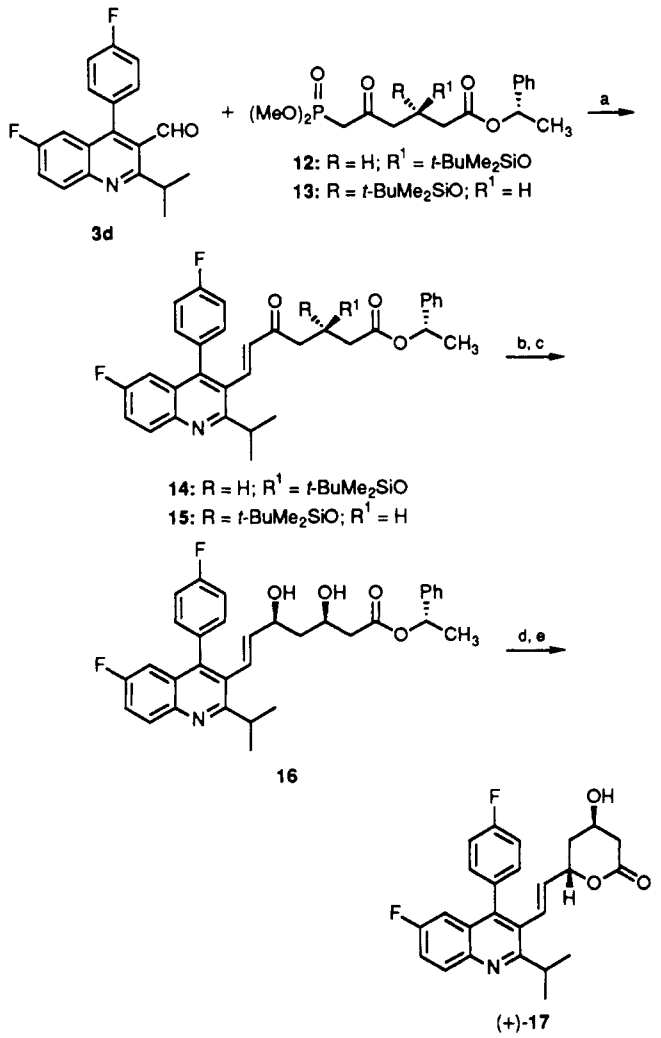
Treatment of benzophenone **18** with ethyl malonyl chloride and silica gel gave 1,2-dihydroquinoline **19** in 88% yield. Chlorination using phosphoryl chloride gave ester **20**, which was then reduced and reoxidized to aldehyde **21**. Nucleophilic substitution of the chloride with dimethylamine gas in toluene at 130 °C (autoclave) gave dimethylamino aldehyde **22**. Aldehyde **22** was then con-

(12) This ratio of diastereomers may be improved to 22:1 by employing (*R*)-1-(1′-naphthyl)ethanol as chiral auxilliary; see: Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374.

(13) Blanchette, M. A.; Choy, C. O.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R. *Tetrahedron Lett.* **1984**, *25*, 2183.

(14) A variety of other conditions were examined, e.g., K_2CO_3/18-crown-6/toluene, $(NH_4)_2CO_3$/toluene, and NaH/THF, however, all of these led to β-elimination products derived from both the starting materials (**12** and **13**) and products (**14** and **15**). See: Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731.

Scheme II[a]



[a] (a) LiCl, DBU, CH_2Cl_2, −10 °C; (b) HF, CH_3CN; (c) $B(Et)_3$, $NaBH_4$, $(CH_3)_3CCO_2H$ then H_2O_2; (d) NaOH then HCl; (e) toluene, Δ.

verted to the desired lactone **26** by employing the chemistry described previously.

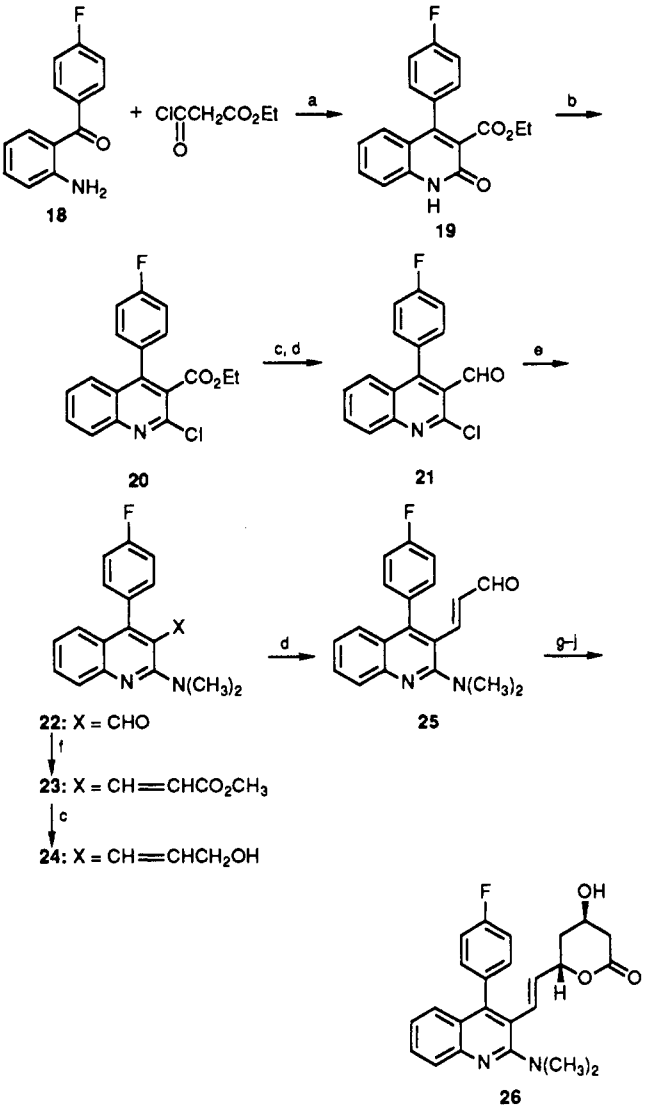
Quinolin-4-ylmevalonolactone **34** was synthesized as shown in Scheme IV. Methyl 3-methyl-4-quinolinecarboxylate[15] (**27**) was reduced to alcohol **28** and then oxidized under Swern conditions to aldehyde **29**. α,β-Unsaturated aldehyde **32** was constructed in an entirely analogous manner to that depicted in Scheme I and was subsequently treated with the dianion of ethyl acetoacetate to yield **33**, which was converted to the target lactone **34** (trans:cis = 23:1).

Biological Results

The lactones listed in Table I were saponified to the 3,5-dihydroxy acids and tested for their ability to inhibit the enzyme HMG-CoA reductase, employing two protocols.[2] Method I (cholesterol synthesis inhibition screen or CSI) measured the rate of conversion of [^{14}C]acetate to cholesterol by employing a crude liver homogenate derived from rats fed a chow diet containing 5% cholestyramine. Method II (HMG-CoA reductase inhibition screen or COR) was a more specific screen employing a partially purified microsomal enzyme preparation to measure the direct conversion of [^{14}C]HMG-CoA to mevalonic acid. The

(15) Lindberg, U. H.; Ulff, B.; Yeoman, G. *Acta. Pharm. Suec.* **1968**, *5*, 441.

Scheme III[a]



[a] (a) CH_2Cl_2 then SiO_2; (b) $POCl_3$, Δ; (c) DIBAL-H, CH_2Cl_2, −78 °C; (d) $(COCl)_2$, DMSO, TEA, −78 °C; (e) $HN(CH_3)_2$, toluene, autoclave, 130 °C; (f) $Ph_3P{=}CHCO_2CH_3$, CH_2Cl_2; (g) $^-CH_2CO^-CHCO_2Et$; (h) $B(Et)_3$, $NaBH_4$, $(CH_3)_3CCO_2H$ then H_2O_2; (i) NaOH then HCl; (j) toluene, Δ.

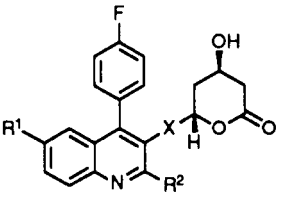
biological activities are displayed in Table I as an IC_{50} (i.e., the concentration needed to inhibit enzyme activity by 50%). Compactin was employed as the internal standard in each testing protocol. The compounds were also evaluated for their ability to inhibit cholesterol biosynthesis in male rats, as determined by the inhibition of the incorporation of sodium [1-^{14}C]acetate into plasma [^{14}C]-cholesterol after po administration of the test substance.[16] This screen was designated the AICS (acute inhibition of cholesterol synthesis) screen.

Most of the compounds tested were more potent than compactin in the in vivo screen and **8b–e** exhibited both in vitro and in vivo potencies comparable to those of mevinolin.

As expected, an isopropyl group at position 2 of the quinolinyl-3-mevalonolactones produced a compound, **8b**,

(16) Alberts, A. W.; Chen, J.; Kuron, J.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3997.

Table I. Physical Properties and in Vitro and in Vivo HMG-CoA Reductase Inhibitory Activities of Quinoline Mevalonolactones I

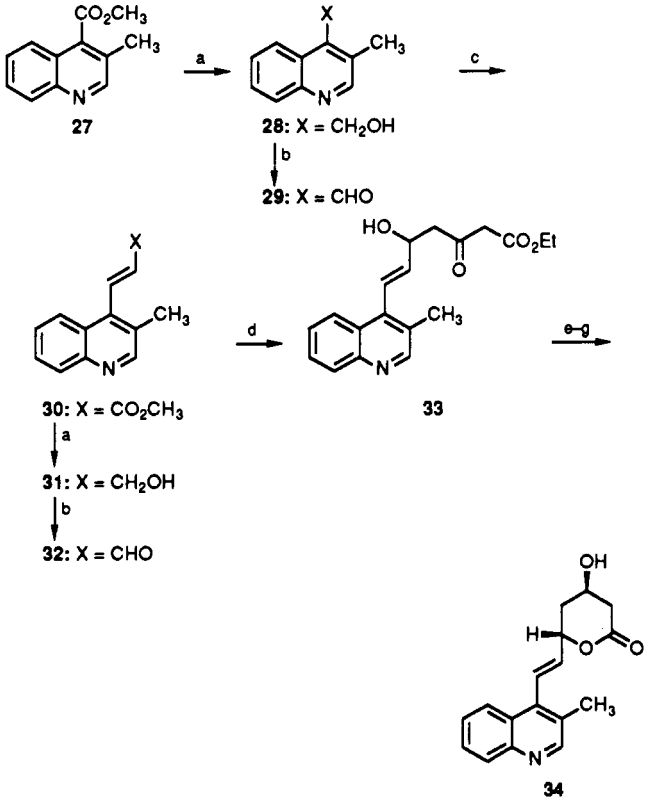


I

no.	R^1	R^2	X	mp, °C	formula[a]	CSI[b,c] IC_{50}, μM	rel (CSI)[d] potency	COR[c,h] IC_{50}, μM	AICS[e] (% inhibn)
compactin						0.030		0.025	36
mevinolin						0.025	118	0.028	72
8a	Cl	CH_3	-CH=CH-	188–190	$C_{23}H_{19}ClFNO_3$	0.4	6.3	0.72	18 (1.5)
8b	Cl	$CH(CH_3)_2$	-CH=CH-	173–175	$C_{25}H_{23}ClFNO_3$	0.032	100	0.025	61 (1.5)
8c	H	$CH(CH_3)_2$	-CH=CH-	168–170	$C_{25}H_{24}FNO_3$	0.042	75.8	0.032	70
10	H	$CH(CH_3)_2$	$-CH_2CH_2-$	199–202	$C_{25}H_{26}FNO_3$	>1.0	<1	-	-
8d	F	$CH(CH_3)_2$	-CH=CH-	174–176	$C_{25}H_{23}F_2NO_3$	0.05	77.6	0.20	68
17	F	$CH(CH_3)_2$	-CH=CH-	foam	$C_{25}H_{23}F_2NO_3 \cdot 0.25C_4H_8O_2$	ND[g]	ND[g]	-	69
11 (*N*-oxide)	F	$CH(CH_3)_2$	-CH=CH-	235–238	$C_{25}H_{23}F_2NO_4$	0.018	112	0.079	47
8e	OCH_3	$CH(CH_3)_2$	-CH=CH-	foam	$C_{26}H_{26}FNO_4$[f]	0.013	100	0.053	60
26	H	$N(CH_3)_2$	-CH=CH-	150–152	$C_{24}H_{23}FN_2O_3 \cdot 0.5C_4H_8O_2$	0.047	13.2	0.35	52
34				198–200	$C_{17}H_{17}NO_3 \cdot 0.25C_4H_8O_2$	>1.0	<1	-	42

[a] Analytical results are within ±0.4% of the theoretical values unless otherwise noted. [b] Cholesterol synthesis inhibition (CSI). Assays of each inhibitor concentration were performed in triplicate, and the precision for compactin was 37%. [c] All compounds tested had a diastereomeric purity of >95% of the trans diastereomer as determined by HPLC and/or 200-MHz NMR. [d] Potency of compactin arbitrarily assigned a value of 100 and the IC_{50} value of the test compound was compared with that of compactin determined simultaneously. [e] All compounds were dosed in DMA/PEG solution of 1.0 mg/kg unless otherwise indicated in parentheses. [f] Anal. Calcd: C, 71.70. Found: C, 70.67. >98% pure by HPLC. [g] Not determined. [h] HMG-CoA reductase inhibition (COR). Assays of each inhibitor concentration were performed in triplicate, and the precision for compactin was 37%.

Scheme IV[a]



[a] (a) DIBAL-H, CH_2Cl_2, -78 °C; (b) $(COCl)_2$, DMSO, TEA, -78 °C; (c) $Ph_3P{=}CHCO_2CH_3$, CH_2Cl_2; (d) $^-CH_2CO^-CHCO_2Et$; (e) $B(Et)_3$, $NaBH_4$, $(CH_3)_3CCO_2H$ then H_2O_2; (f) $NaOH^-$ then HCl; (g) toluene, Δ.

significantly more potent both in vitro and in vivo than the corresponding 2-methyl compound **8a**. Compound **10**, which has a saturated two-carbon bridging unit between the quinoline moiety and the mevalonolactone, was considerably less potent than the corresponding unsaturated bridge containing compound **8c**.

As previous studies suggested that the 4-(4-fluorophenyl) and 2-(1-methylethyl) substitution afforded optimum potency, attention was focused on variations at position 6 of the quinoline ring. From the limited number of compounds prepared (i.e., **8b–e**), it can be seen that varying the substitution at position 6 did not significantly effect either in vivo or in vitro potencies. The dimethylamino-containing compound **26** retained in vivo potency when compared to the corresponding isopropyl-containing compound **8c**, but was somewhat less potent in vitro.

N-Oxide **11** was as potent in vitro as compactin and mevinolin and more potent than the corresponding free base but was slightly less potent in vivo.

Quinolin-4-ylmevalonolactone **34** was considerably less potent than either compactin or mevinolin in vitro, however it was comparable to compactin when tested in vivo. The source of the in vivo activity for **34**, despite its lack of in vitro activity, is unclear.

Conclusion

A series of quinoline mevalonolactones was prepared and evaluated for their ability to inhibit the enzyme HMG-CoA reductase in vitro and cholesterol biosynthesis in vivo. By focusing on compounds possessing the 4-(4-fluorophenyl) and 2-(1-methylethyl) substituents found to be optimum in previous studies, several compounds, i.e., **8b**, **8e**, and **11**, were identified that were of comparable potency to compactin and mevinolin both in vitro and in vivo. Modifications at position 6 of the quinoline ring had little effect on potency.

In conclusion it has been shown that the quinoline nucleus can be used as a suitable replacement for the hexahydronaphthalene ring present in the fungal metabolites compactin and mevinolin. Compounds have been described which are equipotent to both naturally occurring HMG-CoA reductase inhibitors under the conditions studied.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. All organic extracts were dried over $MgSO_4$ except where otherwise noted. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on a Nicolet MX-1 FT-IR spectrometer. Nuclear magnetic resonance spectra were determined on either a Varian EM-390 or a Varian XL-200 spectrometer. Chemical shifts are expressed as parts per million downfield from internal tetramethylsilane. Elemental analyses were determined on a Perkin-Elmer 240C elemental analyzer. HPLC analyses were performed on a Varian 5500 HPLC with a UV 200 detector (wavelength was 251 nm) and an octadecylsilane column [Alltech Econisil C18; mobile phase, 50:50 0.05 M citric acid (pH = 4.0)–CH_3CN]. Optical rotations were performed on a Perkin-Elmer 241 polarimeter. The detailed protocols of the in vitro biological assays are described in ref 2.

Methyl 4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinecarboxylate (1c). A solution of methyl 4-methyl-3-oxopentanoate (14.7 g, 0.102 mol), (2-aminophenyl)-4-(fluorophenyl)methanone[15] (18.34 g, 0.085 mol), and a small amount of *p*-TSA in toluene (400 mL) was heated under reflux with azeotropic removal of water for 5 h. The solution was then cooled and concentrated in vacuo. Flash chromatography of the residue, eluting with 10% ethyl acetate–hexane, gave **1c** (7.66 g, 28%): ^{1}H NMR ($CDCl_3$) δ 8.05 (d, 1 H), 7.72–6.95 (m, 7 H), 3.52 (s, 3 H), 3.16 (heptet, 1 H), 1.40 (d, 6 H) ppm. Anal. ($C_{20}H_{18}FNO_2$) C, H, N.

4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinemethanol (2c). To a solution of **1c** (7.66 g, 0.024 mol) in dichloromethane (100 mL) at −78 °C under an atmosphere of nitrogen was added 55 mL of a 1.0 M solution of DIBAL-H. The resulting solution was stirred for 3 h before quenching with saturated aqueous sodium sulfate (20 mL). After warming to room temperature, the solution was filtered through Celite and the resulting filtrate dried and concentrated in vacuo to yield 6.61 g (94%) of **2c**: ^{1}H NMR ($CDCl_3$) δ 7.97 (d, 1 H), 7.57–6.93 (m, 7 H), 4.52 (bs, 2 H), 3.62 (heptet, 1 H), 1.9 (bs, 1 H), 1.43 (d, 6 H) ppm. Anal. ($C_{19}H_{18}FN_2O$) C, H, N.

4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinecarboxaldehyde (3c). To a solution of oxalyl chloride (2.3 mL, 0.027 mol) in anhydrous dichloromethane (50 mL), at −78 °C under an atmosphere of nitrogen, was added dimethyl sulfoxide (3.8 mL, 0.053 mol). After complete addition the resulting solution was stirred for 15 min at −78 °C and then a solution of **2c** (6.05 g, 0.02 mol) in dichloromethane (50 mL) was added dropwise. This was stirred for a further 1 h at −78 °C and then quenched by the addition of triethylamine (14.3 mL, 0.103 mol) and saturated aqueous ammonium chloride solution (15 mL). The organic layer was separated and the aqueous layer was extracted with additional dichloromethane. The combined organic layers were dried, filtered, and concentrated in vacuo to yield **3c** (6.38 g, quant.) as a pale yellow solid: mp 119–121 °C; ^{1}H NMR ($CDCl_3$) δ 9.92 (s, 1 H), 8.02 (d, 1 H), 7.72–7.52 (m, 1 H), 7.37–6.98 (m, 6 H), 3.94 (heptet, 1 H), 1.38 (d, 6 H) ppm. Anal. ($C_{19}H_{16}FNO$) C, H, N.

Methyl (*E*)-3-[4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]-2-propenoate (4c). Methyl (triphenylphosphoranylidene)acetate (7.5 g, 0.024 mol) and **3c** (6.38 g, 0.021 mol) in dichloromethane (100 mL) were stirred at room temperature under nitrogen for 72 h. The solution was then concentrated in vacuo. Flash chromatography on silica gel, eluting with hexanes–ethyl acetate, gave **4c** (5.62 g, 74%) as a pale orange solid: mp 147–149 °C; ^{1}H NMR ($CDCl_3$) δ 7.96 (d, 1 H), 7.72–7.04 (m, 8 H), 5.58 (d, 1 H), 3.63 (s, 3 H), 3.38 (heptet, 1 H), 1.35 (d, 6 H) ppm. Anal. ($C_{22}H_{20}FNO_2$) C, H, N.

(*E*)-3-[4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]-2-propen-1-ol (5c). To a solution of **4c** (5.62 g, 0.016 mol) in dichloromethane (100 mL) at −78 °C under an atmosphere of nitrogen was added 37.7 mL of a 1.0 M solution of DIBAL-H. The resulting solution was stirred for 2 h at −78 °C and then quenched by addition of saturated aqueous sodium sulfate (15 mL). After warming to room temperature, the solution was filtered through Celite. The resulting filtrate was dried and concentrated in vacuo. The residue was flash chromatographed, eluting with 10% ethyl acetate–hexanes, to yield **5c** (4.7 g, 91%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.99 (d, 1 H), 7.60–6.97 (m, 7 H), 6.48 (d, 1 H), 5.45 (dt, 1 H), 4.00 (bs, 2 H), 3.48 (heptet, 1 H), 2.05 (bs, 1 H), 1.38 (d, 6 H) ppm.

(*E*)-3-[4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]-2-propenal (6c). To a solution of oxalyl chloride (1.66 mL, 0.019 mol) in anhydrous dichloromethane (25 mL), at −78 °C under an atmosphere of nitrogen, was added dimethyl sulfoxide (2.75 mL, 0.038 mol) in dichloromethane (25 mL). The resulting solution was stirred for 15 min at −78 °C and then a solution of **5c** (4.7 g, 0.015 mol) in dichloromethane (50 mL) was added dropwise. This was stirred for 1 h and then quenched by the addition of triethylamine (10.2 mL, 0.073 mol) and saturated aqueous ammonium chloride solution (15 mL). The organic layer was separated and the aqueous layer was extracted with additional dichloromethane. The combined organic layers were dried, filtered, and concentrated in vacuo to yield **6c** (4.37 g, 94%): ^{1}H NMR ($CDCl_3$) δ 9.36 (d, 1 H), 7.96 (d, 1 H), 7.63–7.00 (m, 8 H), 5.90 (dd, 1 H), 3.4 (heptet, 1 H), 1.4 (d, 6 H) ppm.

Ethyl (*E*)-7-[4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]-5-hydroxy-3-oxo-6-heptenoate (7c). Ethyl acetoacetate (2.25 g, 0.017 mol) in anhydrous THF (25 mL) was added dropwise to a stirred suspension of sodium hydride (60% oil suspension, 0.74 g, 0.018 mol) in anhydrous THF (25 mL) at 0 °C under a nitrogen atmosphere. When gas evolution was complete, a 2.4 M solution (7.2 mL, 0.017 mol) of *n*-butyllithium in hexanes was added over 30 min. This was then treated with a solution of **6c** (3.68 g, 0.011 mol) in anhydrous THF added dropwise over 30 min. The resulting solution was stirred for 1 h at −78 °C and then quenched by the addition of glacial acetic acid (15 mL) with vigorous stirring. The resulting mixture was then partitioned between diethyl ether and water. After separation of the phases, the aqueous layer was reextracted with diethyl ether, and the combined organic extracts were washed with saturated aqueous sodium bicarbonate and dried. The solvents were removed in vacuo, and the residue was flash chromatographed with hexanes–ethyl acetate as eluant to yield 5.1 g (95%) of the title compound **7c** as an orange oil: ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 1 H), 7.64–7.17 (m, 7 H), 6.62 (d, 1 H), 5.34 (dd, 1 H), 4.59 (m, 1 H), 4.21 (q, 2 H), 3.48 (heptet, 1 H), 3.41 (s, 2 H), 2.44 (d, 2 H), 1.38 (d, 6 H), 1.29 (t, 3 H) ppm.

[4α,6β(*E*)]-6-[2-[4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (8c). To a room temperature solution of triethylborane (7.2 mL of a 1 M THF solution; 0.007 mol) under a dry-air atmosphere was added, with stirring, a catalytic amount of pivalic acid (0.7 g, 0.0007 mol). The resulting solution was stirred at room temperature for 10 min before a THF (25 mL) solution of **7c** (3.0 g, 0.007 mol) was added dropwise. The resulting solution was stirred at room temperature for a further 15 min before cooling to −78 °C. Methanol (5 mL) was added followed by the addition of sodium borohydride (0.28 g, 0.007 mol) in one portion. Vigorous effervescence ensued. This mixture was stirred at −78 °C for 6 h. It was then quenched by pouring into ice-cold 30% hydrogen peroxide (10 mL). The mixture was allowed to warm slowly to room temperature and then was partitioned between chloroform and water. The organic layer was washed extensively with water, dried, and concentrated in vacuo to yield 3.07 g of the corresponding 1,3-diols as a mixture of erythro and threo diastereomers which were used without any further purification.

This residue was then redissolved in THF (50 mL) and methanol (5 mL) and treated with 1 N aqueous sodium hydroxide (6.7 mL). The resulting solution was stirred at room temperature for 2 h and then concentrated to dryness. The residue was then partitioned between water and ether. The ether layer was extracted with 1 N aqueous NaOH. The aqueous layers were combined, acidified with concentrated HCl, and extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with water, and dried. Removal of the solvents in vacuo yielded a yellow foam which was dissolved in toluene (100 mL) and heated for 3 h at reflux with azeotropic removal of water. The cooled solution was concentrated and the residue flash chromatographed on silica gel, eluting with 50% hexanes–ethyl acetate to yield **8c** (1.26 g, 56%) as a white solid, which was shown to be a 97:3 mixture of trans and cis diastereomers by HPLC: mp 168–170

°C; ^{1}H NMR ($CDCl_3$) δ 8.02 (d, 1 H), 7.71 (dt, 1 H), 7.51–7.28 (m, 6 H), 6.69 (d, 1 H), 5.48 (dd, 1 H), 5.24 (bs, 1 H), 5.10–5.00 (m, 1 H), 4.0 (bs, 1 H), 3.48 (heptet, 1 H), 2.67–2.31 (m, 2 H), 1.57–1.42 (m, 2 H), 1.33 (d, 6 H) ppm; IR (KBr) 3430, 2967, 1715, 1514, 1256, 1224, 1160, 1067, 974 cm^{-1}. Anal. ($C_{25}H_{24}FNO_3$) C, H, N.

Compounds **8a–e** were synthesized by the general method outlined in Scheme I and exemplified for compound **8c**; their physical and biological properties are listed in Table I.

[4α,6β(*E*)]-6-[2-[6-Fluoro-4-(4-fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one, *N*-Oxide (11). A dichloromethane solution (100 mL) of **8d** and *m*-CPBA was heated under reflux for 6 h under an atmosphere of nitrogen. The solution was then cooled and washed with saturated aqueous sodium bicarbonate solution. The organic layer was then dried, filtered, and concentrated in vacuo to yield an orange foam (1.24 g), which was flash chromatographed (eluant, 30% ethyl acetate–hexanes) to yield **11** (0.77 g, 74%) as a white solid: mp 235–238 °C; ^{1}H NMR ($CDCl_3$) δ 8.81 (dd, 1 H), 7.49–7.41 (m, 1 H), 7.20 (d, 4 H), 7.01 (dd, 1 H), 6.53 (d, 1 H), 5.44 (dd, 1 H), 5.18–5.13 (m, 1 H), 5.02 (bs, 1 H), 4.15–4.09 (m, 1 H), 3.74 (m, 1 H), 2.79 (bs, 2 H), 2.60 (d, 2 H), 1.55 (d, 6 H) ppm; IR (KBr) 3430, 3260, 1730, 1624, 1513, 1303, 1248, 1218, 1049, 831 cm^{-1}. Anal. ($C_{25}H_{23}F_2NO_4$) C, H, N.

The compounds bearing a saturated two-carbon spacer between the quinoline nucleus and the lactone moiety can be synthesized in an entirely similar manner to that of lactones **8a–e**. The experimental details for the key reduction of the α,β-unsaturated esters **4** is exemplified below for the preparation of compound **9**.

Methyl 3-[4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]propanoate (9). Compound **4c** (10.0 g, 0.029 mol) and 10% Pd/C (0.75 g) were stirred in methanol (250 mL) at room temperature under 50 psi of hydrogen gas. After 5 h, the suspension was filtered and the filtrate concentrated in vacuo to yield 10.14 g of an orange oil. Trituration with hexanes afforded 6.06 g (60%) of **9** as an off-white solid: mp 117–119 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (d, 1 H), 7.62 (t, 1 H), 7.33 (t, 1 H), 7.29–7.16 (m, 5 H), 3.64 (s, 3 H), 3.44 (heptet, 1 H), 2.96 (t, 2 H), 2.39 (t, 2 H), 1.44 (d, 6 H) ppm. Anal. ($C_{22}H_{22}FNO_2$) C, H, N.

[*R*-(*R,*R**)]-1-Phenylethyl 3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-7-[6-fluoro-4-(4-fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]-5-oxo-6-heptenoate (14).** To a solution of **3d** (0.6 g, 0.002 mol) and β-ketophosphonates (**12–13**, 8:1 mixture of diastereomers) (1.35 g, 0.003 mol) in dichloromethane (10 mL) at −10 °C under a nitrogen atmosphere was added a small amount of LiCl and DBU (2.85 mL, 0.019 mol). The resulting orange solution was stirred at −10 °C for 1.5 h and then quenched by addition of ice-cold phosphoric acid (0.5 M). The organic layer was separated, washed with water, dried, filtered, and concentrated in vacuo to yield a yellow oil (1.65 g). Flash chromatography on silica gel, eluting with 10% ethyl acetate–hexanes gave recovered aldehyde **3d** (0.29 g, 0.0009 mol, 48%), **14–15** (0.42 g, 0.0006 mol, 33%), and recovered β-ketophosphonate **12–13**: ^{1}H NMR ($CDCl_3$) δ 7.98 (dd, 1 H), 7.51 (d, 1 H), 7.33–6.84 (m, 11 H), 5.89 (d, 1 H), 5.77 (q, 1 H), 4.45 (m, 1 H), 3.34 (heptet, 1 H), 2.59 (d, 2 H), 2.40 (d, 2 H), 1.48 (d, 3 H), 1.33 (d, 6 H), 0.78 (s, 9 H), 0.01 (s, 6 H) ppm.

[4*R*-[4α,6β(*E*)]]-6-[2-[6-Fluoro-4-(4-fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (17). A solution of 48% aqueous HF (0.36 mL, 0.0007 mol) in acetonitrile (3 mL) was added to a solution of **14–15** (0.42 g, 0.0006 mol) in acetonitrile (3 mL). The resulting solution was stirred at room temperature for 1.5 h. It was then diluted with diethyl ether (20 mL) and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated in vacuo to give the desilylated compound (0.31 g, 0.0006 mol, 89%) as a colorless oil, which was used in the next step without any further purification: ^{1}H NMR ($CDCl_3$) δ 8.02 (dd, 1 H), 7.58 (d, 1 H), 7.39–6.83 (m, 11 H), 5.93 (d, 1 H), 5.85 (q, 1 H), 4.34 (m, 1 H), 3.34 (heptet, 1 H), 2.59 (d, 2 H), 2.48 (d, 2 H), 1.52 (d, 3 H), 1.37 (d, 6 H) ppm.

The alcohols were then dissolved in anhydrous THF (5 mL) containing pivalic acid (0.006 g, 0.00006 mol) under a dry-air atmosphere at room temperature. To this solution was added triethylborane (0.63 mL of a 1 M THF solution; 0.0006 mol). The resulting solution was stirred at room temperature for 10 min before cooling to −78 °C. Methanol (1 mL) was added, followed by sodium borohydride (0.024 g, 0.0006 mol) in one portion. Vigorous effervescence ensued. This mixture was stirred at −78 °C for 6 h and then quenched by pouring into ice-cold 30% hydrogen peroxide (1 mL). The mixture was allowed to warm slowly to room temperature and then partitioned between chloroform and water. The organic layer was washed extensively with water, dried, and concentrated in vacuo to yield a foam (0.25 g) which contained compound **16** as its major component.

The crude product was then dissolved in THF (5 mL) and methanol (0.5 mL) and treated with 1 N aqueous sodium hydroxide (0.46 mL). This solution was stirred at room temperature for 3 h, and then all solvents were removed in vacuo. The residue was partitioned between diethyl ether and water. The aqueous layer was acidified with 1 N hydrochloric acid, extracted with ethyl acetate, dried, filtered, and concentrated in vacuo to yield a yellow foam, which was redissolved in toluene (60 mL) and heated for 6 h at reflux with azeotropic removal of water. The cooled solution was concentrated and the residue flash chromatographed on silica gel, eluting with 30% ethyl acetate–hexanes, to give **17** (0.035 g, 18%) as a white foam: $[\alpha]_D = +3.4°$ ($c = 0.235$, $CHCl_3$); HPLC analysis of the corresponding (*R*)-(+)-α-methylbenzylamide derivative indicated an enantiomeric purity of 89% ee; ^{1}H NMR ($CDCl_3$) δ 8.09 (dd, 1 H), 7.47–7.37 (m, 1 H), 7.27–7.18 (m, 4 H), 6.99 (dd, 1 H), 6.68 (d, 1 H), 5.38 (dd, 1 H), 5.20–5.10 (m, 1 H), 4.25–4.19 (m, 1 H), 3.46 (heptet, 1 H), 2.77–2.52 (m, 2 H), 1.83–1.26 (m, 9 H) ppm. Anal. ($C_{25}H_{23}F_2NO_3 \cdot 0.25C_4H_8O_2$) C, H, N.

Ethyl 4-(4-Fluorophenyl)-1,2-dihydro-2-oxo-3-quinolinecarboxylate (19). Ethyl malonyl chloride (125 g, 0.84 mol) was added in portions to a solution of **18**[17] in dichloromethane (1 L) at 0 °C under an atmosphere of nitrogen. The reaction mixture was warmed slowly (~1 h) to room temperature, dried, and concentrated to an approximate volume of 600 mL. Silica gel (50 g) was then added. The resulting suspension was stirred overnight at room temperature, and filtered, and the silica gel was washed extensively with ethyl acetate. The filtrate was then concentrated and the residue triturated with hexanes to yield **19** (192 g, 88%) as a white solid: mp 204–206 °C; ^{1}H NMR ($CDCl_3$) δ 12.60 (bs, 1 H), 7.60–7.10 (m, 8 H), 4.17 (q, 2 H), 1.04 (t, 3 H) ppm. Anal. ($C_{18}H_{14}FNO_3$) C, H, N.

Ethyl 2-Chloro-4-(4-fluorophenyl)-3-quinolinecarboxylate (20). A solution of **19** (12.8 g, 0.041 mol) in phosphorus oxychloride (40 mL) was heated to reflux under an atmosphere of nitrogen for 1 h. It was then cooled and concentrated in vacuo and the resulting residue neutralized by the careful addition of cold 1 N sodium hydroxide solution. This was then extracted with ethyl acetate; the organic solution was filtered through a small bed of silica gel to yield **20** (13.2 g, 98%) as a white solid: mp 113–114 °C; ^{1}H NMR ($CDCl_3$) δ 8.02 (d, 1 H), 7.75–7.70 (m, 1 H), 7.52–7.43 (m, 2 H), 7.34–7.28 (m, 2 H), 7.20–7.12 (m, 2 H), 4.14–4.07 (q, 2 H), 1.02 (t, 3 H) ppm. Anal. ($C_{18}H_{13}ClFNO_2$) H, N, Cl, F; C: calcd, 65.56; found, 66.17.

2-Chloro-4-(4-fluorophenyl)-3-quinolinecarboxaldehyde (21). Compound **20** was reduced to the corresponding alcohol, 2-chloro-4-(4-fluorophenyl)-3-quinolinemethanol, in 83% yield in a manner analogous to the reduction of compounds **1a–e** to compounds **2a–e** in Scheme I: mp 159–160 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 1 H), 7.79–7.70 (m, 1 H), 7.53–7.22 (m, 6 H), 4.67 (d, 2 H), 2.24 (t, 1 H) ppm. Anal. ($C_{16}H_{11}ClFNO$) C, H, N.

This compound was then oxidized to **21** in a manner analogous to the oxidation of compounds **2a–e** to compounds **3a–e** in Scheme I: mp 168–169.5 °C; yield 90%; ^{1}H NMR ($CDCl_3$) δ 10.25 (s, 1 H), 8.12 (d, 1 H), 7.91–7.83 (m, 1 H), 7.57–7.53 (m, 2 H), 7.36–7.22 (m, 4 H) ppm. Anal. ($C_{16}H_9ClFNO$) C, H, N.

2-(Dimethylamino)-4-(4-fluorophenyl)-3-quinolinecarboxaldehyde (22). A solution of **21** (5.28 g, 0.019 mol) and dimethylamine (15 mL) in toluene (75 mL) was heated in an autoclave at 123–126 °C for 14 h. It was then cooled and concentrated in vacuo. The residue was partitioned between ethyl acetate and saturated aqueous potassium carbonate solution. The organic layer was dried, filtered, and concentrated in vacuo. The residue was flash chromatographed on silica gel, eluting with 10%

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ethyl acetate–hexanes, to yield **22** (4.2 g, 77%) as an orange solid: ^{1}H NMR ($CDCl_3$) δ 9.73 (s, 1 H), 7.78–6.96 (m, 8 H), 3.10 (s, 6 H) ppm. Anal. ($C_{18}H_{15}FN_2O$) C, H, N.

Methyl (*E*)-3-[2-(dimethylamino)-4-(4-fluorophenyl)-3-quinolinyl]-2-propenoate (23) was prepared analogously to compounds **4a–e** in Scheme I: yield 92%; ^{1}H NMR ($CDCl_3$) δ 7.78–6.87 (m, 9 H), 5.98 (d, 1 H), 3.60 (s, 3 H), 2.95 (s, 6 H) ppm. Anal. ($C_{21}H_{19}FN_2O_2$) C, H, N.

(*E*)-3-[2-(Dimethylamino)-4-(4-fluorophenyl)-3-quinolinyl]-2-propen-1-ol (24) was prepared analogously to compounds **5a–e** in Scheme I: yield 98%; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 1 H), 7.50–7.30 (m, 1 H), 7.20–6.98 (m, 6 H), 6.31 (d, 1 H), 5.72 (dt, 1 H), 3.99 (bd, 2 H), 2.96 (s, 6 H), 1.54 (bs, 1 H) ppm. Anal. ($C_{20}H_{19}FN_2O$) H; C: calcd, 74.51; found, 72.52; N: calcd, 8.69; found, 7.84.

(*E*)-3-[2-(Dimethylamino)-4-(4-fluorophenyl)-3-quinolinyl]-2-propenal (25) was prepared analogously to compounds **6a–e** in Scheme I: yield 92%; ^{1}H NMR ($CDCl_3$) δ 9.35 (d, 1 H), 7.75 (d, 1 H), 7.58–6.98 (m, 8 H), 6.32 (dd, 1 H), 2.99 (s, 6 H) ppm. Anal. ($C_{20}H_{17}FN_2O$) H, N; C: calcd, 74.98; found, 72.85.

[4α,6β(*E*)]-6-[2-[2-(Dimethylamino)-4-(4-fluorophenyl)-3-quinolinyl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (26) was prepared in 29% overall yield from compound **25** in an analogous manner to the preparation of lactones **8a–e** from aldehydes **6a–e**: mp 150–152 °C; ^{1}H NMR ($CDCl_3$) δ 7.83 (d, 1 H), 7.57–7.50 (m, 1 H), 7.26–7.16 (m, 6 H), 6.49 (d, 1 H), 5.66 (dd, 1 H), 5.16–5.06 (m, 1 H), 4.28–4.25 (m, 1 H), 3.01 (s, 6 H), 2.75–2.60 (q, 2 H), 2.07 (bs, 1 H), 1.82–1.51 (m, 1 H) ppm. Anal. ($C_{24}H_{23}FN_2O_3 \cdot 0.5C_4H_8O_2$) C, H, N.

3-Methyl-4-quinolinemethanol (28) was prepared in 73% yield via a DIBAL-H reduction of **27**:[15] ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1 H), 8.17–7.90 (m, 2 H), 7.68–7.42 (m, 2 H), 5.05 (s, 2 H), 2.46 (s, 3 H), 2.20 (bs, 1 H) ppm.

3-Methyl-4-quinolinecarboxaldehyde (29) was prepared in 70% yield from **28** via a Swern oxidation: ^{1}H NMR ($CDCl_3$) δ 10.77 (s, 1 H), 8.68 (s, 1 H), 8.52–8.41 (m, 1 H), 8.03–7.87 (m, 1 H), 7.67–7.34 (m, 2 H), 2.67 (s, 3 H) ppm.

Methyl (*E*)-3-(3-methyl-4-quinolinyl)-2-propenoate (30) was prepared in 76% yield via treatment of **29** with methyl (triphenylphosphoranylidene)acetate in an analogous manner to the preparation of compounds **4a–e** in Scheme I: ^{1}H NMR ($CDCl_3$) δ 8.70 (s, 1 H), 8.10–7.34 (m, 5 H), 6.21 (d, 1 H), 3.80 (s, 3 H), 2.42 (s, 3 H) ppm. Anal. ($C_{14}H_{13}NO_2$) C, H, N.

(*E*)-3-(3-Methyl-4-quinolinyl)-2-propen-1-ol (31) was prepared in 71% yield from **30** via DIBAL-H reduction: ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1 H), 8.10–7.85 (m, 2 H), 7.66–7.33 (m, 2 H), 6.92 (d, 1 H), 6.11 (dt, 1 H), 4.35 (bs, 3 H), 2.46 (s, 3 H) ppm.

(*E*)-3-(3-Methyl-4-quinolinyl)-2-propenal (32) was prepared in 71% yield from **31** via a Swern oxidation. ^{1}H NMR ($CDCl_3$) δ 9.75 (d, 1 H), 8.63 (s, 1 H), 8.02–7.14 (m, 5 H), 6.38 (dd, 1 H), 2.41 (s, 3 H) ppm.

[4α,6β(*E*)]-6-[2-(3-Methyl-4-quinolinyl)ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (34) was prepared in 10% overall yield from aldehyde **32**. The low yield is due to inefficient extraction of the dihydroxy acid from the aqueous phase during the acidification procedure: mp 198–200 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1 H), 7.94–7.87 (m, 2 H), 7.55–7.34 (m, 2 H), 6.87 (d, 1 H), 5.92 (dd, 1 H), 5.46–5.37 (m, 1 H), 4.90 (bs, 1 H), 4.26 (bs, 1 H), 2.62 (d, 2 H), 2.33 (s, 3 H), 2.15–2.03 (m, 1 H), 1.89–1.76 (m, 1 H) ppm.

In Vivo Acute Inhibition of Cholesterol Synthesis Assay (AICS). Male Sprague–Dawley rats (250 g body weight), previously fed 2.5% cholestyramine for 3 days, were randomly divided into groups (N = 5/group) and given a single dose of vehicle (controls) or compound by an oral gavage at the indicated doses. One hour after drug dosing, all rats were injected intraperitoneally with sodium [1-^{14}C]acetate (20.0 μCi/rat in 0.3 mL of saline). After 50 min, blood samples were taken, plasma was obtained by centrifugation, and plasma [^{14}C]cholesterol was measured after saponification and extraction.

Acknowledgment. We thank Dr. F. A. MacKellar and staff for analytical and spectral determinations, and last but not least Ms. Patty Elka for manuscript preparation.

Disubstituted Tetrahydrofurans and Dioxolanes as PAF Antagonists

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A new series of disubstituted tetrahydrofuran and dioxolane derivatives were prepared and evaluated for their PAF antagonist activity in the PAF-induced in vitro platelet-aggregation and in vivo hypotension tests. Several of these compounds exhibited more potent activity than the structurally related 2-[*N*-acetyl-*N*-[[[[2-methoxy-3-[(octadecylcarbamoyl)oxy]propoxy]carbonyl]amino]methyl]-1-ethylpyridinium chloride (CV-6209, **3**) in the in vitro assay, whereas all showed less potency in the in vivo test. The role of both the substituent nature and the placement and number of oxygen atoms in the ring are discussed. A qualitative SAR study was carried out on these nuclei.

Platelet activating factor (PAF, 1) is a naturally occurring phospholipid first described in 1972.[1] It is produced by stimulated basophils, neutrophils, platelets, macrophages, endothelial cells, and IgE-sensitized bone marrow cells.[2] PAF is involved in a wide range of biological actions such as stimulation of platelets and leukocytes, bronchoconstriction, hypotension, negative inotropic cardiac effects, and increase in vascular permeability.[3-5] In vivo experiments have demonstrated PAF's role in several pathological conditions,[6] such as asthma,[7] inflammation,[8] anaphylactic shock,[9] gastric ulceration,[10] and

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