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Synthesis and Biological Evaluations of Quinoline-based HMG-CoA Reductase Inhibitors

Mikio Suzuki,[a,*] Hiroshi Iwasaki,[b] Yoshihiro Fujikawa,[b] Masaki Kitahara,[c] Mitsuaki Sakashita[b] and Ryozo Sakoda[a]

[a]*Central Research Laboratories, Nissan Chemical Industries, Ltd., 722-1 Tsuboi-cho, Funabashi, Chiba 274-8507, Japan*
[b]*Pharmaceuticals Division, Nissan Chemical Industries, Ltd., 7-1, Kanda Nishiki-cho 3-chome, Chiyoda-ku, Tokyo 101-0054, Japan*
[c]*Biological Research Laboratories, Nissan Chemical Industries, Ltd., 1470 Shiraoka, Shiraoka-cho, Minamisaitama-gun, Saitama 349-0294, Japan*

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Abstract—A series of quinoline-based 3,5-dihydroxyheptenoic acid derivatives were synthesized from quinolinecarboxylic acid esters by homologation, aldol condensation with ethyl acetoacetate dianion, and reduction of 3-hydroxyketone to evaluate their ability to inhibit the enzyme HMG-CoA reductase in vitro. In agreement with previous literature, a strict structural requirement exists on the external ring, and 4-fluorophenyl is the most active in this system. For the central ring, substitution on positions 6, 7, and 8 of the central quinoline nucleus moderately affected the potency, whereas the alkyl side chain on the 2-position had a more pronounced influence on activity. Among the derivatives, NK-104 (pitavastatin calcium), which has a cyclopropyl group as the alkyl side chain, showed the greatest potency. We found that further modulation and improvement in potency at inhibiting HMG-CoA reductase was obtained by having the optimal substituents flanking the desmethylmevalonic acid portion, that is, 4-fluorophenyl and cyclopropyl, instead of the usual isopropyl group.

Introduction

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase is the major rate-limiting enzyme in cholesterol biosynthesis. The inhibitors of this enzyme, termed hypocholesterolemic agents, offer an important remedy for primary or secondary prevention of various kinds of atherosclerotic diseases.[1] Since the discovery of the naturally occurring fungal metabolites compactin[2a,b] and lovastatin,[2c,d] and the microbially transformed pravastatin,[2e] a HMG-CoA reductase inhibitor has been the most attractive target for medicinal researchers. Because these lead compounds have the structurally complicated hexahydronaphthalene ring system as a lipophilic anchor, numerous attempts to find a structurally refined artificial inhibitor with simple aromatic and heteroaromatic motifs have been undertaken. These efforts have focused on an enhancement of the in vitro and in vivo potency, and a refinement of the pharmacokinetic profile.[3a,b] As a result of an early search, the Merck group found biphenyl compound **1** as a potent inhibitor, and proposed a structural motif allowing for high affinity against the target enzyme:[4] the desmethylmevalonic acid portion, the pharmacophore that interacts with the HMG binding domain of the target enzyme, connected to a benzene ring (central ring) by a linking element (a two-carbon spacer), flanked on one side by an aromatic ring (external ring) and on the other side by an alkyl substituent (side chain).

A further extensive optimization study by Kathawala[5] on the effects of modulation of substituents R^a, R^b, and R^c in an indole compound **2** (five- and six-member ring) revealed that a 4-fluorophenyl, and an isopropyl, group are preferable substituents for the external ring and the side chain, respectively (Fig. 1).

After this report, numerous monocyclic or polycyclic ring systems have been used as the central ring to evaluate their potency. Roth et al.[6] carried out a systematical leading QSAR study on a pyrrole compound **3** to investigate the effect of a monocyclic five-member

*Corresponding author. Fax: +81-47-465-9389; e-mail: suzukimi@nissanchem.co.jp

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heteroaromatic compound. Values of various steric parameters for the structural requirements of the external ring and the alkyl side chain R^a were also elucidated. Regarding bicyclic ring systems, a limited examination on a quinoline compound **4** (six- and six-member ring) was reported by Sliskovic et al.[7] This study demonstrated that an isopropyl group at position 2 of the quinoline nucleus (i.e., R^a) is preferable to a methyl or a dimethylamino, and the substituent R^b at position 6 does not affect the inhibitory activity.

In this paper, we describe our efforts toward optimization of potency using a quinoline as the central ring. To study this effect, we prepared quinoline-based 3,5-dihydroxyheptenoic acid derivatives in which the desmethylmevalonic acid portion was linked through a *trans*-ethylene group to the 3-position of the quinoline. We initially investigated more precisely the effects of modulation of substituents at other positions of the central and external ring. Furthermore, comparatively little effort has been directed toward the modification of the alkyl side chain, despite the significant effect this moiety has in vitro potency. Therefore, we also varied the substituent at position 2 of the quinoline nucleus in order to clarify these structural effects in detail.

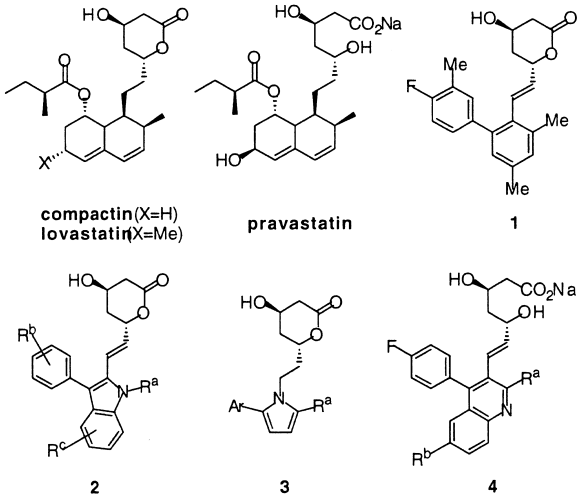
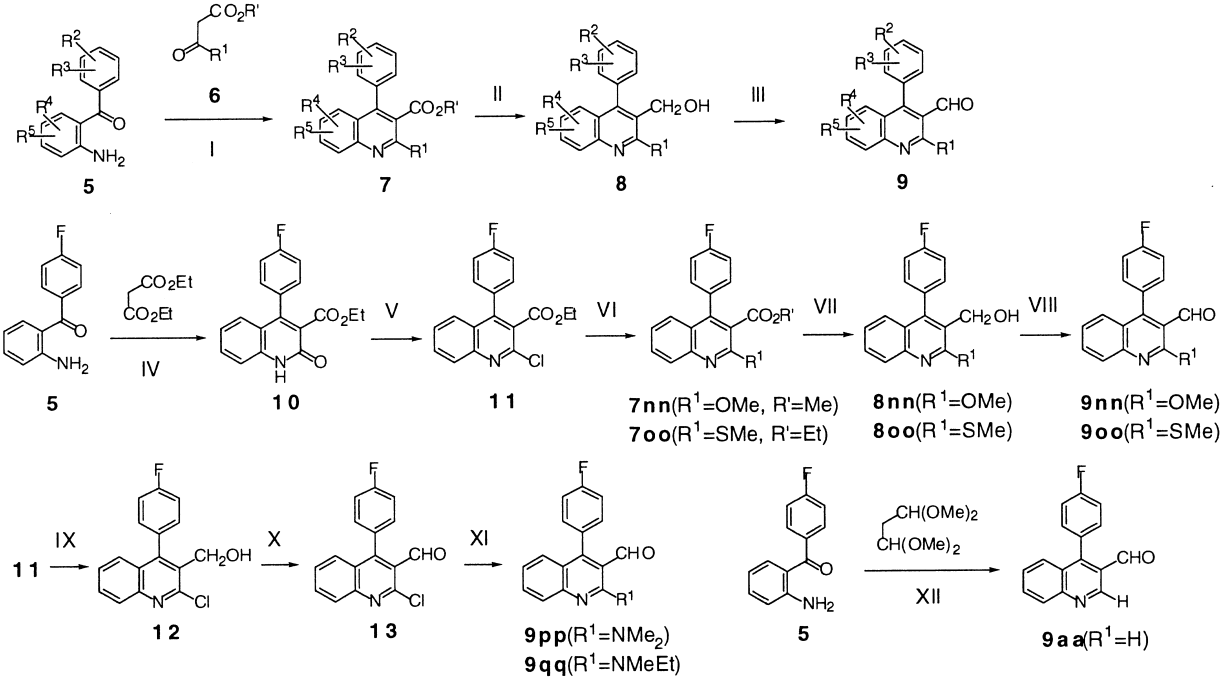


Figure 1.

Chemistry

Synthesis of quinolinecarbaldehyde, 9

Preparation of the key intermediate, aldehyde **9** required for the elaboration of quinoline-based 3,5-dihydroxyheptenoic acid derivatives, is shown in Scheme 1. As for the derivative with an alkyl or an aryl as the 2-position substituent R^1, ester **7** was prepared by acid catalyzed Friedlander reaction of 2-aminobenzophenone **5** with 3-ketoester **6**. Such a bulky 3-ketoester as methyl pivaloylacetate (i.e., R^1 = *tert*-butyl) gave a very low yield of the target ester using classical reaction conditions, with H_2SO_4 in acetic acid.[8] Our revised reaction conditions, with methane sulfonic acid in refluxing benzene,[9] gave a more moderate yield. The Dibal reduction and the PCC oxidation of the resulting ester, **7**, afforded aldehyde **9**. This aldehyde, with a methoxy group on the 2-position (R^1 = OMe, **9nn**), was prepared via ester **7nn** following a slightly modified

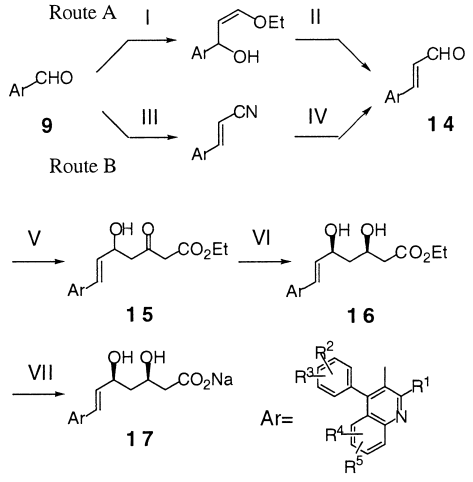


Scheme 1. Synthesis of **9**. Reagents and conditions: (I) H_2SO_4, AcOH, reflux or methanesulfonic acid, benzene, reflux; (II): DIBAH, toluene, −25 °C; (III) PCC, AcONa, CH_2Cl_2, rt; (IV) piperidine, reflux; (V) $POCl_3$, reflux; (VI) **7nn** Na, MeOH, rt; **7oo** MeSNa aq, THF, MeOH, reflux; (VII) **8nn**: DIBAH, toluene, −40 °C; **8oo** DIBAH, toluene, −75 °C; (VIII) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C; (IX) DIBAH, CH_2Cl_2, −78 °C; (X) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C; (XI) amine, toluene, 140 °C in autoclave; (XII) $ZnCl_2$, toluene, reflux.

procedure of Tawada et al.[10] Condensation reaction of 2-aminobenzophenone **5** (R^2 = 4-F, R^3, R^4 and R^5 = H) with diethyl malonate in the presence of piperidine furnished 2-quinolone-3-carboxylate **10**. Compound **10** was tranformed into chloroester **11** by chlorination with phosphorus oxychloride. Subsequent reaction of **11** with over 2.5 equivalent of sodium methoxide in methanol resulted in conversion of the chlorine atom to a methoxy group, with a concomitant ester exchange at the 3-position to give ester **7nn** (R^1 = OMe, R' = Me). This ester was converted to the corresponding aldehyde **9nn** (R^1 = OMe) by the Dibal reduction and the following DMSO oxidation of the resulting alcohol **8nn**. Ester **7oo** (R^1 = SMe, R' = Et) was obtained by the reaction of **11** with sodium methiolate applying the method of Natsugari and his co-workers.[11] It was transformed to aldehyde **9oo** (R^1 = SMe) in a manner analogous to that employed in the synthesis of **9nn**. The synthesis of aldehyde **9pp** (R^1 = NMe_2) was achieved by the method described by Sliskovic et al.[7] Thus, the Dibal reduction of **11** followed by DMSO oxidation of chloroalcohol **12** and nucleophilic substitution with dimethylamine of the resulting chloroaldehyde **13** gave the aldehyde. Chloroaldehyde **13** was also transformed to aldehyde **9qq** (R^1 = NMeEt) with *N*-ethyl-*N*-methylamine similarly to **9pp** described above. The aldehyde with no substituent on the 2-position (R^1 = H, **9aa**) was prepared by the ring closure reaction of the 2-aminobenzophenone **5** (R^2 = 4-F, R^3, R^4 and R^5 = H) with malonaldehyde bis(dimethylacetal) in the presence of $ZnCl_2$, according to the method described by Walser et al.[12]

Synthesis of the quinoline-based 3,5-dihydroxyheptenoic acid sodium salts, 17

Scheme 2 delineates the preparation of the quinoline-based 3,5-dihydroxyheptenoic acid derivative of aldehyde **9**. This synthesis requires five steps to attach the desmethylmevalonic acid portion to aldehyde **9**. Homologation of aldehydes **9a–t** to the corresponding propenals **14a–t** was accomplished by the reaction of the aldehydes with *cis*-2-ethoxyvinyllithium, which was generated from the transmethalation of *cis*-1-ethoxy-2-tri-*n*-butyl-stannyl-ethylene and hydrolysis of the resulting intermediate adducts with *p*-toluenesulfonic acid (Route A).[13a,b] Alternatively, aldehydes **9aa–qq** were converted to propenals **14aa–qq** by the Emmons–Horner coupling reaction with diethyl cyanomethylphosphonate, and the Dibal reduction of the resulting α,β-unsaturated nitriles (Route B). An aldol condensation of **14** with ethyl acetoacetate dianion yielded racemic 5-hydroxy-3-ketoester **15**. Partially stereoselective reduction of **15a–t** with $NaBH_4$ in methanol at room temperature afforded 3,5-dihydroxyesters **16a–t** (approximately *syn*/*anti* = 7:3).[14] Highly stereoselective chelation-controlled *syn* reduction[15] of **15aa–qq** was conducted with diethylmethoxyborane and sodium borohydride to give the corresponding 3,5-dihydroxyesters **16aa–qq** (approximately *syn*/*anti* = > 97:3).[14]



Scheme 2. Synthesis of **17**. Reagents and conditions: (I) *n*-Bu_3SnCH=CHOEt, *n*-Buli, THF, −78 °C; (II): PTS, THF, H_2O, rt; (III): $(EtO)_2POCH_2CN$, NaOHaq, $(n\text{-}C_8H_{17})_3MeNCl$, toluene, rt; (IV) DIBAH, toluene, −10 °C; (V) $CH_3COCH_2CO_2Et$, NaH, *n*-Buli, THF, −15 °C; (VI) Method A: $NaBH_4$, EtOH, rt; Method B: Et_2BOMe, $NaBH_4$, THF, MeOH, −78 °C; (VII) (i) NaOHaq, EtOH, rt; (ii) freeze dry.

These 3,5-dihydroxyesters **16** were converted to the corresponding sodium salts **17** for biological evaluations by freeze-drying after saponification with aqueous NaOH.

Results and Discussion

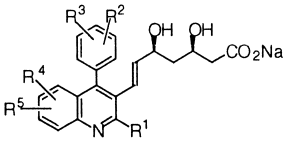
Effects of modification of the substituents on the central ring (R^1, R^4 and R^5) and on the external ring (R^2 and R^3)

At first, the approximate effects of modification of the substituents on the central and the external ring were examined. Most of the known artificial inhibitors have an isopropyl substituent as the alkyl side chain, R^1. Since an isopropyl group on an aromatic ring is readily metabolised by oxidation giving an aromatic carboxylic acid,[16a–d] we tried to replace the isopropyl moiety with a structurally similar, but more metabolically stable, cyclopropyl group. The quinoline-based 3,5-dihydroxyheptenoic acid sodium salts **17a–t** listed in Table 1 were evaluated for their ability to inhibit sterol synthesis in a cell-free system using a mixture of microsome fraction and semipurified-cytosolic fraction isolated from rat liver as the enzyme sources in vitro. All biological tests were conducted under the same experimental conditions with pravastatin as a reference for direct comparison. The activities were determined by decreased incorporation of sodium [2-^{14}C] acetate into non-saponifiable lipids. The relative potencies were obtained by comparison of IC_{50} values of compounds **17a–t** with that of pravastatin.

Summary of results obtained in each categories: (i) Effects of modification of R^1 (central ring); Replacement of the isopropyl in **17b**, **17m**, and **17s** with a cyclopropyl group to provide **17c**, **17p**, and **17t**, respectively, resulted in retention or enhancement of activity. In particular, with the external ring held constant as 4-

fluorophenyl, the cyclopropyl analogues displayed several times more potency than the corresponding isopropyl derivatives (**17b** vs **17c**, **17s** vs **17t**), which were comparable in potency to pravastatin. (ii) Effects of modification of R^2 and R^3 (external ring); As shown in the previous literature, holding the substituent R^1 constant as isopropyl, the strict structural requirement in this moiety was found. Substitution on the external ring (**17d**–**l**) was generally detrimental to potency, aside from the known 4-fluoro (**17b**), which was nearly equipotent than the unsubstituted analogue (**17a**). Moreover, movement of the fluoro from the *para* (**17b**) to the *ortho* position (**17j**), or addition of a methyl group in the *meta* position (**17d**), diminished potency. (iii) Effects of modification of R^4 and R^5 (central ring); The introduction of chloro, methyl, and methoxy group to the 6-, 7-, and 8-positions of the quinoline nucleus showed constant or moderately increased potency (**17a** vs **17m** and **17r**; **17b** vs **17n**, **17o**, **17q**, and **17s**; **17c** vs **17t**).

Table 1. Inhibition of hepatic cholesterol 'de novo' synthesis in vitro[a,b] (effects of modification of R^1, R^2, R^3, R^4, and R^5)



No.	R^1	R^2	R^3	R^4	R^5	Relative potency[c]
17a	*i*-Pr	H	H	H	H	15
17b	*i*-Pr	4-F	H	H	H	18
17c	*c*-Pr	4-F	H	H	H	100
17d	*i*-Pr	4-F	3-Me	H	H	8
17e	*i*-Pr	4-Cl	H	H	H	8
17f	*i*-Pr	4-Me	H	H	H	3
17g	*i*-Pr	4-CF_3	H	H	H	2
17h	*i*-Pr	4-OMe	H	H	H	4
17i	*i*-Pr	4-OPh	H	H	H	<1
17j	*i*-Pr	2-F	H	H	H	11
17k	*i*-Pr	2-Cl	H	6-Cl	H	3
17l	*i*-Pr	3-Me	5-Me	H	H	3
17m	*i*-Pr	H	H	6-Cl	H	30
17n	*i*-Pr	4-F	H	6-Cl	H	26
17o	*i*-Pr	4-F	H	6-Cl	8-Cl	54
17p	*c*-Pr	H	H	6-Cl	H	36
17q	*i*-Pr	4-F	H	6-Me	H	36
17r	*i*-Pr	H	H	7-Me	H	11
17s	*i*-Pr	4-F	H	6-OMe	7-OMe	17
17t	*c*-Pr	4-F	H	6-OMe	7-OMe	111
Pravastatin[d]						100

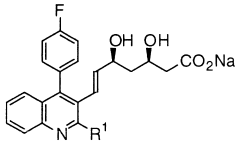
[a]Compounds were tested for their ability to inhibit hepatic cholesterol bio-synthesis in vitro with semipurified-cytosolic fraction and microsome fraction from rat liver: a measure of the rate of decreased incorporation of [^{14}C]acetate to non-saponifiable lipids.
[b]Compounds isolated as a 7:3 mixture of *syn*/*anti* diols as determined by HPLC and/or PNMR spectroscopy.
[c]Potencies were obtained by comparison of IC_{50} values of compounds **17a**–**t** with that of the internal standard pravastatin. Parameters were calculated using a logistic curve fit of dose response data from three or five dose points. The response at each dose was the mean response of triplicate determinations.
[d]Pravastatin averaged $IC_{50} = 4.2$ nM and was used in every run as an internal standard. For estimation of relative inhibitory potencies, pravastatin was assigned a value of 100.

Effects of modification of the substituent R^1 on the central ring

Using the optimal 4-fluorophenyl as the external ring, the structure–activity relationships of the 2-position substituents were explored in detail. Quinoline-based 3,5-dihydroxyesters **17aa**–**qq** (R^2 = 4-F, R^3, R^4, R^5 = H) were evaluated for their ability to inhibit HMG-CoA reductase obtained from rat liver. IC_{50} measurements showing the decreased rate of incorporation of [^{14}C] acetate into mevalonic acid demonstrated the inhibitory activity of the compounds. The results of substitution on position 2 are shown in Table 2.

The potency was dramatically altered with the 2-position substituent: (i) The 2-position unsubstituted derivative **17aa** (R^1 = H) showed no detectable inhibition, suggesting that a lipophilic interaction in this region is essential in inhibiting the target enzyme. (ii) The inhibitory potency increased with length of the 2-substituent from methyl (**17bb**) through ethyl (**17cc**), with the greatest effect shown with isopropyl (**17ee**), which was comparable to lovastatin in activity. However, increasing the length of the substituent to three carbons, *n*-propyl (**17dd**) resulted in loss of activity and showed a length limitation of the 2-substituent. The analogues with isobutyl (**17gg**) and *sec*-butyl (**17hh**) possessed

Table 2. Inhibition of solubilized rat liver HMG-CoA reductase in vitro[a,b] (effects of modification of R^1)



No.	R^1	IC_{50} (nM)[c]
17aa	H	>1000(5)
17bb	Me	241(5)
17cc	Et	44(5)
17dd	*n*-Pr	76(5)
17ee	*i*-Pr	19(7)
17ff	*n*-Bu	618(5)
17gg	CH_2CHMe_2	71(5)
17hh[d]	CHMeEt	74(5)
17ii	*t*-Bu	343(7)
17jj	*c*-Pr	4.1(7)
17kk	*c*-Hex	67(5)
17ll	Ph	377(5)
17mm	CF_3	140(7)
17nn	OMe	124(7)
17oo	SMe	484(7)
17pp	NME_2	184(7)
17qq	NMeEt	209(7)
Lovastatin		12(5)

[a]Compounds were assayed against HMG-CoA reductase with a partially purified microsomal enzyme preparation from rat liver: a measure of the direct conversion of [^{14}C]HMG-CoA to [^{14}C]-mavalonic acid.
[b]Compounds tested had a diastereomeric purity of >97% ds of the *syn* diastereomer as determined by HPLC and/or PNMR spectroscopy.
[c]Parameters were calculated using a logistic curve fit of dose response data with the indicated number (in parentheses) of dose points. The response at each dose was the mean response of duplicate determinations.
[d]Compound **17hh** was prepared from DL-ethyl 2-methylbutyrylacetate.

potency similar to that of **17dd**, but the *n*-butyl analogue, **17ff** was practically inactive. (iii) The *tert*-butyl derivative, **17ii** showed a large decrease in activity when compared with **17ee**, taking into account the chain length. A structural limitation exists in not only the chain length but also the bulkiness of the substituent R^1 (i.e., size and shape). Therefore, as Roth and his coworkers noted,[6] other factors which may influence conformation of the 3,5-dihydroxyheptenoic acid portion should be considered. (iv) As already described in the previous test, approximately a 5-fold increase in potency was realized when an isopropyl group in **17ee** was replaced by a more compact cyclopropyl moiety (**17jj**). The IC_{50} value was as high as 4.1 nM, and turned out to be the optimum potency in this investigation. (v) The *c*-hexyl analogue, **17kk** was a moderate inhibitor considering its substituent volume. This showed nearly 1/3.5 times the potency of **17ee**. However, aromatization of the cyclohexane ring gave a phenyl derivative **17ll**, with significantly diminished activity. (vi) Changing the electronic property of the substituents R^1 via introduction of a trifluoromethyl group (**17mm**) failed to improve the potency over the isopropyl derivative, **17ee**. (vii) Replacement of the ethyl group in **17cc** with the methoxy and the methylthio gave **17nn** and **17oo**, respectively. They displayed about one third and one eleventh of the potency of **17cc**, respectively. (viii) The activity of the dimethylamino derivative **17pp** was reduced by a factor of about 10 relative to the isopropyl derivative **17ee**, as already reported in the quinoline series by Sliskovic et al.[7] Replacement of the *sec*-butyl group in **17hh** with a *N*-ethyl-*N*-methylamino group to provide **17qq** also diminished activity. It is suggested that not only a steric parameter but also an electric parameter would be involved. (ix) Interestingly, we found a rank order of in vitro potency in the investigation on 3,5-dihydroxyheptenoic acid derivatives with a six-member quinoline as the central ring: cyclopropyl > isopropyl > cyclohexyl > trifluoromethyl > methyl > *tert*-butyl, which is quite different from that of 3,5-dihydroxheptanoic acid derivatives with a five-member pyrrole reported by Roth et al.,[5] namely, isopropyl > trifluoromethyl > *tert*-butyl > cyclopropyl > methyl > cyclohexyl. This may be due to the spatial relationships between the desmethylmevalonic acid portion, the external ring, and the alkyl side chain somewhat exchanged by changing the central ring from a small ring to a larger one. In addition, replacement of the bridging group resulted in a substantial conformational change in this moiety, namely, a single bond in Roth's study and a double bond in our series. Based on these results, further precise QSAR analysis will be published elsewhere.[17]

Conclusion

A series of quinoline-based 3,5-dihydroxyheptenoic acid derivatives was synthesized to evaluate their ability to inhibit the enzyme HMG-CoA reductase in vitro. First, in agreement with the previous literature, a strict structural requirement exists on the external ring, and 4-fluorophenyl was found to be most active in this system. On the central ring, substitution at positions 6, 7, and 8 of the central quinoline nucleus moderately affected the potency, whereas the alkyl side chain on the 2-position definitively influenced activity. We found that further modulation and improvement in potency at inhibiting HMG-CoA reductase was obtained with the optimal substituents flanking the desmethylmevalonic acid portion, that is 4-fluorophenyl and cyclopropyl, instead of the usual isopropyl group.

NK-104 (pitavastatin calcium:[18] monocalcium bis [(3*R*, 5*S*, 6*E*)-7-(2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl)-3,5-dihydroxy-6-heptenoate], the chiral calcium salt form of **17jj**, shows remarkably potent anti-lipidemic activity,[19] and is now awaiting registration in Japan and is under clinical development in America and European countries. The lipophilic anchor moiety in each inhibitor plays an important role, which affects not only the in vitro potency but also the pharmacokinetic profile. This drug has superior bio-availability and long-duration drug concentration in plasma, on the basis of entero-hepatic circulation and metabolical resistance. It has been speculated that these favorable metabolic and pharmacokinetic characteristics of the drug support efficacy in clinical studies as a highly potent hypolipidemic agent in humans (Fig. 2).[20]

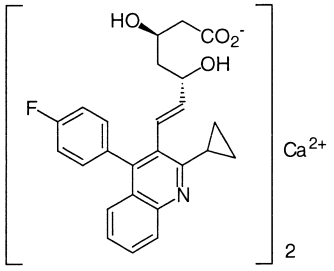


Figure 2. NK-104.

In the field of medicinal chemistry, the rational approach of analysing the three dimensional structure of target proteins has become an important method for the design and discovery of new targets. Recentry, X-ray analysis of the co-crystallization of human HMG-CoA reductase with the inhibitors was reported.[21] It was demonstrated that the COOH-terminal residues of HMGR are disordered, revealing a shallow hydrophobic groove that accommodates the hydrophobic moieties of the inhibitors. The discovery of a further optimized inhibitor would be possible in the future using crystal structures and analysis of the target enzyme–inhibitor complex.

Experimental

Syntheses

General methods. Melting points were determined with a Yanagimoto Micro Melting Point Apparatus; Yanaco Model MP-500V, and are uncorrected. IR spectra were recorded on a Horiba Fourier Transform Infrared Spectrometer FT-210 and Spectradesk SD-20 with 3M

IR Cards (Type 61-100-12) Microporous Polyethylene Film. Electron-impact ionization (EI) mass spectra were recorded on a JEOL JMS-D300 or a JEOL SX102A spectrometer. Fast-atom bombardment (FAB) and Field Disorption (FD) mass spectra were recorded on a JEOL JMS-DX300 or a JOEL LX1000 spectrometer. Matrix assisted laser disorption ionization (MALDI) mass spectra were recorded on a Applied Biosystems Vojager DE-Pro. FAB spectra were recorded in a glycerol matrix. Time of flight mass (TOFMS) spectra were recorded with internal standard, PEG400. EI-High resolution mass spectra (EI-HRMS) were recorded on a JEOL SX102A spectrometer. FAB-High resolution mass spectra (FAB-HRMS) were recorded on a JEOL LX1000 spectrometer. ^{1}H and ^{13}C NMR spectra were measured at 300, 400, and 500 MHz using a JEOL JNM-ECP 300 FT NMR SYSTEM, a Varian Unity INOVA, and a JEOL JNM-ECP-500 FT NMR SYSTEM respectively. Chemical shifts are given in parts per million downfield from tetramethylsilane as the internal standard, whereas coupling constants (*J*) are in hertz in $CDCl_3$ or DMSO-d_6. Two-dimensional DQF-COSY and HMQC experiments were recorded in order to assist with spectal assignment. HPLC analyses were performed using a Shimadzu LC-10A, a SPD-10A UV detector, a CTO-6A Column Oven, and a C-R6A Chromatopac.

All of the reactions at low temperature were carried out in an atmosphere of inert gas. The usual work up refers to washing of organic layers with brine, drying over anhydrous magnesium or sodium sulfate, and evaporating off the solvents under reduced pressure. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography on silica gel precoated Kieselgel $60F_{254}$ Merck plates, with detection under 254 nm UV lamp and/or by spraying with a diluted potassium permanganate solution. Column chromatographies were performed with Merck 60–200 mesh or Daiso 63–210 μm silica gel.

Materials. Some of the substituted 2-aminobenzophenone **5** and 3-ketoester **6** are not commercially available, and were prepared according to literature methods. The substituted 2-aminobenzophenones with fluoro, trifluoromethyl, methoxy, and benzyloxy substituents were prepared through the inverse addition of a Grignard reagent to a 3,1-benzoxazin-4-ones, which was obtained by the reaction of anthranilic acid with acetic anhydride,[22a,b] 2-amino-4′-fluorobenzophenone was also prepared from anthranilic acid, by protection of the amino group with p-toluenesulfonyl, chlorination with phosphorus pentachloride, and Friedel–Crafts reaction with fluorobenzene in the presence of $AlCl_3$.[22c,d] Methyl cyclopropanecarbonyl-acetate (R^1 = cyclopropyl) was prepared by acylation of Meldrum's acid with cyclopropanecarbonyl chloride in the presence of pyridine, followed by successive methanolysis.[23a] Ethyl cyclopropanecarbonylacetate, which was prepared from cyclopropyl methyl ketone by carbethoxylation with ethyl carbonate in the presence of sodium hydride, was also used as a starting material.[23b] Ethyl isovalerylacetate ($R^1 = CH_2CHMe_2$), DL-ethyl 2-methylbutyrylacetate (R^1 = CHMeEt), and ethyl cyclohexanecarbonylacetate (R^1 = *c*-hexyl) were prepared by the reaction of dilithio dianion of monoethyl malonate with isovaleryl chloride, DL-2-methylbutyryl chloride, and cyclohexanecarbonyl chloride, respectively.[23c] Tetrahydrofuran was freshly distilled from sodium metal and benzophenone under nitrogen. Methylene chloride was purchased anhydrous and methanol-free from Kanto, and used as received. Other reagents and solvents were reagent grade where available and were used without further purification unless otherwise stated.

Friedlander synthesis of quinolinecarboxylate by Fehnel's procedure

Methyl 2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinecarboxylate, 7c (step I in Scheme 1). 3.39 g (15.8 mmol) of 2-amino-4′-fluorobenzophenone, 2.91 g (20.5 mmol) of methyl cyclopropanecarbonylacetate and 0.2 mL of concentrated sulfuric acid were dissolved in 17 mL of glacial acetic acid, and the mixture was heated at 100 °C for 10 h. The reaction mixture was then cooled and poured slowly with stirring into an ice-cold solution of 45 mL of concentrated aqueous ammonia in 120 mL of water. The resultant suspension was allowed to stand overnight in a refrigerator. The crude product was collected, washed with water, and recrystallized from a small amount of ethanol to obtain 3.74 g (73.9%) of the title compound as a white powder: mp 126.0–127 °C; MS [EI, M^+] *m*/*z* 321; ^{1}H MNR (300 MHz, $CDCl_3$) δ 1.0 (m, 2H), 1.4 (m, 2H), 2.2 (m, 1H), 3.63 (s, 3H), 7.2–7.5 (m, 6H), 7.7 (m, 1H), 8.0 (m, 1H) ppm.

The starting alkyl and aryl substituted esters, **7a**–**t** were prepared in a manner analogous to the method described above by a classical-type acid catalyzed Friedlander synthesis according to Fehnel.[8]

Friedlander synthesis of quinolinecarboxylate by the revised procedure

Ethyl 2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinecarboxylate, 7jj (step I in Scheme 1). 280.0 g (1.30 mol) of 2-amino-4′-fluorobenzophenone and 213.3 g (1.37 mol) of ethyl cyclopropanecarbonylacetate were suspended in 2.8 L of molecular sieve-dehydrated benzene. 125.0 g (1.30 mol) of methanesulfonic acid was added with stirring to the suspension. The mixture was refluxed for 10 h for azeotropic dehydration with a Dean–Stark trap. 500 mL of water was added and the mixture cooled to 50 °C. The resulting solution was neutralized with a solution of 61.5 g of NaOH in 500 mL of water. After separation, the organic layer was washed with water. 10 g of activated charcoal was added and filtered on a Celite bed. 3.2 L of the solvent was evaporated under reduced pressure. The solution was diluted with 840 mL of petroleum ether at 30–40 °C, and stirred at 10 °C for 1 h. The mixture was cooled to 0 °C and a further 840 mL of petroleum ether was added and stirred for 2 h. The precipitated crystals were filtered, washed with 420 mL of petroleum ether and dried at 40 °C under pressure to obtain 413.1 g (94.9%) of the title compound as colorless prisms: mp 73.5–75.5 °C; IR (film)

1728, 1228 cm^{-1}; MS [EI, M^+] *m/z* 335; HR-MS [EI, M^+] calcd for $C_{21}H_{18}FNO_2$ *m/z* 335.1322, found 335.1340; ^1H MNR (400 MHz, $CDCl_3$) δ1.02 (t, 3H, *J* = 7 Hz), 1.0–1.1 (m, 2H), 1.3–1.4 (m, 2H), 2.2–2.3 (m, 1H), 4.12 (q, 2H, *J* = 7 Hz), 7.2 (m, 2H), 7.3–7.4 (m, 3H), 7.5 (m, 1H), 7.7 (m, 1H), 8.0 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 162.9 (d, $^1J_{C\text{-}F}$ = 248.0 Hz), 158.4, 148.0, 144.4, 131.8 (d, $^4J_{C\text{-}F}$ = 3.4 Hz), 131.4 (2C, d, $^3J_{C\text{-}F}$ = 8.0 Hz), 130.1, 129.2, 127.9, 126.1, 126.0, 125.0, 115.4 (2C, d, $^2J_{C\text{-}F}$ = 21.8 Hz), 61.5, 15.5, 13.9, 10.5 ppm.

The starting alkyl and aryl substituted esters, **7bb–mm** were prepared in a manner analogous to the method described above.

2-Cyclopropyl-4-(4-fluorophenyl)-3-quinolinemethanol, 8c (step II in Scheme 1). 28.8 mL (28.8 mmol) of a 1.0 M toluene solution of DIBAL-H was added to a solution of methyl 2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinecarboxylate, **7c** (3.70 g, 11.5 mmol) in anhydrous toluene (35 mL) at 0 °C under an atmosphere of nitrogen. The resulting solution was stirred for 2 h at 0 °C before quenching with a saturated aqueous ammonium chloride solution. The mixture was added to 50 mL of ethyl ether and the organic layer was separated. A gelled product was dissolved by the addition of an aqueous sodium hydroxide solution and extracted with ethyl ether. The organic layers were combined, dried over magnesium sulfate and filtered. The solvent was evaporated to dryness to yield 3.23 g (95.7%) of the crude title compound **8c** as a white powder: mp 132–133 °C; IR (film) 1605, 1513, 1494, 1224, 1159, 1065, 840, 764 cm^{-1}; MS [EI, M^+] *m/z* 293; HRMS [EI, M^+] calcd for $C_{19}H_{16}FNO$ *m/z* 293.1216, found 293.1262; ^1H MNR (300 MHz, $CDCl_3$) δ 1.1 (m, 2H), 1.3–1.4 (m, 2H), 1.73 (m, 1H), 2.6 (m, 1H), 4.74 (s, 2H), 7.2–7.3 (m, 6H), 7.6 (m, 1H), 8.0 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6 (d, $^1J_{C\text{-}F}$ = 247.5 Hz), 162.2, 147.3, 146.4, 132.4 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 131.3 (2C, d, $^3J_{C\text{-}F}$ = 8.1 Hz), 129.2 (2C), 128.9, 126.4, 126.1, 125.5, 115.5 (2C, d, $^2J_{C\text{-}F}$ = 21.9 Hz), 59.7, 14.5, 9.8 (2C) ppm.

The alkyl and aryl substituted alcohols, **8a–t** and **8bb–mm** were prepared in a manner analogous to the method described above.

2-Cyclopropyl-4-(4-fluorophenyl)-3-quinolinecarboxaldehyde, 9c (step III in Scheme 1). 3.54 g (16.42 mmol) of pyridinium chlorochromate and 0.42 g of anhydrous sodium acetate (5.13 mmol) were suspended in 40 mL of anhydrous dichloromethane. A solution of 3.01 g (10.26 mmol) of 2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinemethanol, **8c** in 10 mL of anhydrous dichloromethane was immediately added to this suspension at room temperature. The mixture was stirred for 1 h. Then, 100 mL of ethyl ether was added, and the mixture was thoroughly mixed. The reaction mixture was filtered through a silica gel layer. The filtrate was distilled off under reduced pressure, and the residue was extracted with diisopropyl ether. The insoluble materials were filtered off, and the filtrate was evaporated in vacuo to give the crude product. This was flash chromatographed on silica gel eluting with $CHCl_3$ to yield 1.69 g (56.5%) of the title compound **9c** as a white powder: mp 149–150 °C; IR (film) 1696,1553, 1512, 1490, 1157, 768 cm^{-1}; MS [EI, M^+] *m/z* 291; HR-MS [EI, M^+] calcd for $C_{19}H_{14}FNO$ *m/z* 291.1059, found 291.1090; ^1H MNR (300 MHz, $CDCl_3$) δ 1.1 (m, 2H), 1.4 (m, 2H), 3.2 (m, 1H), 7.2–7.5 (m, 6H), 7.7–7.8 (m, 1H), 8.0 (m, 1H), 10.06 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6, 163.0 (d, $^1J_{C\text{-}F}$ = 249.8 Hz), 161.6, 152.8, 148.9, 131.9 (2C, d, $^3J_{C\text{-}F}$ = 8.1 Hz), 131.8, 129.9 (d, $^4J_{C\text{-}F}$ = 4.0 Hz), 129.2, 126.5, 126.2, 126.1, 125.2, 115.8 (2C, d, $^2J_{C\text{-}F}$ = 21.9 Hz), 14.5, 11.3 (2C) ppm.

The alkyl and aryl substituted aldehydes, **9a–t** and **9bb–mm** were prepared in a manner analogous to the method described above.

The aldehyde with a methoxy group on the 2 position (**9nn**) was synthesized through the reaction route (IV→V→VI→VII→VIII in Scheme 1) in an analogous manner to the preparation of some methoxyquinoline derivatives reported by Tawada et al.[9]

Ethyl 4-(4-fluorophenyl)-1,2-dihydro-2-oxo-3-quinolinecarboxylate, 10 (step IV in Scheme 1). A mixture of 15.00 g (69.8 mmol) of 2-amino-4′-fluorobenzophenone **5**, 16.77 g (105 mmol) of diethyl malonate, and piperidine (2.99 g, 35.1 mmol) was heated at 170 °C for 6 days. After cooling, the resulting mixture was recrystallized from ethanol and dried under reduced pressure at 40 °C to afford 13.12 g (60.4%) of **10** as a faintly yellow powder: ^1H MNR (300 MHz, $CDCl_3$) δ 1.02 (t, 3H, *J* = 7 Hz), 4.12 (q, 2H, *J* = 7 Hz), 7.10–7.60 (m, 8H), 12.80 (bs, 1H) ppm. ^1H NMR data of **10** were identical with that of the literature data[7] prepared through an alternative method by the condensation reaction of 2-amino-4′-fluorobenzophenone **5** with ethyl malonyl chloride.

Ethyl 2-chloro-4-(4-fluorophenyl)-3-quinolinecarboxylate, 11 (Step V in Scheme 1). A mixture of **10** (23.95 g, 77 mmol) and phosphorus oxychloride (127.5 g, 83 mmol) was refluxed for 2 h. After removal of the excess $POCl_3$ by distillation under reduced pressure, the resulting mixture was extracted with 250 mL of ethyl acetate, filtered, washed with saturated aqueous $NaHCO_3$ solution and brine and dried over magnesium sulfate. Removal of the solvent by evaporation to dryness under reduced pressure afforded 20.47 g (80.7%) of the title compound **11** as a pale yellow powder: mp 104–111 °C; IR (film) 1722, 1605, 1557, 1492, 1400, 1227, 1024, 768 cm^{-1}; MS [EI, M^+] *m/z* 329; HRMS [EI, M^+] calcd for $C_{18}H_{13}ClFNO_2$ *m/z* 329.0618, found 329.0612; ^1H MNR (300 MHz, $CDCl_3$) δ1.09 (t, 1H, *J* = 7 Hz), 4.17 (q, 2H, *J* = 7 Hz), 7.2–7.3 (m, 2H), 7.3–7.4 (m, 2H), 7.5–7.6 (m, 2H), 7.8 (m, 1H), 8.1 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 163.1 (d, $^1J_{C\text{-}F}$ = 249.2 Hz), 147.9, 147.5, 145.8, 131.4, 131.2 (2C, d, $^3J_{C\text{-}F}$ = 8.7 Hz), 130.3 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 128.9, 127.8, 127.7, 126.4, 125.7, 115.6 (2C, d, $^2J_{C\text{-}F}$ = 21.9 Hz), 62.0, 13.7 ppm.

^1H NMR data of **11** were identical with that of the literature data.[7]

Methyl 4-(4-fluorophenyl)-2-methoxy-3-quinolinecarboxylate, 7nn (step VI in Scheme 1). 500 mg of sodium was dissolved in anhydrous methanol (30 mL). To this solution was added **11** (3.00 g, 9.1 mmol) in anhydrous methanol (100 mL) at room temperature. The resulting solution was stirred for 1 day at room temperature. After removal of the solvent by distillation under reduced pressure, the residue was extracted with 100 mL of ethyl acetate, washed with water and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. This was flash chromatographed on silica gel, eluting with 20% ethyl acetate-hexanes, to yield 2.80 g (98.9%) of the title compound **7nn** as a pale yellow powder: mp 105–109 °C; IR (film) 1734, 1599, 1500, 1445, 1386, 1232, 1091, 766 cm^{-1}; MS [EI, M^+] *m/z* 311; HR-MS [EI, M^+] calcd for $C_{18}H_{14}FNO_3$ *m/z* 311.0958, found 311.0995; ^1H MNR (300 MHz, $CDCl_3$) δ 3.63 (s, 3H), 4.14 (s, 3H), 7.2–7.3 (m, 6H), 7.6 (m, 1H), 7.9 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 162.9 (d, $^1J_{C\text{-}F} = 248.1$ Hz), 157.9, 147.6, 146.7, 131.2, 131.1 (2C, d, $^3J_{C\text{-}F} = 8.7$ Hz), 130.5, 127.6, 126.4 (d, $^1J_{C\text{-}F} = 3.5$ Hz), 124.7, 123.7, 118.9, 115.5 (2C, d, $^2J_{C\text{-}F} = 21.3$ Hz), 54.0, 52.4 ppm.

Ethyl 4-(4-fluorophenyl)-2-methylthio-3-quinolinecarboxylate, 7oo (step VI in Scheme 1). The methylthio derivative was prepared from **11** in a manner analogous to the preparation described by Natsugari et al.[10] 56 mL (120 mmol) of a 15% aqueous solution of methyl mercaptan sodium salt was added to a solution of **11** (4.00 g, 12.1 mmol) in anhydrous tetrahydrofuran (240 mL) and anhydrous methanol (80 mL) at room temperature. The resulting solution was refluxed for 6 h. After removal of the solvent by distillation under reduced pressure, the residue was extracted with 100 mL of ethyl acetate, washed with water, dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting product was flash chromatographed on silica gel, eluting with $CHCl_3$, to yield 3.84 g (84.3%) of the title compound **7oo** as a pale yellow powder: mp 138–140 °C; IR (film) 1716, 1604, 1571, 1550, 1513, 1491, 1393, 1236, 1161, 1122, 765 cm^{-1}; MS [EI, M^+] *m/z* 341; HRMS [EI, M^+] calcd for $C_{19}H_{16}FNO_2S$ *m/z* 341.0886, found 341.0833; ^1H MNR (300 MHz, $CDCl_3$) δ 1.03 (t, 3H, $J = 7$ Hz), 4.11 (q, 2H, $J = 7$ Hz), 7.2–7.5 (m, 6H), 7.7 (m, 1H), 8.0 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 162.9 (d, $^1J_{C\text{-}F} = 248.1$ Hz), 156.2, 148.1, 144.8, 131.4 (d, $^4J_{C\text{-}F} = 3.5$ Hz), 131.2 (2C, d, $^3J_{C\text{-}F} = 8.7$ Hz), 130.6, 130.5, 128.3, 126.4, 125.9, 124.4, 115.4 (2C, d, $^2J_{C\text{-}F} = 21.3$ Hz), 61.6, 13.7, 13.5 ppm.

4-(4-Fluorophenyl)-2-methoxy-3-quinolinemethanol, 8nn (step VII in Scheme 1). To a solution of **7nn** (4.20 g, 13.5 mmol) in anhydrous toluene (30 mL) at −40 °C under an atmosphere of nitrogen was added 31 mL (31 mmol) of a 1.0 M toluene solution of DIBAL-H. The resulting solution was stirred for 2.5 h before quenching with methanol (0.14 g). The mixture was warmed to room temperature, and was added to 50 mL of toluene, washed with 10% of aqueous sodium hydroxide solution then brine, dried over magnesium sulfate, filtered, and evaporated to dryness yielding 3.65 g (95.5%) of the title compound **8nn** as a pale yellow powder: mp 143–144 °C; IR (film) 1597, 1500, 1443, 1385, 1325, 1223, 1161, 1007, 844, 764 cm^{-1}; MS [EI, M^+] *m/z* 283; HRMS [EI, M^+] calcd for $C_{17}H_{14}FNO_2$ *m/z* 283.1009, found 283.1023; ^1H MNR (300 MHz, $CDCl_3$) δ 2.56 (t, 1H, $J = 7$ Hz), 4.19 (s, 3H), 4.52 (d, 2H, $J = 7$ Hz), 7.2–7.3 (m, 6H), 7.6 (m, 1H), 7.9 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7 (d, $^1J_{C\text{-}F} = 247.5$ Hz), 160.7, 148.0, 145.9, 131.6 (d, $^4J_{C\text{-}F} = 3.5$ Hz), 131.4 (2C, d, $^3J_{C\text{-}F} = 8.1$ Hz), 129.5, 127.3, 126.6, 125.1, 124.3, 122.1, 115.5 (2C, d, $^2J_{C\text{-}F} = 21.3$ Hz), 58.6, 53.8 ppm.

4-(4-Fluorophenyl)-2-methylthio-3-quinolinemethanol, 8oo (Step VII in Scheme 1). 34 mL (34 mmol) of a 1.0 M toluene solution of DIBAL-H was added to a solution of **7oo** (3.38 g, 9.9 mmol) in anhydrous toluene (30 mL) at −75 °C under an atmosphere of nitrogen. The resulting solution was stirred for 5.5 h before quenching with methanol (0.43 g). The mixture was warmed to room temperature, and was added to 100 mL of 5% methanol-chloroform. This was washed with 10% aqueous sodium hydroxide solution and then brine, dried over magnesium sulfate, filtered, and evaporated to dryness yielding 2.90 g (97.9%) of the title compound **8oo** as a faintly yellow powder: mp 143–144 °C; IR (film) 1597, 1500, 1443, 1385, 1325, 1223, 1161, 1007, 844, 764 cm^{-1}; MS [EI, M^+] *m/z* 283; HR-MS [EI, M^+] calcd for $C_{17}H_{14}FNO_2$ *m/z* 283.1009, found 283.1023; ^1H MNR (300 MHz, $CDCl_3$) δ 2.56 (t, 1H, $J = 7$ Hz), 4.19 (s, 3H), 4.52 (d, 2H, $J = 7$ Hz), 7.2–7.3 (m, 6H), 7.6 (m, 1H), 7.9 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7 (d, $^1J_{C\text{-}F} = 248.1$ Hz), 159.6, 147.5, 146.1, 131.6 (d, $^4J_{C\text{-}F} = 3.5$ Hz), 131.4 (2C, d, $^3J_{C\text{-}F} = 8.1$ Hz), 129.6, 128.8, 128.1, 126.7, 125.6, 125.4, 115.5 (2C, d, $^2J_{C\text{-}F} = 21.9$ Hz), 59,5, 13.1 ppm.

4-(4-Fluorophenyl)-2-methoxy-3-quinolinecarboxaldehyde, 9nn (step VIII in Scheme 1). Dimethyl sulfoxide (2.65 g, 33.9 mmol) was added to a solution of oxalyl chloride (2.19 g, 17.3 mmol) in anhydrous dichloromethane (30 mL), at −78 °C under an atmosphere of nitrogen. After complete addition the resulting solution was stirred for 20 min at −78 °C and then a solution of **8nn** (3.61 g, 12.8 mmol) in dichloromethane (40 mL) was added dropwise. This was stirred for a further 2 h at −70 °C and then quenched by the addition of triethylamine (6.67 g, 65.9 mmol) and saturated aqueous ammonium chloride solution (15 mL). The organic layer was separated and washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. This was flash chromatographed on silica gel, eluting with 10% ethyl acetate-hexanes, to yield 2.44 g (67.8%) of the title compound as a pale yellow powder: mp 160–161 °C; IR (film) 1694, 1579, 1517, 1498, 1382, 1224, 760 cm^{-1}; MS [EI, M^+] *m/z* 281; HR-MS [EI, M^+] calcd for $C_{17}H_{12}FNO_2$ *m/z* 281.0852, found 281.0833; ^1H MNR (300 MHz, $CDCl_3$) δ 4.21 (s, 3H), 7.2–7.4 (m, 6H), 7.7 (m, 1H), 7.9 (m, 1H), 10.17 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.3, 162.9 (d, $^1J_{C\text{-}F} = 248.6$ Hz), 160.2, 154.0, 148.1, 132.2, 131.3 (2C, d, $^3J_{C\text{-}F} = 8.1$ Hz), 130.3 (d, $^4J_{C\text{-}F} = 3.5$ Hz), 127.5 (2C), 124.9, 124.7, 118.2, 115.6 (2C, d, $^2J_{C\text{-}F} = 21.9$ Hz), 54.0 ppm.

4-(4-Fluorophenyl)-2-methylthio-3-quinolinecarboxaldehyde, 9oo (step VIII in Scheme 1). Dimethyl sulfoxide (2.25 g, 28.8 mmol) was added to a solution of oxalyl chloride (1.83 g, 14.4 mmol) in anhydrous dichloromethane (30 mL), at −78 °C under an atmosphere of nitrogen. After complete addition the resulting solution was stirred for 15 min at −78 °C and then a solution of **8oo** (2.15 g, 71.9 mmol) in dichloromethane (40 mL) was added dropwise. This was stirred for a further 5 h at −70 °C and then quenched by the addition of triethylamine (5.53 g, 54.6 mmol) and saturated aqueous ammonium chloride solution (15 mL). The organic layer was separated and washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. This was flash chromatographed on silica gel, eluting with 5% methanol–$CHCl_3$, to yield 1.64 g (76.8%) of the title compound as a pale yellow powder: mp 136–140 °C; IR (film) 1686, 1607, 1539, 1512, 1227, 1054, 764 cm^{-1}; MS [EI, M^+] *m/z* 297; HRMS [EI, M^+] calcd for $C_{17}H_{12}FNOS$ *m/z* 297.0623, found 297.0598; ^1H MNR (300 MHz, $CDCl_3$) δ 2.70 (s, 3H), 7.2–7.5 (m, 6H), 7.8 (m, 1H), 8.0 (m, 1H), 9.95 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.4, 163.1 (d, $^1J_{C\text{-}F} = 249.8$ Hz), 159.8, 154.4, 148.9, 132.7, 131.9 (2C, d, $^3J_{C\text{-}F} = 8.7$ Hz), 129.3 (d, $^2J_{C\text{-}F} = 4.0$ Hz), 128.5, 127.0, 126.0 (2C), 124.3, 115.8 (2C, d, $^2J_{C\text{-}F} = 21.9$ Hz), 13.8 ppm.

The aldehyde with a dimethylamino group on the 2 position was prepared from **11** according to the method described by Sliskovic et al.[7]

2-Chloro-4-(4-fluorophenyl)-3-quinolinemethanol, 12 (step IX in Scheme 1). 70 mL (70 mmol) of a 1.0 M toluene solution of DIBAL-H was added to a solution of **11** (10.00 g, 30.3 mmol) in anhydrous dichloromethane (130 mL) at −78 °C under an atmosphere of nitrogen. The resulting solution was stirred for 5 h before quenching with saturated aqueous sodium sulfate (26 mL). The mixture was warmed to room temperature, and the resulting precipitate was filtered off. The cake was washed with dichloromethane, and the washings were combined with the filtrate and evaporated to dryness yielding 8.30 g (95.3%) of the title compound **12** as a pale yellow powder: mp 154–159 °C; IR (film) 1605, 1558, 1513, 1492, 1394, 1228, 1159, 1047, 842, 765 cm^{-1}; MS [EI, M^+] *m/z* 287; HR-MS [EI, M^+] calcd for $C_{16}H_{11}ClFNO$ *m/z* 287.0513, found 287.0517; ^1H MNR (300 MHz, $CDCl_3$) δ 2.35 (bs, 1H), 4.66 (s, 2H), 7.2–7.5 (m, 6H), 7.7–7.8 (m, 1H), 8.0–8.1 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9 (d, $^1J_{C\text{-}F} = 249.2$ Hz), 151.5, 150.3, 147.0, 131.3 (2C, d, $^3J_{C\text{-}F} = 8.1$ Hz), 131.1 (d, $^4J_{C\text{-}F} = 3.5$ Hz), 130.6, 129.4, 128.6, 127.3, 127.0, 126.8, 115.7 (2C, d, $^2J_{C\text{-}F} = 21.9$ Hz), 60.3 ppm.

^1H NMR data of **12** were identical with that of the literature data.[7]

2-Chloro-4-(4-fluorophenyl)-3-quinolinecarboxaldehyde, 13 (R^1 = Cl, step X in Scheme 1). Dimethyl sulfoxide (3.81 g, 48.8 mmol) was added to a solution of oxalyl chloride (3.15 g, 24.8 mmol) in anhydrous dichloromethane (50 mL), at −78 °C under an atmosphere of nitrogen. After complete addition the resulting solution was stirred for 15 min at −78 °C and then a solution of **12** (5.30 g, 18.4 mmol) in dichloromethane (50 mL) was added dropwise. This was stirred for a further 4 h at −78 °C and then quenched by the addition of triethylamine (9.59 g, 94.8 mmol) and saturated aqueous ammonium chloride solution (15 mL). The organic layer was separated and the organic layer was dried, filtered, concentrated in vacuo, and washed with hexanes to yield a pale yellow powder. This was flash chromatographed on silica gel, eluting with 50% ethyl acetate–hexanes, to yield 4.82 g (91.8%) of the title compound **13** as a faintly yellow powder: mp 166–167 °C; IR (film) 1698, 1544, 1515, 1491, 1382, 1224, 1044, 851, 765 cm^{-1}; MS [EI, M^+] *m/z* 285; HR-MS [EI, M^+] calcd for $C_{16}H_9ClFNO$ *m/z* 285.0357, found 285.0304; ^1H MNR (300 MHz, $CDCl_3$) δ 7.1–7.4 (m, 6H), 7.6 (m, 1H), 7.7–7.8 (m, 1H), 9.84 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8, 163.1 (d, $^1J_{C\text{-}F} = 249.2$ Hz), 153.5, 148.7, 148.4, 133.0, 131.3 (2C, d, $^3J_{C\text{-}F} = 8.1$ Hz), 129.3 (d, $^4J_{C\text{-}F} = 4.0$ Hz), 128.9, 128.0, 127.4, 126.7, 125.1, 115.8 (2C, d, $^2J_{C\text{-}F} = 21.9$ Hz) ppm.

^1H NMR data of **13** were identical with that of the literature data.[7]

2-(Dimethylamino)-4-(4-fluorophenyl)-3-quinolinecarboxaldehyde, 9pp ($R^1 = NMe_2$, step XI in Scheme 1). A solution of **13** (2.50 g, 8.76 mmol) and dimethylamine (17 g) in toluene (50 mL) was heated in an autoclave at 130–140 °C for 5.5 h. It was then cooled and concentrated in vacuo. The residue was extracted with $CHCl_3$, washed with saturated aqueous sodium hydrogen carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated and the residue was flash chromatographed on silica gel, eluting with $CHCl_3$ to yield 2.18 g (84.6%) of the title compound as a yellow powder: mp 125–128 °C; IR (film) 1684, 1605, 1547, 1513, 1389, 1226, 760 cm^{-1}; MS [EI, M^+] *m/z* 294; HRMS [EI, M^+] calcd for $C_{18}H_{15}FN_2O$ *m/z* 294.1168, found 294.1163; ^1H MNR (300 MHz, $CDCl_3$) δ 3.13 (s, 6H), 7.2–7.4 (m, 6H), 7.6–7.7 (m, 1H), 7.8 (m, 1H), 9.84 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.6, 163.0 (d, $^1J_{C\text{-}F} = 248.6$ Hz), 157.1, 155.4, 149.2, 132.3, 132.0 (2C, d, $^3J_{C\text{-}F} = 8.7$ Hz), 130.7 (d, $^4J_{C\text{-}F} = 3.5$ Hz), 127.1, 127.0, 123.0 (2C), 118.3, 115.5 (2C, d, $^2J_{C\text{-}F} = 21.9$ Hz), 41.9 ppm.

^1H NMR data of **9pp** were identical with that of the literature data.[7]

The aldehyde with a *N*-ethyl-*N*-methylamino group on the 2 position was prepared from **13** analogously to compound **9pp**.

4-(4-Fluorophenyl)-*N*-ethyl-*N*-methylamino-3-quinolinecarboxaldehyde, 9qq (R^1 = NMeEt, step XI in Scheme 1). The *N*-methyl-*N*-ethylamino derivative was prepared analogously to the dimethyl derivative. A solution of **13** (2.20 g, 7.71 mmol) and *N*-ethylmethylamine (10.0 g, 169 mmol) in toluene (40 mL) was heated in an autoclave at 140 °C for 6 h. It was then cooled and concentrated in vacuo. The residue was extracted with $CHCl_3$, washed with saturated aqueous sodium hydrogen

carbonate and brine, and dried over magnesium sulfate. The solvent was evaporated and the residue was flash chromatographed on silica gel, eluting with 10% ethyl acetate-hexanes, to yield 2.11 g (88.9%) of the title compound as an orange powder: mp 77–79 °C; IR (film) 1684, 1605, 1545, 1513, 1397, 1228, 760 cm^{-1}; MS [EI, M^+] *m/z* 308; HR-MS [EI, M^+] calcd for $C_{19}H_{17}FN_2O$ *m/z* 308.1325, found 308.1250; ^1H MNR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, *J* = 7 Hz), 3.03 (s, 3H), 3.62 (q, 2H, *J* = 7 Hz), 7.1–7.4 (m, 6H), 7.6 (m, 1H), 7.7–7.8 (m, 1H), 9.84 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 162.9 (d, $^1J_{C\text{-}F}$ = 248.6 Hz), 157.0, 154.6, 149.1, 132.0, 131.9 (2C, d, $^3J_{C\text{-}F}$ = 8.1 Hz), 130.8 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 127.1 (2C), 123.0, 118.7, 115.4 (2C, d, $^2J_{C\text{-}F}$ = 21.9 Hz), 48.1, 38.8, 12.5 ppm.

The 2 position unsubstituted derivative, **9aa** was prepared from 2-amino-4′-fluorobenzophenone and 1,1,3,3-tetramethoxypropane in a manner analogous to the preparation described by Walser et al.[12]

4-(4-Fluorophenyl)-3-quinolinecarboxaldehyde, 9aa (R^1 = H, step XII in Scheme 1). A mixture of 2.50 g (11.6 mmol) of 2-amino-4′-fluorobenzophenone, 2.86 g (17.4 mmol) of 1,1,3,3-tetramethoxypropane, 1.58 g (11.6 mmol) of zinc chloride and 50 mL of toluene was heated to reflux for 2 h. After the solvent was removed by evaporation, the residue was extracted with 100 mL of $CHCl_3$. The solution was washed with water and brine, dried over magnesium sulfate, and evaporated. The resulting brown oil was chromatographed with silica gel using 50% (v/v) of ethyl acetate in *n*-hexane. Washing of the eluent with *n*-hexane yielded 1.01 g (34.7%) of the title compound as a pale yellow powder: mp 122–128 °C; IR (film) 1694, 1607, 1575, 1513, 1498, 1228, 765 cm^{-1}; MS [EI, M^+] *m/z* 251; HR-MS [EI, M^+] calcd for $C_{16}H_{10}FNO$ *m/z* 251.0746, found 251.0822; ^1H MNR (300 MHz, $CDCl_3$) δ 7.3–7.4 (m, 4H), 7.5–7.7 (m, 2H), 7.8–7.9 (m, 1H), 8.2 (m, 1H), 9.43 (s, 1H), 9.97 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.2, 163.3 (d, $^1J_{C\text{-}F}$ = 250.4 Hz), 152.1, 150.1, 148.2, 132.2 (2C, d, $^3J_{C\text{-}F}$ = 8.1 Hz), 132.5, 130.1, 128.4 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 127.8, 127.1, 126.6, 125.5, 115.9 (2C, d, $^2J_{C\text{-}F}$ = 21.9 Hz) sppm.

The propenals, **14a**–**t** were synthesized via a carbonyl homologation with *cis*-2-ethoxyvinyllithium according to Wollenberg et al.[13]

2-Cyclopropyl-3-(3-ethoxy-1-hydroxy-2-propenyl)-4-(4-fluorophenyl) quinoline (route A: step I in Scheme 2). 6.28 g (17.43 mmol) of *cis*-1-ethoxy-2-(tri-*n*-butylstannyl)ethylene was dissolved in anhydrous tetrahydrofuran (10 mL), and the solution was cooled to −78 °C under an atmosphere of nitrogen. To this solution, 10.25 mL of 15 wt% *n*-butyllithium in *n*-hexane solution was added dropwise. The mixture was stirred for 1 h. Then, a solution of aldehyde **9c** (1.45 g, 4.98 mmol) in 10 mL of anhydrous tetrahydrofuran was added dropwise. The reaction mixture was stirred for 2 h at −78 °C. Then, 2 mL of saturated aqueous ammonium chloride solution was added to quench the reaction. Diethyl ether was added to the mixture, and the organic layer was separated, washed with brine, dried over magnesium sulfate, and filtered. The solvent was distilled off under reduced pressure, and the residue was extracted with acetonitrile. The solution was washed with *n*-hexane repeatedly to remove the stannyl ingredient. The solvent was evaporated in vacuo to yield the title compound as a colorless oil. This material was submitted to the next step without purification.

The other aldehydes, **9a**–**t** were analogously converted to the corresponding adducts, and the intermediate was submitted to the next step without purification.

(*E*)-3-[2-Cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-2-propenal, 14c (route A: step II in Scheme 2). The ethoxypropenylquinoline was dissolved in 20 mL of tetrahydrofuran, and 5 mL of water and 100 mg of *p*-toluenesulfonic acid were added. The mixture was stirred for 24 h at room temperature. The reaction solution was extracted with diethyl ether a few times. The extracts were washed with brine and dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed over silica, eluting with 2.5% methanol-chloroform, to yield 1.06 g (67.1%) of the title compound as a white powder: mp 136–142 °C; IR (film) 1685, 1605, 1554, 1513, 1489, 1225, 1159, 1122, 765 cm^{-1}; MS [EI, M^+] *m/z* 317; HR-MS [EI, M^+] calcd for $C_{21}H_{16}FNO$ *m/z* 317.1216, found 317.1245; ^1H MNR (300 MHz, $CDCl_3$) δ 1.1 (m, 2H), 1.4 (m, 2H), 2.4 (m, 1H), 6.45 (dd, 1H, *J* = 8 and 16 Hz), 7.2–7.4 (m, 6H), 7.56 (d, 1H, *J* = 16 Hz), 8.0 (m, 1H), 9.51 (d, 1H, *J* = 8 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4, 162.7 (d, $^1J_{C\text{-}F}$ = 248.6 Hz), 159.4, 150.0, 147.6, 146.4, 135.6, 131.9 (d, $^4J_{C\text{-}F}$ = 4.0 Hz), 131.5 (2C, d, $^3J_{C\text{-}F}$ = 8.1 Hz), 130.2, 129.0, 126.4, 126.3, 126.1, 125.6, 115.9 (2C, d, $^2J_{C\text{-}F}$ = 21.3 Hz), 16.5, 10.6 (2C) ppm.

The other aldehydes, **9a**–**t** were converted to the corresponding propenals **14a**–**t** in a manner analogously.

The propenals **14aa**–**qq** were synthesized via a Emmons–Horner coupling of aldehydes **9aa**–**qq** with diethyl (cyanomethyl)phosphonate, and a DIBAL-H reduction of the corresponding adducts.

(*E*)-3-[2-Cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-2-propenenitrile (route B: step III in Scheme 2). A 20% aqueous sodium hydroxide solution (25 g) was added dropwise under vigorous stirring at room temperature to a solution of aldehyde **9jj** (11.0 g, 37.9 mmol), diethyl (cyanomethyl)phosphonate (8.1 g, 45.5 mmol), and trioctylmethylammonium chloride (306.5 mg, 0.8 mmol) in anhydrous toluene (88 mL). The mixture was stirred for 2 h at room temperature, and 50 mL of water was added. The organic layer was separated, and then 25 mL of brine was added. The mixture was neutralized with 1 N hydrochloric acid, washed with water then brine, dried over sodium sulfate, filtered, and concentrated in reduced pressure. The resulting solution was heated at 100 °C, and 75 g of *n*-hexane was added. After cooling, the precipitate was collected, washed with *n*-hexane, and dried in high vacuum to yield 10.1 g (85.1%) of the title compound as a white crystal: mp 145–146 °C; IR (film) 1605, 1558, 1513, 1489, 1224, 1159, 766 cm^{-1}; MS [EI,

M^+] *m/z* 314; HR-MS [EI, M^+] calcd for $C_{21}H_{15}FN_2$ *m/z* 314.1219, found 314.1252; ^{1}H MNR (300 MHz, $CDCl_3$) δ 1.1 (m, 2H), 1.4 (m, 2H), 2.3 (m, 1H), 5.58 (d, 1H, $J=17$ Hz), 7.2–7.4 (m, 6H), 7.52 (d, 1H, $J=17$ Hz), 7.6–7.7 (m, 1H), 8.0 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8 (d, $^1J_{C\text{-}F}=249.2$ Hz), 159.1, 147.9, 147.6, 146.3, 131.6 (d, $^4J_{C\text{-}F}=4.0$ Hz), 131.4 (2C, d, $^3J_{C\text{-}F}=8.1$ Hz), 130.3, 129.0, 126.4, 126.2, 125.8, 125.6, 117.4, 116.1 (2C, d, $^2J_{C\text{-}F}=21.4$ Hz), 104.0, 16.5, 10.4 (2C) ppm.

The other aldehydes, **9aa–qq** were analogously converted to the corresponding adduct, and the intermediate was submitted to the next step without purification.

(*E*)-3-[2-Cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-2-propenal, 14jj (route B: step IV in Scheme 2). 37.6 mL (37.6 mmol) of a 1 M solution of diisobutylaluminum hydride in toluene at −10 °C was added dropwise under an atmosphere of nitrogen to a solution of the nitrile (9.9 g, 31.6 mmol) in anhydrous toluene (100 mL). The mixture was stirred for 1 h at −15 °C, and was then quenched with ethanol. 8.5 mL of 1 N hydrochloric acid was then added to this solution, and the resulting suspension was filtered over Celite. The cake was washed repeatedly with ethyl acetate, and the washings were combined with the filtrate. The solution was washed with 1 N hydrochloric acid then brine. 60 mL of water was added to the organic layer and this was neutralized with saturated aqueous sodium hydrogen carbonate solution, washed with water then brine, dried over sodium sulfate, and filtered. 80 mL of cyclohexane was added and the solution was then concentrated under reduced pressure until the total weight became 30 g. The resulting solution was heated at 60 °C, 40 mL of *n*-hexane was added, and the solution was cooled to 0 °C. The precipitate was collected, washed with *n*-hexane, and dried in high vacuum at 60 °C for 1.5 h to yield 8.66 g (86.5%) of the title compound as a white crystal: The spectra of **14jj** were identical with those of **14c** from route A.

Ethyl (*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-5-hydroxy-3-oxo-6-heptenoate, 15jj (step V in Scheme 2). A solution of ethyl acetoacetate (3.26 g, 25.0 mmol) in anhydrous tetrahydrofuran (10 mL) at −40 °C was added dropwise during oversp = 0.25 > min under an atmosphere of nitrogen to a suspension of sodium hydride (661 mg, 27.6 mmol, 60%) in anhydrous tetrahydrofuran (30 mL). The solution was stirred for 30 min at −30 °C. A solution of *n*-butyllithium in hexane (15.7 mL of a 1.6 M solution, 25.0 mmol) was added over 5 min. The reaction mixture was stirred for 30 min at −20 °C. A solution of 4.0 g (12.5 mmol) of propenal **14jj** in dry tetrahydrofuran (10 mL) was added dropwise at −15 °C over 6 min to this solution. The reaction mixture was stirred for 3 h at −10 °C. To quench the reaction, 15 mL of acetic acid in tetrahydrofuran (15 mL) was slowly added. 30 mL of water and 40 mL of ethyl acetate were added to this solution, separated, washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting mixture was recrystallized from 80 mL of cyclohexane and 40 mL of *n*-hexane, washed with *n*-hexane, and dried at 60 °C in high vacuum to yield 4.66 g (83.5%) of **15jj** as a faintly yellow powder: mp 90–93 °C; IR (film) 1740, 1713, 1604, 1513, 1489, 1222, 1158, 1026, 835, 765 cm^{-1}; MS [EI, M^+] *m/z* 447; HR-MS [EI, M^+] calcd for $C_{27}H_{26}FNO_4$ *m/z* 447.1846, found 447.1870; ^{1}H MNR (300 MHz, $CDCl_3$) δ 1.0 (m, 2H), 1.29 (t, 3H, $J=7$ Hz), 1.3 (m, 2H), 2.4 (m, 1H), 2.54 (d, 2H, $J=5$ Hz), 2.7 (m, 1H), 3.43 (s, 2H), 4.21 (q, 2H, $J=7$ Hz), 4.6 (m, 1H), 5.58 (dd, 1H, $J=6$ and 16 Hz), 6.67 (d, 1H, $J=16$ Hz), 7.2–7.3 (m, 6H), 7.6 (m, 1H), 8.0 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 166.7, 162.2 (d, $^1J_{C\text{-}F}=246.9$ Hz), 160.6, 146.8, 144.3, 138.0, 133.4 (d, $^4J_{C\text{-}F}=3.5$ Hz), 131.9 (2C, d, $^3J_{C\text{-}F}=8.2$ Hz), 131.8, 129.0, 128.9, 128.8, 126.4, 126.0, 125.4, 115.3 (2C, d, $^2J_{C\text{-}F}=21.3$ Hz), 68.2, 61.6, 49.8, 49.0, 15.9, 14.1, 10.2 (2C) ppm.

All other propenals, **14a–t** and **14aa–qq**, were analogously converted to the corresponding 5-hydroxy-3-keto esters **15a–t** and **15aa–qq**.

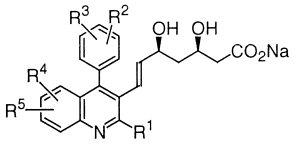
Ethyl (*E*)-3,5-dihydroxy-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-hept-6-enoate (step VI in Scheme 2)

Method A: partially stereoselective reduction. 1.04 g (2.33 mmol) of compound **15c** was dissolved in 10 mL of anhydrous ethanol in an atmosphere of nitrogen, and was cooled at 0 °C. 94 mg (2.49 mmol) of sodium borohydride was added to the solution, and stirred for 1 h. To quench the reaction, 1 mL of a 10% hydrochloric acid was then added to the mixture. This was extracted with diethyl ether three times, and the organic layer separated. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed over silica, eluting with 5% methanol–chloroform to yield 429 mg (41.1%) of **16c** as a white powder: mp 103–104 °C; MS [EI, M^+] *m/z* 449; ^{1}H MNR (400 MHz, $CDCl_3$) δ 1.0 (m, 2H), 1.29 (t, 3H, $J=7$ Hz), 1.3–1.6 (m, 2H), 2.3–2.4 (m, 1H), 2.42 (s, 2H), 3.2 (m, 1H), 3.7 (m, 1H), 4.1 (m, 1H), 4.19 (q, 2H, $J=7$ Hz), 4.4 (m, 1H), 5.58 (dd, 1H, $J=6$, 16 Hz), 6.64 (d, 1H, $J=16$ Hz), 7.2–7.4 (m, 6H), 7.6 (m, 1H), 7.9–8.0 (m, 1H) ppm. The *syn*/*anti* ratio of the sample was determined by HPLC (68.2:31.8; Nucleosil 50-5, 4.6×250 mm, 10% isopropanol and *n*-hexane, 1.0 mL/min, 35 °C, 254 nm; retention time: erythro 10.3 min, threo 9.2 min) and by ^{1}H NMR (68:32; 500 MHz by comparing the relative intensities of the methylene proton signal on the 3 position in the desmethylmavalonic acid chain; chemical shift: erythro 4.15 ppm, threo 4.05 ppm). All other 5-hydroxy-3-keto esters **15a–t** were analogously converted to the corresponding 3,5-dihydroxyesters **16a–t**.

Method B: stereoselective reduction. A solution of diethylmethoxyborane in tetrahydrofuran (10.7 mL of a 1 M solution, 10.7 mmol) was added dropwise under an atmosphere of nitrogen at room temperature to a solution of 5-hydroxy-3-keto ester **15jj** (3.09 g, 8.9 mmol) in anhydrous tetrahydrofuran (56 mL) and anhydrous methanol (6.7 g). After stirring for 1 h at −75 °C,

sodium borohydride (404 mg, 10.7 mmol) was added over 1 min. The solution was stirred for 3 h at −75 °C, and was quenched with 2.14 g of acetic acid in 2 mL of tetrahydrofuran at −75 °C. The resulting mixture was added to 70 mL of ethyl acetate and 60 mL of water, separated, washed with brine and saturated aqueous sodium hydrogencarbonate solution, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was taken up several times in 50 mL of methanol and this solvent was evaporated in vacuo at 60 °C to complete the conversion of the unpolar boron ester of the diol to free diol. The residue was recrystallized from methylenechloride and *n*-hexane twice to yield 2.34 g (58.5%) of **16jj** as a white powder: mp 102–105 °C; IR (film) 1717, 1604, 1564, 1513, 1489, 1411, 1221, 1158, 835, 764 cm^{-1}; MS [EI, M^+] *m/z* 449; HR-MS [EI, M^+] calcd for $C_{27}H_{28}FNO_4$ *m/z* 449.2003, found 449.2021; ^1H MNR (300 MHz, $CDCl_3$) δ 1.0 (m, 2H), 1.29 (t, 3H, $J = 7$ Hz), 1.3–1.6 (m, 2H), 2.3–2.4 (m, 1H), 2.43 (s, 2H), 3.2 (m, 1H), 3.6 (m, 1H), 4.1–4.2 (m, 1H), 4.19 (q, 2H, $J = 7$ Hz), 4.4 (m, 1H), 5.58 (dd, 1H, $J = 6$, 16 Hz), 6.64 (d, 1H, $J = 16$ Hz), 7.2–7.3 (m, 6H), 7.6 (m, 1H), 7.9–8.0 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 162.2 (d, $^1J_{C\text{-}F} = 246.9$ Hz), 160.8, 146.8, 144.2, 139.8, 133.5 (d, $^4J_{C\text{-}F} = 3.5$ Hz), 132.0 (d, $^3J_{C\text{-}F} = 7.5$ Hz), 131.8 (d, $^3J_{C\text{-}F} = 8.1$ Hz), 129.4, 128.9, 128.7, 126.1, 126.0, 125.7, 125.4, 115.3 (2C, d, $^2J_{C\text{-}F} = 21.3$ Hz), 68.0, 60.9, 42.4, 41.5, 15.9, 14.2, 10.3, 10.2 (2C) ppm; The *syn*/*anti*

Table 3. Characterization of the target compounds **17a–t**



No.	R^1	R^2	R^3	R^4	R^5	Mp (°C)[a]	IR ν C=O (cm^{-1})[b]	MALDI-TOFMS (*m/z*) $[M-Na+2H]^+$		
								Without I.S.	With I.S.[c]	
									Calculated for	Measured for
17a	*i*-Pr	H	H	H	H	196–197	1569	406	$C_{25}H_{28}NO_4$ 406.2013	406.2076
17b	*i*-Pr	4-F	H	H	H	207–209	1570	424	$C_{25}H_{27}NO_4F$ 424.1919	424.1929
17c	*c*-Pr	4-F	H	H	H	197–199	1569	422	$C_{25}H_{25}NO_4F$ 422.1762	422.1852
17d	*i*-Pr	4-F	3-Me	H	H	195–200	1570	438	$C_{26}H_{29}NO_4F$ 438.2075	438.2055
17e	*i*-Pr	4-Cl	H	H	H	193–202	1572	440	$C_{25}H_{27}NO_4Cl$ 440.1623	440.1659
17f	*i*-Pr	4-Me	H	H	H	187–200	1572	420	$C_{26}H_{30}NO_4$ 420.2169	420.2215
17g	*i*-Pr	4-CF3	H	H	H	200–212	1570	474	$C_{26}H_{27}NO_4F_3$ 474.1887	474.1982
17h	*i*-Pr	4-OMe	H	H	H	178–193	1570	436	$C_{26}H_{30}NO_5$ 436.2119	436.2195
17i	*i*-Pr	4-OPh	H	H	H	180–189	1589	498	$C_{31}H_{32}NO_5$ 498.2275	498.2338
17j	*i*-Pr	2-F	H	H	H	193–201	1570	424	$C_{25}H_{27}NO_4F$ 424.1919	424.1935
17k	*i*-Pr	2-Cl	H	6-Cl	H	203–209	1570	474	$C_{25}H_{26}NO_4Cl_2$ 474.1233	474.1283
17l	*i*-Pr	3-Me	5-Me	H	H	192–197	1566	434	$C_{27}H_{32}NO_4$ 434.2326	434.2390
17m	*i*-Pr	H	H	6-Cl	H	195–198	1565	440	$C_{25}H_{27}NO_4Cl$ 440.1623	440.1699
17n	*i*-Pr	4-F	H	6-Cl	H	193–198	1570	458	$C_{25}H_{26}NO_4FCl$ 458.1529	458.1522
17o	*i*-Pr	4-F	H	6-Cl	8-Cl	183–187	1570	492	$C_{25}H_{25}NO_4FCl_2$ 492.1139	492.1232
17p	*c*-Pr	H	H	6-Cl	H	204–210	1570	438	$C_{25}H_{25}NO_4Cl$ 438.1467	438.1517
17q	*i*-Pr	4-F	H	6-Me	H	204–208	1570	438	$C_{26}H_{29}NO_4F$ 438.2075	438.2166
17r	*i*-Pr	H	H	7-Me	H	170–175	1564	420	$C_{26}H_{30}NO_4$ 420.2169	420.2194
17s	*i*-Pr	4-F	H	6-OMe	7-OMe	239–245	1572	484	$C_{27}H_{31}NO_6F$ 484.2130	484.2133
17t	*c*-Pr	4-F	H	6-OMe	7-OMe	234–238	1571	482	$C_{27}H_{29}NO_6F$ 482.1973	482.2014

[a]All compounds melted with decomposition.
[b]Film (3M IR Cards).
[c]Internal standard: PEG400.

ratio of the sample was determined by HPLC (98.2:1.8, *vide supra*) and by ^{1}H NMR (98 : 2, *vide supra*).

All other 5-hydroxy-3-keto esters **15aa–qq** were analogously converted to the corresponding 3,5-dihydroxy-esters **16aa–qq**.

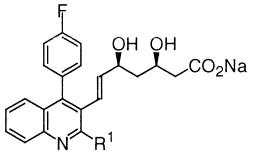
Sodium (*E*)-3,5-dihydroxy-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-hept-6-enoate (step VII in Scheme 2). 0.5 N aqueous sodium hydroxide solution (0.96 mL, 0.48 mmol) was added dropwise to a solution of compound **16jj** (0.22 g, 0.49 mmol) in ethanol (10 mL). This was stirred for 1 h at room temperature. The mixture was concentrated under reduced pressure, 5 mL of distilled water was added, washed with diethyl ether, and the layers were separated. The aqueous layer was filtered, and was freeze-dried to obtain 200 mg (92.0%) of **17jj** as a hygroscopic white powder: mp 97–125 °C; IR (film) 1602, 1569, 1513, 1489, 1411, 1221, 1158, 1065, 835, 761 cm^{-1}; MS [FAB, $(M+H)^+$] *m/z* 444; FAB-HR-MS [$(M+H)^+$] calcd for $C_{25}H_{24}FNNaO_4$ *m/z* 444.1587, found 444.1554; ^{1}H MNR (300 MHz, DMSO-d_6) δ 1.0–1.5 (m, 6H), 1.7–2.1 (m, 2H), 2.5 (m, 1H), 3.5 (m, 1H), 4.1 (m, 1H), 5.61 (dd, 1H, $J=6$, 16 Hz), 6.49 (d, 1H, $J=16$ Hz), 7.2–7.4 (m, 6H), 7.6 (m, 1H), 7.86 (d, 1H, $J=9$ Hz) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.4, 161.6 (d, $^1J_{C\text{-}F}=244.6$ Hz), 160.6, 145.9, 143.6, 142.4, 133.1 (d, $^4J_{C\text{-}F}=2.9$ Hz), 132.1 (d, $^3J_{C\text{-}F}=8.1$ Hz), 131.8 (d, $^3J_{C\text{-}F}=8.1$ Hz), 129.7, 128.8, 128.4, 125.7, 125.6 (2C), 122.9, 115.2 (2C, d, $^2J_{C\text{-}F}=21.3$ Hz), 68.8, 65.7, 44.8, 43.5, 15.3, 10.7 (2C) ppm.

All other 3,5-dihydroxyesters **16** were converted to the corresponding sodium salts **17**. The spectra data of **17a–t** and **17aa–qq** were shown in Tables 3–6.

Biological evaluations

Inhibition of hepatic cholesterol 'de novo' synthesis in vitro. Compounds **17a–17t** were evaluated for their ability to inhibit hepatic cholesterol 'De Novo' synthesis in vitro. Enzyme solution was prepared from liver of male Wistar

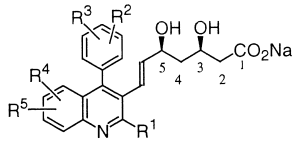
Table 4. Characterization of the target compounds **17aa–qq**



No.	R^1	MP (°C)[a]	IR ν C=O (cm^{-1})[b]	MS (FAB) (*m/z*)	FAB-HR-MS	
					Calculated for	Measured
17aa	H	139–147	1570	404 $[M+H]^+$	$C_{22}H_{20}FNNaO_4$ 404.1274	404.1459
17bb	Me	124–130	1570	418 $[M+H]^+$	$C_{23}H_{22}FNNaO_4$ 418.1430	418.1303
17cc	Et	134–137	1570	432 $[M+H]^+$	$C_{24}H_{24}FNNaO_4$ 432.1587	432.1559
17dd	n-Pr	139–142	1570	446 $[M+H]^+$	$C_{25}H_{26}FNNaO_4$ 446.1744	446.1805
17ee	*i*-Pr	121–138	1570	446 $[M+H]^+$	$C_{25}H_{26}FNNaO_4$ 446.1743	446.1780
17ff	*n*-Bu	120–131	1570	460 $[M+H]^+$	$C_{26}H_{28}FNNaO_4$ 460.1900	460.1891
17gg	CH_2CHMe_2	91–126	1570	460 $[M+H]^+$	$C_{26}H_{28}FNNaO_4$ 460.1900	460.2015
17hh	CHMeEt	88–124	1570	460 $[M+H]^+$	$C_{26}H_{28}FNNaO_4$ 460.1900	460.2062
17ii	*t*-Bu	101–132	1570	460 $[M+H]^+$	$C_{26}H_{28}FNNaO4$ 460.1900	460.1970
17jj	*c*-Pr	97–125	1569	444 $[M+H]^+$	$C_{25}H_{24}FNNaO_4$ 444.1587	444.1554
17kk	*c*-Hex	104–144	1570	486 $[M+H]^+$	$C_{28}H_{30}FNNaO_4$ 486.2056	486.2169
17ll	Ph	112–147	1570	480 $[M+H]^+$	$C_{28}H_{24}FNNaO_4$ 480.1588	480.1541
17mm	CF_3	104–116	1570	472 $[M+H]^+$	$C_{23}H_{19}F_4NnaO_4$ 472.1147	472.1194
17nn	OMe	106–128	1571	434 $[M+H]^+$	$C_{23}H_{22}FNNaO_5$ 434.1380	434.1305
17oo	SMe	116–138	1568	450 $[M+H]^+$	$C_{23}H_{22}FNNaO_4S$ 450.1152	450.1177
17pp	NMe_2	110–133	1570	447 $[M+H]^+$	$C_{24}H_{25}FN_2NaO_4$ 447.1696	447.1620
17qq	NMeEt	87–119	1570	461 $[M+H]^+$	$C_{25}H_{27}FN_2NaO_4$ 461.1853	461.1797

[a]All compounds melted with decomposition.
[b]Film (3M IR Cards).

Table 5. ^{1}H and ^{13}C NMR spectra of **17a–t**



No.	^{1}H NMR (δ; ppm) 300 MHz in DMSO-d_6	^{13}C NMR (δ; ppm)[a] 75 MHz in DMSO-d_6					
		C-1	C-1	C-1	C-1	C-1	R^1/R^2-R^5
17a	0.8–1.3 (m, 2H), 1.32 (d, 6H, J = 7 Hz), 1.7–2.0 (m, 2H), 3.4–3.6 (m, 2H), 4.1 (m, 1H), 5.39 (dd, 1H, J = 6, 16 Hz), 6.47 (d, 1H, J = 16 Hz), 7.2–7.5 (m, 7H), 7.6 (m, 1H), 7.98 (d, 1H, J = 8 Hz)	176.1	43.5	65.6	44.9	68.6	*i*-Pr: 22.0 (2C), 32.2
17b	0.9–1.3 (m, 2H), 1.31 (d, 6H, J = 7 Hz), 1.6–2.0 (m, 2H), 3.4–3.6 (m, 2H), 4.1 (m, 1H), 5.39 (dd, 1H, J = 6, 16 Hz), 6.47 (d, 1H, J = 16 Hz), 7.2–7.5 (m, 6H), 7.7 (m, 1H), 7.99 (d, 1H, J = 8 Hz)	176.5	43.4	65.7	44.8	68.6	*i*-Pr: 22.0 (2C), 32.3
17c	0.9–1.4 (m, 6H), 1.7–2.1 (m, 2H), 2.5 (m, 1H), 3.5 (m, 1H), 4.1 (m, 1H), 5.60 (dd, 1H, J = 6, 16 Hz), 6.48 (d, 1H, J = 16 Hz), 7.2–7.4 (m, 6H), 7.6 (m, 1H), 7.87 (d, 1H, J = 9 Hz)	176.5	43.4	65.7	44.8	68.8	c-Pr: 10.7 (2C), 15.3
17d	0.9–1.3 (m, 2H), 1.31 (d, 6H, J = 7 Hz), 1.7–2.1 (m, 2H), 2.28 (s, 3H), 3.4–3.6 (m, 2H), 4.1 (m, 1H), 5.42 (dd, 1H, J = 6 and 16 Hz), 6.46 (d, 1H, J = 16 Hz), 7.0–7.5 (m, 5H), 7.7 (m, 1H), 7.98 (d, 1H, J = 8 Hz)	176.4	43.4	64.4	44.8	68.6	*i*-Pr: 22.0 (2C), 32.3 Me: 14.2
17e	0.9–1.3 (m, 2H), 1.29 (d, 6H, J = 7 Hz), 1.7–2.1 (m, 2H), 3.4–3.6 (m, 2H), 4.1 (m, 1H), 5.40 (dd, 1H, J = 6, 16 Hz), 6.48 (d, 1H, J = 16 Hz), 7.2–7.6 (m, 6H), 7.7 (m, 1H), 7.99 (d, 1H, J = 8 Hz)	176.3	43.4	65.7	44.7	68.6	*i*-Pr: 22.0 (2C), 32.3
17f	0.8–1.3 (m, 2H), 1.31 (d, 6H, J = 7 Hz), 1.7–2.0 (m, 2H), 2.41 (s, 3H), 3.4–3.6 (m, 2H), 4.1 (m, 1H), 5.40 (dd, 1H, J = 6, 16 Hz), 6.46 (d, 1H, J = 16 Hz), 7.0–7.4 (m, 6H), 7.7 (m, 1H), 7.97 (d, 1H, J = 8 Hz)	176.4	43.5	65.7	44.9	68.7	*i*-Pr: 22.0 (2C), 32.2 Me: 20.9
17g	0.7–1.3 (m, 2H), 1.33 (d, 6H, J = 7 Hz), 1.6–2.0 (m, 2H), 3.4–3.6 (m, 2H), 4.1 (m, 1H), 5.2–5.4 (m, 1H), 6.50 (d, 1H, J = 16 Hz), 7.2–7.9 (m, 7H), 8.01 (d, 1H, J = 8 Hz)	176.2	43.3	66.0	44.5	68.8	*i*-Pr: 21.9 (2C), 32.3
17h	0.9–1.3 (m, 2H), 1.31 (d, 6H, J = 7 Hz), 1.7–2.0 (m, 2H), 3.4–3.6 (m, 2H), 3.85 (s, 3H), 4.1 (m, 1H), 5.40 (dd, 1H, J = 6, 16 Hz), 6.46 (d, 1H, J = 16 Hz), 7.0–7.5 (m, 6H), 7.7 (m, 1H), 7.96 (d, 1H, J = 8 Hz)	176.0	43.4	65.7	44.9	68.7	*i*-Pr: 22.0 (2C), 32.2 OMe: 55.1
17i	1.0–1.4 (m, 2H), 1.31 (d, 6H, J = 7 Hz), 1.7–2.1 (m, 2H), 3.4–3.6 (m, 2H), 3.85 (s, 3H), 4.1 (m, 1H), 5.41 (dd, 1H, J = 6, 16 Hz), 6.51 (d, 1H, J = 16 Hz), 7.1–7.5 (m, 11H), 7.7 (m, 1H), 7.98 (d, 1H, J = 8 Hz)	176.4	43.4	65.9	44.7	68.7	*i*-Pr: 22.0 (2C), 32.3
17j	0.8–1.3 (m, 2H), 1.33 (d, 6H, J = 7 Hz), 1.7–2.0 (m, 2H), 3.4–3.6 (m, 2H), 4.1 (m, 1H), 5.42 (dd, 1H, J = 6, 16 Hz), 6.55 (d, 1H, J = 16 Hz), 7.2–7.6 (m, 6H), 7.7 (m, 1H), 8.01 (d, 1H, J = 8 Hz)	176.4	43.7	64.4	44.9	67.2	*i*-Pr: 21.9 (2C), 32.4
17k	0.8–1.3 (m, 2H), 1.32 (d, 6H, J = 7 Hz), 1.7–2.0 (m, 2H), 3.4–3.6 (m, 2H), 4.1 (m, 1H), 5.4–5.5 (m, 1H), 6.52 (d, 1H, J = 16 Hz), 7.0–7.7 (m, 6H), 8.04 (d, 1H, J = 8 Hz)	176.3	43.5	65.5	44.9	68.3	*i*-Pr: 21.8 (2C), 32.4
17l	0.8–1.3 (m, 2H), 1.32 (d, 6H, J = 7 Hz), 1.7–2.0 (m, 2H), 2.32 (s, 6H), 3.4–3.6 (m, 2H), 4.1 (m, 1H), 5.44 (dd, 1H, J = 6, 16 Hz), 6.26 (d, 1H, J = 16 Hz), 6.8–7.4 (m, 5H), 7.6 (m, 1H), 7.96 (d, 1H, J = 8 Hz)	176.4	43.4	65.6	45.1	68.6	*i*-Pr: 22.0 (2C), 32.2 Me: 20.9 (2C)
17m	0.8–1.3 (m, 2H), 1.32 (d, 6H, J = 7 Hz), 1.7–2.0 (m, 2H), 2.32 (s, 6H), 3.4–3.6 (m, 2H), 4.1 (m, 1H), 5.41 (dd, 1H, J = 6, 16 Hz), 6.48 (d, 1H, J = 16 Hz), 7.2–7.5 (m, 6H), 7.7 (m, 1H), 8.01 (d, 1H, J = 8 Hz)	176.4	43.4	65.5	44.8	68.4	*i*-Pr: 21.9 (2C), 32.3
17n	0.9–1.3 (m, 2H), 1.31 (d, 6H, J = 7 Hz), 1.7–2.0 (m, 2H), 3.4–3.6 (m, 2H), 4.1 (m, 1H), 5.41 (dd, 1H, J = 6, 16 Hz), 6.46 (d, 1H, J = 16 Hz), 7.2–7.4 (m, 5H), 7.7 (m, 1H), 8.02 (d, 1H, J = 8 Hz)	176.0	43.4	65.7	44.8	68.5	*i*-Pr: 21.9 (2C), 32.3

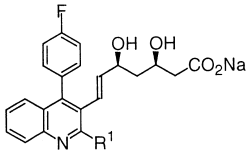
(*continued on next page*)

Table 5 (*continued*)

No.	^{1}H NMR (δ; ppm) 300 MHz in DMSO-d_6	^{13}C NMR (δ; ppm)[a] 75 MHz in DMSO-d_6					
		C-1	C-1	C-1	C-1	C-1	R^1/R^2-R^5
17o	0.9–1.3 (m, 2H), 1.34 (d, 6H, J = 7 Hz), 1.7–2.1 (m, 2H), 3.4–3.6 (m, 2H), 4.1 (m, 1H), 5.45 (dd, 1H, J = 6, 16 Hz), 6.47 (d, 1H, J = 16 Hz), 7.1–7.4 (m, 5H), 8.00 (s, 1H)	176.3	43.4	65.6	44.7	68.4	*i*-Pr: 21.9 (2C), 32.7
17p	0.9–1.4 (m, 6H), 1.7–2.0 (m, 2H), 2.5–2.6 (m, 1H), 3.5–3.6 (m, 1H), 4.1 (m, 1H), 5.5–5.7 (m, 1H), 6.50 (d, 1H, J = 16 Hz), 7.1–7.7 (m, 7H), 7.88 (d, 1H, J = 8 Hz)	176.5	43.6	65.5	44.8	68.6	*c*-Pr: 11.0 (2C), 15.4
17q	0.9–1.4 (m, 6H), 1.30 (d, 6H, J = 7 Hz), 1.7–2.0 (m, 2H), 2.34 (s, 3H), 3.4–3.6 (m, 2H), 4.1 (m, 1H), 5.36 (dd, 1H, J = 6, 16 Hz), 6.44 (d, 1H, J = 16 Hz), 7.0–7.5 (m, 6H), 7.88 (d, 1H, J = 8 Hz)	175.8	43.4	65.7	44.9	68.7	*i*-Pr: 22.0 (2C), 32.1 Me: 21.3
17r	0.9–1.4 (m, 2H), 1.30 (d, 6H, J = 7 Hz), 1.7–2.1 (m, 2H), 2.48 (s, 3H), 3.4–3.6 (m, 2H), 4.1 (m, 1H), 5.36 (dd, 1H, J = 6, 16 Hz), 6.46 (d, 1H, J = 16 Hz), 7.1–7.5 (m, 7H), 7.78 (s, 1H)	175.3	43.2	65.3	44.7	68.6	*i*-Pr: 22.1 (2C), 32.2 Me: 21.1
17s	0.9–1.4 (m, 2H), 1.27 (d, 6H, J = 7 Hz), 1.7–2.0 (m, 2H), 2.48 (s, 3H), 3.4–3.6 (m, 2H), 3.58 (s, 3H), 3.92 (s, 3H), 4.1 (m, 1H), 5.29 (dd, 1H, J = 6, 16 Hz), 6.39 (d, 1H, J = 16 Hz), 7.1–7.4 (m, 6H)	176.1	43.5	65.8	44.8	68.8	*i*-Pr: 22.2 (2C), 31.9 OMe: 55.2, 55.7
17t	0.9–1.3 (m, 6H), 1.7–2.0 (m, 2H), 2.4–2.5 (m, 1H), 3.4–3.6 (m, 1H), 3.58 (s, 3H), 3.91 (s, 3H), 4.1 (m, 1H), 5.5–5.6 (m, 1H), 6.42 (d, 1H, J = 16 Hz), 7.1–7.4 (m, 6H)	176.4	43.6	65.8	44.7	69.0	*c*-Pr: 10.2 (2C), 15.1 OMe: 55.1, 55.6

[a]Only characteristic signals are shown, because of the complexity caused by contamination of the *anti*-isomer.

Table 6. ^{1}H and ^{13}C NMR spectra of **17aa**–**qq**



No.	^{1}H NMR (δ; ppm) 300 MHz in DMSO-d_6	^{13}C NMR (δ; ppm) 75 MHz in DMSO-d_6
17aa	1.4–1.7 (m, 2H), 1.8–2.2 (m, 2H), 3.8 (m, 1H), 4.2 (m, 1H), 6.33 (d, 1H, J = 16 Hz), 6.54 (dd, 1H, J = 6, 16 Hz), 7.3–7.6 (m, 6H), 7.7 (m, 1H), 8.06 (d, 1H, J = 8 Hz), 9.24 (s, 1H)	176.5, 161.9 (d, $^1J_{C\text{-}F}$ = 245.2 Hz), 148.7, 146.5, 142.5, 137.9, 131.9 (2C, d, $^3J_{C\text{-}F}$ = 8.1 Hz), 131.6 (d, $^4J_{C\text{-}F}$ = 2.9 Hz), 129.2, 128.8, 127.6, 127.1, 126.8, 125.8, 122.9, 115.7 (2C, d, $^2J_{C\text{-}F}$ = 21.9 Hz), 69.0, 66.0, 44.8, 43.7
17bb	1.0–1.1 (m, 1H), 1.3–1.4 (m, 1H), 1.7–1.9 (m, 1H), 1.9–2.1 (m, 1H), 2.70 (s, 3H), 3.5 (m, 1H), 4.1 (m, 1H), 5.48 (dd, 1H, J = 6, 16 Hz), 6.38 (d, 1H, J = 16 Hz), 7.2–7.5 (m, 6H), 7.7 (m, 1H), 7.96 (d, 1H, J = 8 Hz)	176.4, 161.6 (d, $^1J_{C\text{-}F}$ = 244.6 Hz),157.4, 145.8, 143.8, 142.1, 133.0 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 132.2 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 131.8 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 129.7, 128.7, 128.3, 126.1, 126.0, 125.7, 123.2, 115.3 (2C, d, $^2J_{C\text{-}F}$ = 19.6 Hz), 68.8, 65.6, 44.8, 43.5, 24.9
17cc	0.9–1.4 (m, 2H), 1.32 (t, 3H, J = 7 Hz), 1.7–2.1 (m, 2H), 3.01 (q, 2H, J = 7 Hz), 3.5 (m, 1H), 4.1 (m, 1H), 5.42 (dd, 1H, J = 6, 16 Hz), 6.43 (d, 1H, J = 16 Hz), 7.2–7.5 (m, 6H), 7.7 (m, 1H), 7.99 (d, 1H, J = 8 Hz)	176.4, 161.6 (d, $^1J_{C\text{-}F}$ = 244.1 Hz), 161.6, 145.9, 144.1, 142.3, 133.2 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 132.2 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 132.0 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 129.6, 128.7, 128.6, 126.0 (2C), 125.7, 122.7, 115.2 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 115.1 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 68.7, 65.7, 44.8, 43.4, 29.6, 12.7
17dd	0.9–1.4 (m, 2H), 1.00 (t, 3H, J = 7 Hz), 1.7–2.1 (m, 2H), 1.8 (m, 2H), 2.97 (t, 2H, J = 8 Hz), 3.5 (m, 1H), 4.1 (m, 1H), 5.41 (dd, 1H, J = 6, 16 Hz), 6.43 (d, 1H, J = 16 Hz), 7.2–7.5 (m, 6H), 7.7 (m, 1H), 7.98 (d, 1H, J = 8 Hz)	161.6 (d, $^1J_{C\text{-}F}$ = 244.6 Hz),160.6, 145.9, 144.1, 142.2, 133.2 (d, $^4J_{C\text{-}F}$ = 2.9 Hz), 132.2 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 132.0 (d, $^3J_{C\text{-}F}$ = 8.7 Hz), 129.7, 128.7, 128.6, 126.0 (2C), 125.7, 122.8, 115.2 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 115.1 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 68.7, 65.6, 44.9, 43.4, 38.4, 21.5, 14.1
17ee	0.9–1.4 (m, 2H), 1.32 (d, 6H, J = 7 Hz), 1.7–2.1 (m, 2H), 3.4–3.6 (m, 2H), 4.1 (m, 1H), 5.40 (dd, 1H, J = 6, 16 Hz), 6.48 (d, 1H, J = 16 Hz), 7.2–7.5 (m, 6H), 7.7 (m, 1H), 7.99 (d, 1H, J = 8 Hz)	176.4, 165.0, 161.5 (d, $^1J_{C\text{-}F}$ = 244.0 Hz), 146.0, 144.3, 142.3, 133.4 (d, $^4J_{C\text{-}F}$ = 2.9 Hz), 132.2 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 132.0 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 129.5, 128.7, 128.6, 126.0 (2C), 125.7, 122.6, 115.0 (2C, d, $^2J_{C\text{-}F}$ = 21.3 Hz), 68.6, 65.7, 44.8, 43.4, 32.3, 22.0 (2C)
17ff	0.9–1.5 (m, 2H), 0.95 (t, 3H, J = 7 Hz), 1.4 (m, 2H), 1.7–2.1 (m, 2H), 1.8 (m, 2H), 2.99 (t, 2H, J = 8 Hz), 3.5 (m, 1H), 4.1 (m, 1H), 5.42 (dd, 1H, J = 6, 16 Hz), 6.43 (d, 1H, J = 16 Hz), 7.2–7.5 (m, 6H), 7.7 (m, 1H), 7.98 (d, 1H, J = 8 Hz)	176.5, 161.6 (d, $^1J_{C\text{-}F}$ = 244.0 Hz), 160.8, 145.9, 144.1, 142.2, 133.2 (d, $^4J_{C\text{-}F}$ = 3.5 Hz),132.2 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 132.0 (d, $^3J_{C\text{-}F}$ = 8.1 Hz),129.7, 128.7, 128.6, 126.0 (2C), 125.7, 122.7, 115.2 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 115.1 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 68.7, 65.7, 44.9, 43.4, 36.1, 30.4, 22.2, 13.9

(*continued on next page*)

Table 6 (*continued*)

No.	^{1}H NMR (δ; ppm) 300 MHz in DMSO-d_6	^{13}C NMR (δ; ppm) 75 MHz in DMSO-d_6
17gg	0.9–1.5 (m, 2H), 0.96 (d, 6H, J = 7 Hz), 1.7–2.1 (m, 2H), 2.3 (m, 1H), 2.89 (d, 2H, J = 7 Hz), 3.5 (m, 1H), 4.1 (m, 1H), 5.39 (dd, 1H, J = 6, 16 Hz), 6.42 (d, 1H, J = 16 Hz), 7.2–7.5 (m, 6H), 7.7 (m, 1H), 7.99 (d, 1H, J = 8 Hz)	176.4, 161.5 (d, $^1J_{C\text{-}F}$ = 244.0 Hz), 160.1, 145.8, 144.1, 142.3, 133.3 (d, $^4J_{C\text{-}F}$ = 2.9 Hz), 132.2 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 132.0 (d, $^3J_{C\text{-}F}$ = 8.7 Hz), 130.1, 128.7, 128.6, 126.0, 125.9, 125.7, 122.9, 115.2 (2C, d, $^2J_{C\text{-}F}$ = 24.2 Hz), 68.6, 65.6, 45.0, 43.4, 27.6, 22.6 (2C)
17hh	0.85 (t, 3H, J = 7 Hz), 0.9–1.4 (m, 2H), 1.28 (d, 3H, J = 6 Hz), 1.5–2.1 (m, 4H), 3.4 (m, 1H), 4.1 (m, 1H), 5.38 (dd, 1H, J = 6, 16 Hz), 6.46 (d, 1H, J = 16 Hz), 7.2–7.5 (m, 6H), 7.7 (m, 1H), 7.98 (d, 1H, J = 8 Hz)	176.5, 164.5, 161.5 (d, $^1J_{C\text{-}F}$ = 244.0 Hz), 146.1, 144.3, 142.3, 133.4 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 132.2 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 132.0 (d, $^3J_{C\text{-}F}$ = 9.2 Hz), 130.1, 128.7, 128.6, 125.9, 125.8, 125.7, 122.8, 115.1 (2C, d, $^2J_{C\text{-}F}$ = 21.3 Hz), 68.6, 65.7, 44.8, 43.4, 29.0, 19.9, 12.1
17ii	0.8–0.9 (m, 1H), 1.50 (s, 9H), 1.2–1.3 (m, 1H), 1.7–2.1 (m, 2H), 3.5 (m, 1H), 4.1 (m, 1H), 5.23 (dd, 1H, J = 5, 16 Hz), 6.67 (d, 1H, J = 16 Hz), 7.2–7.3 (m, 5H), 7.4–7.5 (m, 1H), 7.7 (m, 1H), 7.97 (d, 1H, J = 8 Hz)	176.4, 165.6, 161.4 (d, $^1J_{C\text{-}F}$ = 244.0 Hz), 146.1, 144.7, 141.2, 134.1 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 132.2 (d, $^3J_{C\text{-}F}$ = 8.7 Hz), 132.0 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 130.6, 129.1, 128.7, 126.2, 125.9, 125.6, 125.0, 115.0 (2C, d, $^2J_{C\text{-}F}$ = 20.8 Hz), 68.5, 66.0, 44.5, 43.3, 30.1 (3C)
17jj	1.0–1.5 (m, 6H), 1.7–2.1 (m, 2H), 2.5 (m, 1H), 3.5 (m, 1H), 4.1 (m, 1H), 5.61 (dd, 1H, J = 6, 16 Hz), 6.49 (d, 1H, J = 16 Hz), 7.2–7.4 (m, 6H), 7.6 (m, 1H), 7.86 (d, 1H, J = 9 Hz)	176.4, 161.6 (d, $^1J_{C\text{-}F}$ = 244.6 Hz), 160.6, 145.9, 143.6, 142.4, 133.1 (d, $^4J_{C\text{-}F}$ = 2.9 Hz), 132.1 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 131.8 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 129.7, 128.8, 128.4, 125.7, 125.6 (2C), 122.9, 115.2 (2C, d, $^2J_{C\text{-}F}$ = 21.3 Hz), 68.8, 65.7, 44.8, 43.5, 15.3, 10.7 (2C)
17kk	0.9–2.1 (m, 14H), 3.2 (m, 1H), 3.5 (m, 1H), 4.1 (m, 1H), 5.41 (dd, 1H, J = 6, 16 Hz), 6.44 (d, 1H, J = 16 Hz), 7.2–7.5 (m, 6H), 7.7 (m, 1H), 7.97 (d, 1H, J = 8 Hz)	176.4, 164.3, 161.5 (d, $^1J_{C\text{-}F}$ = 244.0 Hz), 146.0, 144.3, 142.2, 133.4 (d, $^4J_{C\text{-}F}$ = 2.9 Hz), 132.2 (d, $^3J_{C\text{-}F}$ = 8.7 Hz), 132.0 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 129.5, 128.7, 128.6, 125.9, 125.8, 125.7, 122.6, 115.1 (2C, d, $^2J_{C\text{-}F}$ = 21.9 Hz), 68.6, 65.7, 45.0, 43.4, 42.5, 31.9 (2C), 26.1 (2C), 25.8
17ll	0.7–0.9 (m, 1H), 1.1–1.3 (m, 1H), 1.6–2.0 (m, 2H), 3.5 (m, 1H), 3.9 (m, 1H), 5.19 (dd, 1H, J = 6, 16 Hz), 6.24 (d, 1H, J = 16 Hz), 7.3–7.8 (m, 12H), 8.06 (d, 1H, J = 8 Hz)	176.4, 161.7 (d, $^1J_{C\text{-}F}$ = 244.6 Hz), 158.5, 145.9, 145.1, 142.3, 140.9, 133.0 (d, $^4J_{C\text{-}F}$ = 2.9 Hz), 132.1 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 131.9 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 129.8 (2C), 129.3, 129.1, 128.5, 128.0, 127.8 (2C), 126.9, 126.4, 125.8, 123.4, 115.5 (d, $^2J_{C\text{-}F}$ = 20.8 Hz), 115.4 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 68.7, 65.5, 44.6, 43.4
17mm	0.9–1.0 (m, 1H), 1.2–1.4 (m, 1H), 1.7–2.1 (m, 2H), 3.5 (m, 1H), 4.1 (m, 1H), 5.50 (dd, 1H, J = 6, 16 Hz), 6.51 (d, 1H, J = 16 Hz), 7.3–7.5 (m, 5H), 7.7 (m, 1H), 7.9 (m, 1H), 8.21 (d, 1H, J = 8 Hz)	176.4, 161.9 (d, $^1J_{C\text{-}F}$ = 244.6 Hz), 148.3, 144.8, 144.4, 144.1, 132.2 (2C, d, $^3J_{C\text{-}F}$ = 9.8 Hz), 132.0 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 130.5, 129.7, 129.4, 128.2 (2C), 126.1, 121.9 (q, $J_{C\text{-}F}$ = 276.9 Hz), 119.4, 115.4 (2C, d, $^2J_{C\text{-}F}$ = 21.4 Hz), 68.3, 65.7, 44.7, 43.4
17nn	1.1–1.2 (m, 1H), 1.3–1.6 (m, 1H), 1.8–2.1 (m, 2H), 3.6 (m, 1H), 4.08 (s, 3H), 4.1 (m, 1H), 6.08 (dd, 1H, J = 6, 16 Hz), 6.30 (d, 1H, J = 16 Hz), 7.18 (d, 1H, J = 7 Hz), 7.2–7.5 (m, 5H), 7.81 (d, 1H, J = 8 Hz)	176.6, 161.8 (d, $^1J_{C\text{-}F}$ = 244.6 Hz), 159.6, 146.4, 144.1, 141.5, 132.7 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 132.0 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 131.6 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 129.2, 126.7, 125.9, 124.9, 124.4, 120.4, 120.0, 115.6 (2C, d, $^2J_{C\text{-}F}$ = 21.3 Hz), 69.3, 65.8, 53.5, 44.9, 43.6
17oo	1.0–1.1 (m, 1H), 1.3–1.4 (m, 1H), 1.7–2.1 (m, 2H), 2.63 (s, 3H),3.6 (m, 1H), 4.1 (m, 1H), 5.62 (dd, 1H, J = 6, 16 Hz), 6.29 (d, 1H, J = 16 Hz), 7.2–7.5 (m, 6H), 7.7 (m, 1H), 7.93 (d, 1H, J = 8 Hz)	176.5, 161.7 (d, $^1J_{C\text{-}F}$ = 244.6 Hz), 159.2, 146.0, 143.5, 143.2, 132.5 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 132.1 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 131.9 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 129.2, 128.8, 127.6, 126.0, 125.5, 125.1, 120.6, 115.3 (2C, d, $^2J_{C\text{-}F}$ = 21.3 Hz), 68.5, 65.7, 44.8, 43.4, 13.2
17pp	1.0–1.1 (m, 1H), 1.3–1.4 (m, 1H), 1.7–2.1 (m, 2H), 2.96 (s, 6H), 3.5–3.6 (m, 1H), 4.1 (m, 1H), 5.58 (dd, 1H, J = 6, 16 Hz), 6.28 (d, 1H, J = 16 Hz), 7.06 (d, 1H, J = 8 Hz), 7.1–7.4 (m, 5H), 7.5 (m, 1H), 7.72 (d, 1H, J = 8 Hz)	176.5, 161.5 (d, $^1J_{C\text{-}F}$ = 244.0 Hz), 159.7, 145.7, 145.1, 139.2, 133.4 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 132.0 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 131.5 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 128.8, 126.8, 125.7, 124.3, 123.5, 123.4, 122.3, 115.3 (2C, d, $^2J_{C\text{-}F}$ = 20.2 Hz), 69.1, 65.8, 44.8, 43.5, 41.8 (2C)
17qq	1.0–1.1 (m, 1H), 1.15 (t, 3H, J = 7 Hz), 1.3–1.4 (m, 1H), 1.7–2.1 (m, 2H), 2.94 (s, 3H), 3.3 (m, 2H), 3.5 (m, 1H), 4.1 (m, 1H), 5.49 (dd, 1H, J = 6, 16 Hz), 6.28 (d, 1H, J = 16 Hz), 7.06 (d, 1H, J = 9 Hz), 7.1–7.4 (m, 5H), 7.5 (m, 1H), 7.72 (d, 1H, J = 8 Hz)	176.4, 161.5 (d, $^1J_{C\text{-}F}$ = 244.0 Hz), 159.5, 145.6, 145.1, 139.3, 133.6 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 132.0 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 131.5 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 128.7, 126.8, 125.7, 124.3, 123.4 (2C), 122.8, 115.2 (2C, d, $^2J_{C\text{-}F}$ = 20.8 Hz), 69.1, 65.8, 47.7, 44.8, 43.5, 38.1, 12.5

rat billialy cannulated and discharged bile for over 24 h. Liver was cut at mid-dark, then the microsomal and supernatant fractions which could be precipitated with 40–80% saturated ammonium sulfate (sup fraction), were prepared from liver homogenate according to the modified method of Knauss et al.[24] For the cholesterol biosynthesis assay, microsome (1.0 mg protein) and sup fractions (1.0 mg protein) were incubated for 2 h at 37 °C in 200 μL of a reaction mixture containing ATP; 1 mM, glutathione; 6 mM, glucose-1-phosphate; 10 mM, and; 0.25 mM, NADP; 0.25 mM, CoA; 0.04 mM and 0.2 mM sodium [2-^{14}C] acetate (56 mCi/mmol, 0.2 μCi) with 4 μL of test compound solution dissolved in water or dimethyl sulfoxide. To stop the reaction and saponify the product, 1 mL of 15% EtOH–KOH was added to the mixture and heated at 75 °C for 1 h. Lipids that were unable to be saponified were extracted with petroleum ether and incorporated [^{14}C] radioactivity was counted. Inhibitory activity of compounds was followed with IC_{50} to show the rate of decreased incorporation of [^{14}C] acetate into lipids that cannot be saponified. Relative potencies were obtained by comparison of IC_{50} values

of compounds **17a**–**17t** with that of the internal standard pravastatin. Pravastatin averaged $IC_{50} = 4.2$ nM and was assigned a value of 100.[25]

Inhibition of solubilized rat liver HMG-CoA reductase in vitro. The inhibitory activity of compounds **17aa**–**17qq** on rat liver HMG-CoA reductase was estimated with soluble-enzyme preparations obtained from the microsomal fraction.[26] The test was performed according to the method described by Heller.[27a,b] HMG-CoA reductase was isolated from rat liver and incubated with [^{14}C]-HMG-CoA and test compounds for 15 min at 37 °C. The reaction was terminated by addition of HCl, and [^{14}C]-mevalonic acid was separated from the intact substrate by column filtration. A reference compound, lovastatin, was tested concurrently at five concentrations to ensure the validity of the results obtained.

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