Bioorganic & Medicinal Chemistry 17 (2009) 7915–7923

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and HMG-CoA reductase inhibition of 2-cyclopropyl-4-thiophenyl-quinoline mevalonolactones

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ARTICLE INFO

Article history:
Received 5 September 2009
Revised 12 October 2009
Accepted 13 October 2009
Available online 30 October 2009

Keywords:
HMG-CoA reductase
Quinoline
Mevalonolactone
Synthesis

ABSTRACT

A novel series of 2-cyclopropyl-4-thiophenyl quinoline-based mevalonolactones were synthesized from the substituted anilines by several reactions. Among them, (4*R*,6*S*)-6-[(*E*)-2-(2-cyclopropyl-6-fluoro-4-(4-fluoro-thiophenyl)-quinoline-3-yl)-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (**1d**), (4*R*,6*S*)-6-[(*E*)-2-(2-cyclopropyl-6-fluoro-4-(3-methoxy-thiophenyl)-quinoline-3-yl)-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (**1f**) and (4*R*,6*S*)-6-[(*E*)-2-(2-cyclopropyl-6-fluoro-4,7-di(3-methoxy-thiophenyl)-quinoline-3-yl)-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (**1q**) showed potent HMG-CoA reductase inhibitory activity comparable with pitavastatin.

1. Introduction

Hypercholesterolemia and cardiovascular disease are major health problems. One approach to reduce hypercholesterolemia is to use the medicines that inhibit the enzymes essential for cholesterol biosynthesis. Hydroxymethylglutaryl-Coenzyme A (HMG-CoA) reductase catalyzes the rate-limiting step in cholesterol biosynthesis. When this synthesis is inhibited, the low density lipoprotein cholesterol (LDL-c) receptor is upregulated and LDL-c is rapidly cleared from the bloodstream.[1] Quinoline-based pitavastatin as a HMG-CoA reductase inhibitor is a highly effective therapeutic agent for the treatment of hypercholesterolemia.[2] After a systematical QSAR study on quinoline compound **A**,[3] Sliskovic and Suzuki et al. discovered that the desmethylmevalonic acid portion was linked through a *trans*-ethylene group to position 3 in quinoline ring, and 4-fluorophenyl and 2-cyclopropyl groups were preferable substituents in order to get the best inhibition on HMG-CoA reductase. The introduction of chloro, methyl or methoxy group to the 6, 7, or 8-position of the quinoline nucleus may increase the inhibitory potency.

As part of our lab's investigations on quinoline derivatives with pharmacological interests,[4] Cai[5] introduced a sulfur atom between the quinoline ring position 4 and 4-fluorophenyl to obtain a series of novel compounds. Compounds **B** and **C** were found approximately three times more potent than rosuvastatin or pitavastatin in inhibiting HMG-CoA reductase. Continuing our pursuit on new quinoline-based HMG-CoA reductase inhibitors, we designed the 2-cyclopropyl-4-phenylthioquinoline-based derivatives (compounds **1**), in which the lactone moiety was connected to position 3 of the quinoline nucleus via a *trans*-ethylene spacer and the nucleus was flanked at position 2 and 4 by cyclopropyl and substituted thiophenyl as the lipophilic groups, and at position 6, 7 by different groups, such as H, F, OCH_3, substituted thiophenyl (Fig. 1). The inhibition on HMG-CoA reductase of these novel 2-cyclopropyl-4-phenylthio-quinoline derivatives will also be reported.

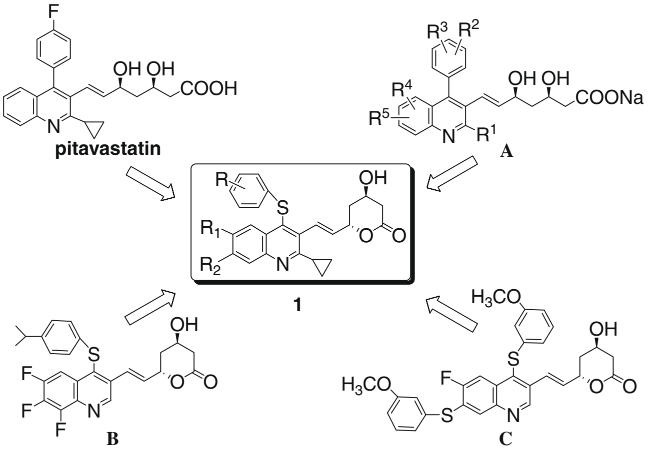

Figure 1. 2-Cyclopropyl-4-thiophenyl-quinolines (**1**).

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doi:10.1016/j.bmc.2009.10.021

2. Chemistry

The 2-cycloproyl-4-thiophenyl quinoline derivatives (**1**) were synthesized in optically pure forms by the general method shown in Scheme 1.

The key intermediate ethyl 2-cyclopropyl-4-chloro-quinoline-3-carboxylates (**5**) were synthesized from anilines and diethyl [chloro(cyclopropyl)methylene]malonate (**2**, prepared from diethyl malonate and cyclopanecarboxylic acid chloride)[6] in three steps. The aromatic nucleophilic substitution (S_NAr) of **5** with 4-fluorothiophenol, 2-methoxythiophenol, 3-methoxythiophenol, 4-methoxythiophenol or 4-isopropylthiophenol was highly regiospecific to afford the 4-monosubstituted (**6a**–**o**) or 4,7-disubstituted (**6p**–**r**) products by controlling the reaction temperature, the type of the base, the solvents as well as the ratio of the substrate to the nucleophile. Characterizations of **6** are shown in Table1.

Compounds **6** were reduced to the alcohols (**7**) by diisobutylaluminum hydride (DIBAL-H). Bromination of alcohols with PBr_3 afforded the bromides (**8**), which were converted to the corresponding phosphorus compounds (**9**) with Ph_2POEt in toluene. The *trans*-olefins (**11**) were generated by Wittig–Horner reaction of **9** with *tert*-butyl (3*R*, 5*S*)-6-oxo-3,5-dihydroxy-3,5-*O*-isopropylidene-hexanoate (**10**) under basic condition. The olefins were deprotected and lactonized with CF_3COOH in CH_2Cl_2 to give the target compounds **1**. Characterizations of **1a**–**r** are shown in Table 2.

3. Biological activity

All the 18 synthesized target compounds **1**, with pitavastatin as the reference, were evaluated for inhibitory activity on rat liver HMG-CoA reductase in vitro, following the method of Kleinsek[7] where by the rate of decrease in absorbance at 340 nm due to the oxidation of NADPH was measured. The enzyme preparation and assay procedures used in this study were the same as those described in the literature.[5,8]

3.1. The preliminary screening

According to the protocol in experiment, the assay system without any inhibitor was taken as the negative control. The test compounds (6.6×10^{-5} M at final concentration) which gave the decreased UV absorbance more than 80% of that in negative control were defined as no significantly active ones and those (totally 10 compounds) giving less than 80% of decreased absorbance would go to the secondary screening (IC_{50} determination).

3.2. IC_{50} determination

The concentration of an inhibitor required to inhibit 50% of the HMG-CoA reductase under the above assay conditions was defined as IC_{50}. The UV absorbance was measured in eight levels (5×10^{-4} M, 1×10^{-4} M, 5×10^{-5} M, 1×10^{-5} M, 5×10^{-6} M, 1×10^{-6} M, 5×10^{-7} M, 1×10^{-7} M at final concentration) for each sample. A statistical analysis was performed by standard curve using mean values of triplicate measurements ($n = 3$). The results are seen in Table 3.

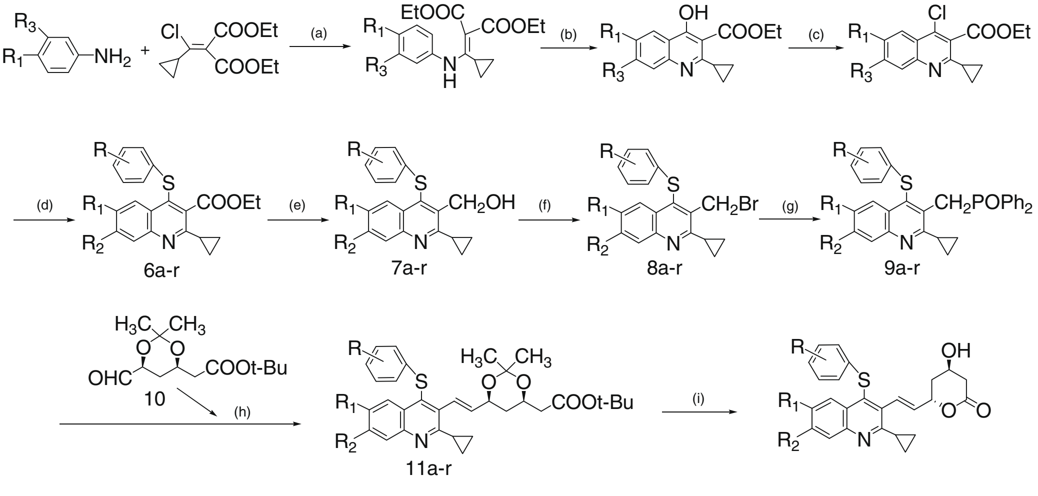
4. Results and discussion

In the preliminary screening among the obtained 18 compounds, 10 compounds were found to possess good or moderate inhibition on HMG-CoA reductase. And the inhibition of three compounds: **1d**, **1f** and **1q** were more potent than that of pitavastatin.

In the early reports for quinoline-based mevalonolactones, it was known that the preferable groups at position 2 and 4 are cyclopropyl and 4-fluorophenyl, respectively. Cai[5] found that the 4-isopropylthiophenyl and 3-methoxythiophenyl were better potent groups than 4-fluorothiophenyl when the sulfur was introduced at position 4 and the 2-substituent was simplified into H. In this paper, 4-fluorothiophenyl was found to be a better group for HMG-CoA reductase inhibition than 4-methoxythiophenyl, 2-methoxythiophenyl and 4-isopropylthiophenyl (**1d** vs **1e**, **1d** vs **1g**, **1d** vs **1h**) and 3-methoxythiophenyl seemed better than 4-fluorothiophenyl (**1f** vs **1d**, **1q** vs **1p**).

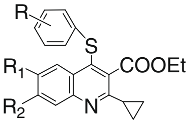
The potency was altered with the different R_1 groups at position 6. The early report showed that replacement of H at position 6 by some small groups, for example, Cl or OCH_3, might enhance the activity in the 4-fluorophenylquinolines.[3b] The present work demonstrated that introduction of F to position 6 might generally give more potency than the OCH_3 or hydrogen counterparts (**1d** vs **1a**, **1d** vs **1i**, **1f** vs **1b**, **1f** vs **1j**).

At the same time, it was found that introduction of fluoro group at position 7 might decreased the activity (**1m** vs **1f**, **1l** vs **1d**). When this post was substituted with the thiophenyl group, it is difficult to conclude the structure–activity relationship.



Scheme 1. Reagents and conditions: (a) K_2CO_3/DMF, 16 h, 100 °C; (b) diphenyl ether, 0.5 h, 170–230 °C; (c) $POCl_3$, toluene, 80 °C; (d) substituted thiophenols, NaH/THF or K_2CO_3/DMF, 6–16 h; (e) DIBAL-H, toluene, 0 °C, 4 h; (f) PBr_3, CH_2Cl_2, rt; (g) Ph_2POEt, toluene, reflux; (h) *n*-BuLi, THF, 0 °C to rt; (i) CF_3COOH, CH_2Cl_2, 0 °C to rt.

Table 1
Characterization of the ethyl ester **6a–o**



Compound	R$_1$	R$_2$	R	Yield (%)	Mp (°C)	^{1}H NMR δ ppm in CDCl$_3$
6a	H	H	*p*-F	87	76–78	8.23 (d, 1H, *J* = 8.4 Hz), 7.97 (d, 1H, *J* = 8.8 Hz), 7.66 (t, 1H, *J* = 7.6 Hz), 7.43 (t, 1H, *J* = 7.6 Hz), 7.28–6.90 (m, 4H), 4.47 (q, 2H, *J* = 7.2 Hz), 2.18–2.13 (m, 1H), 1.40–1.36 (m, 5H), 1.12–1.07 (m, 2H)
6b	H	H	*m*-OCH$_3$	83	75–77	8.25 (d, 1H, *J* = 8.4 Hz), 8.01 (d, 1H, *J* = 8.4 Hz), 7.66 (t, 1H, *J* = 8.0 Hz), 7.44 (t, 1H, *J* = 8.0 Hz), 7.14–6.68 (m, 4H), 4.46 (q, 2H, *J* = 7.2 Hz), 3.71 (s, 3H), 2.20–2.16 (m, 1H), 1.43–1.38 (m, 2H), 1.36 (t, 3H, *J* = 7.2 Hz), 1.13–1.08 (m, 2H)
6c	H	H	*p*-CH(CH$_3$)$_2$	83	Oil	8.29 (d, 1H, *J* = 8.4 Hz), 8.02 (d, 1H, *J* = 8.0 Hz) 7.66 (t, 1H, *J* = 8.4 Hz), 7.44 (t, 1H, *J* = 8.0 Hz), 7.19–7.06 (m, 4H), 4.43 (q, 2H, *J* = 7.2 Hz), 2.85–2.81 (m, 1H), 2.19–2.14 (m, 1H), 1.42–1.38 (m, 2H), 1.35 (t, 3H, *J* = 7.2 Hz), 1.20 (d, 6H, *J* = 6.8 Hz), 1.12–1.07 (m,2H)
6d	F	H	*p*-F	57	112–114	7.93 (dd, 1H, *J* = 9.2, 5.6 Hz), 7.82 (dd, 1H, *J* = 10, 2.8 Hz), 7.41–7.37 (m, 1H), 7.25–6.89 (m, 4H), 4.45 (q, 2H, *J* = 7.2 Hz), 2.13–2.09 (m, 1H), 1.35 (t, 3H, *J* = 7.2 Hz), 1.34–1.31 (m, 2H), 1.09–1.04 (m, 2H)
6e	F	H	*o*-OCH$_3$	87	116–118	7.93 (dd, 1H, *J* = 9.2, 5.6 Hz), 7.84 (dd, 1H, *J* = 10, 2.8 Hz), 7.41–7.36 (m, 1H), 7.15–6.68 (m, 4H), 4.40 (q, 2H, *J* = 7.2 Hz), 3.92 (s, 3H), 2.15–2.10 (m, 1H), 1.35–1.33 (m, 2H), 1.28 (t, 3H, *J* = 7.2 Hz), 1.08–1.03 (m, 2H)
6f	F	H	*m*-OCH$_3$	76	105–107	7.93 (dd, 1H, *J* = 9.2, 5.6 Hz), 7.84 (dd, 1H, *J* = 10, 2.8 Hz), 7.42–7.37 (m, 1H), 7.13–6.74 (m, 4H), 4.44 (q, 2H, J = 7.2 Hz), 3.69 (s, 3H), 2.14–2.10 (m, 1H), 1.35–1.31 (m, 2H), 1.32 (t, 3H, *J* = 7.2 Hz), 1.09–1.04 (m, 2H)
6g	F	H	*p*-OCH$_3$	53	114–115	7.92–7.86 (m, 2H), 7.39–7.34 (m, 1H), 7.27–6.75 (m, 4H), 4.45 (q, 2H, *J* = 7.2 Hz), 3.73 (s, 3H), 2.12–2.08 (m, 1H), 1.37 (t, 3H, *J* = 7.2 Hz), 1.33–1.29 (m, 2H), 1.07–1.02 (m, 2H)
6h	F	H	*p*-CH(CH$_3$)$_2$	88	104–106	7.92 (dd, 1H, *J* = 9.2, 5.6 Hz), 7.87 (dd, 1H, *J* = 10, 2.8 Hz), 7.40–7.36 (m, 1H), 7.16–7.05 (m, 4H), 4.42 (q, 2H, *J* = 7.2 Hz), 2.83–2.79 (m, 1H), 2.25–2.21 (m, 1H), 1.33 (t, 3H, *J* = 7.2 Hz), 1.35–1.30 (m, 2H), 1.16 (d, 6H, *J* = 7.2 Hz), 1.08–1.03 (m, 2H)
6i	OCH$_3$	H	*p*-F	89	95–97	7.89 (d, 1H, *J* = 9.2 Hz), 7.46 (d, 1H, *J* = 2.8 Hz), 7.31–6.91 (m, 5H), 4.48 (q, 2H, *J* = 7.2 Hz), 3.76 (s, 3H), 2.15–2.11 (m, 1H), 1.38 (t, 3H, *J* = 7.2 Hz), 1.35–1.31 (m, 2H), 1.08–1.03 (m, 2H)
6j	OCH$_3$	H	*m*-OCH$_3$	81	80–82	7.90 (d, 1H, *J* = 9.2 Hz), 7.49 (d, 1H, *J* = 2.8 Hz), 7.30 (dd, 1H, *J* = 9.6, 2.8 Hz), 7.15–6.69 (m, 4H), 4.48 (q, 2H, *J* = 7.2 Hz), 3.74 (s, 3H), 3.70 (s, 3H), 2.17–2.13 (m, 1H), 1.37 (t, 3H, *J* = 7.2 Hz), 1.35–1.32 (m, 2H), 1.09–1.04 (m, 2H)
6k	OCH$_3$	H	*p*-CH(CH$_3$)$_2$	73	Oil	7.89 (d, 1H, *J* = 8.8 Hz), 7.48 (d, 1H, *J* = 2.8 Hz), 7.28 (dd, 1H, *J* = 8.8, 2.8 Hz), 7.22–7.07 (m, 4H), 4.46 (q, 2H, *J* = 7.2 Hz), 3.71 (s, 3H), 2.85–2.82 (m, 1H), 2.16–2.12 (m, 1H), 1.37 (t, 3H, *J* = 7.2 Hz), 1.34–1.31 (m, 2H), 1.20 (d, 6H, *J* = 6.8 Hz), 1.07–1.03 (m, 2H)
6l	F	F	*p*-F	89	114–116	7.96 (dd, 1H, *J* = 11.6, 8.4 Hz), 7.69 (dd, 1H, *J* = 11.2, 8.0 Hz), 7.26–6.92 (m, 4H), 4.46 (q, 2H, *J* = 7.2 Hz), 2.12–2.08 (m, 1H), 1.36 (t, 3H, *J* = 7.2 Hz), 1.34–1.31 (m, 2H), 1.11–1.07 (m, 2H)
6m	F	F	*m*-OCH$_3$	84	115–117	7.97 (dd, 1H, *J* = 11.6, 8.4 Hz), 7.75 (dd, 1H, *J* = 11.2, 8.0 Hz), 7.16–6.70 (m, 4H), 4.44 (q, 2H, *J* = 7.2 Hz), 3.72 (s, 3H), 2.14–2.10 (m, 1H), 1.38–1.32 (m, 5H), 1.13–1.08 (m, 2H)
6n	F	F	*p*-OCH$_3$	87	110–112	7.94 (dd, 1H, *J* = 11.6, 8.8 Hz), 7.59 (dd, 1H, *J* = 11.2, 7.6 Hz), 7.22–6.70 (m, 4H), 4.39 (q, 2H, *J* = 7.2 Hz), 3.68 (s, 3H), 2.05–2.01 (m, 1H), 1.32 (t, 3H, *J* = 7.2 Hz), 1.27–1.23 (m, 2H), 1.03–0.98 (m, 2H)
6o	F	F	*p*-CH(CH$_3$)$_2$	76	90–92	8.00 (dd, 1H, *J* = 11.6, 8.4 Hz), 7.67 (dd, 1H, *J* = 11.2, 8.0 Hz), 7.17–7.07 (m, 4H), 4.42 (q, 2H, *J* = 7.2 Hz), 2.85–2.81 (m, 1H), 2.13–2.08 (m, 1H), 1.36–1.30 (m, 5H), 1.19 (d, 6H, *J* = 7.2 Hz), 1.10–1.05 (m, 2H)
6p	F	S-C$_6$H$_4$-4-F	*p*-F	84	93–95	7.81 (d, 1H, *J* = 10.8 Hz), 7.55–6.90 (m, 9H), 4.43 (q, 2H, *J* = 7.2 Hz), 2.08–2.04 (m, 1H), 1.34 (t, 3H, *J* = 7.2 Hz), 1.25–1.21 (m, 2H), 1.04–0.99 (m, 2H)
6q	F	S-C$_6$H$_4$-3-OCH$_3$	*m*-OCH$_3$	87	Oil	7.83 (d, 1H, *J* = 10.8 Hz), 7.56 (d, 1H, *J* = 7.6 Hz), 7.34–6.68 (m, 8H), 4.42 (q, 2H, *J* = 7.2 Hz), 3.79 (s, 3H), 3.71 (s, 3H), 2.10–2.06 (m, 1H), 1.34 (t, 3H, *J* = 7.2 Hz), 1.27–1.22 (m, 2H), 1.04–0.99 (m, 2H)
6r	F	S-C$_6$H$_4$-4-CH(CH$_3$)$_2$	*p*-CH(CH$_3$)$_2$	82	Oil	7.85 (d, 1H, *J* = 10.8 Hz), 7.47–7.06 (m, 9H), 4.39 (q, 2H, *J* = 7.2 Hz), 2.98–2.94 (m, 1H), 2.84–2.80 (m, 1H), 2.10–2.06 (m, 1H), 1.35–1.17 (m, 17H), 1.01–0.97 (m, 2H)

5. Conclusion

A series of 2-cyclopropyl-4-thiophenyl quinoline-based mevalonolactones was synthesized to evaluate their inhibition on HMG-CoA reductase in vitro. It was found that substitution with a variety of thiophenyl groups at position 4 in quinoline resulted in retention or enhancement of the inhibition, and the preferable groups were 4-fluorothiophenyl and 3-methoxythiophenyl. Additionally, the introduction of fluoro group at position 6 of the quinoline nucleus moderately increased the potency. (4*R*,6*S*)-6-[(*E*)-2-(2-Cyclopropyl-6-fluoro-4-(4-fluoro-thiophenyl)-quinoline-3-yl)-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (**1d**), (4*R*,6*S*)-6-[(*E*)-2-(2-cyclopropyl-6-fluoro-4-(3-methoxy-thiophenyl)-quinoline-3-yl)-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (**1f**) and (4*R*,6*S*)-6-[(*E*)-2-(2-cyclopropyl-6-fluoro-4,7-di(3-methoxy-thiophenyl)-quinoline-3-yl)-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (**1q**) were found to possess the activity comparable to pitavastatin in HMG-CoA reductase inhibition.

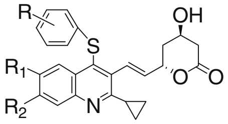
6. Experimental

Melting points were determined on an Electrothermal Melting Point Apparatus and were uncorrected. ^{1}H NMR spectra were recorded at 400 MHz on a Varian Inova-400 spectrometer in CDCl$_3$ or DMSO-d_6 with chemical shifts (δ) given in ppm relative to TMS as an internal standard. Mass spectra were recorded by an Q-TOF Mass Spectrometer using electrospray ionization (ESI).

6.1. Diethyl [cyclopropyl(aniline)methylene]malonate (3a)

A mixture of aniline (11.16 g, 0.12 mol), **2** (24.7 g, 0.1 mol), anhydrous K$_2$CO$_3$ (33.1 g, 0.24 mol), and DMF (130 mL) was stirred

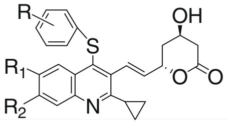
Table 2
Characterization of the ethyl ester **1a**–**r**[a]



Compound	$[\alpha]_D^{25}$	Yield (%)	Mp (°C)	MS (M+H)$^+$	^{1}H NMR δ ppm in CDCl$_3$
1a	−15.7, *c* 1, CHCl$_3$	61	150–152	436	8.32 (d, 1H, J = 8.4 Hz), 7.98 (d, 1H, J = 8.4 Hz), 7.65 (t, 1H, J = 8.0 Hz), 7.44 (t, 1H, J = 8.0 Hz), 7.10 (dd, 1H, J = 16.4, 1.6 Hz), 7.02–6.88 (m, 4H), 5.97 (dd, 1H, J = 16.0, 6.0 Hz), 5.40–5.35 (m, 1H), 4.44–4.39 (m, 1H), 2.83–2.65 (m, 2H), 2.49–2.43 (m, 1H), 2.06–1.81 (m, 3H, changed to 2H by addition of D$_2$O), 1.39–1.33 (m, 2H), 1.08–1.04 (m, 2H)
1b	−22.8, *c* 1, CHCl$_3$	60	36–38	448	8.35 (d, 1H, J = 8.4 Hz), 7.96 (d, 1H, J = 8.4 Hz), 7.65 (t, 1H, J = 8.0 Hz), 7.44 (t, 1H, J = 8.0 Hz), 7.11–6.53 (m, 4H), 5.96 (dd, 1H, J = 16.4, 6.0), 5.36–5.32 (m, 1H), 4.34 (br, 1H), 3.71 (s, 3H), 2.81–2.61 (m, 2H), 2.50–2.45 (m, 1H), 1.97–1.77 (m, 3H, changed to 2H by addition of D$_2$O), 1.37–1.34 (m, 2H), 1.07–1.03 (m, 2H)
1c	−25.9, *c* 1, CHCl$_3$	62	125–127	460	8.38 (d, 1H, J = 8.4 Hz), 7.99 (d, 1H, J = 7.6 Hz), 7.65 (t, 1H, J = 8.0 Hz), 7.44 (t, 1H, J = 8.0 Hz), 7.09 (dd, 1H, J = 16.4, 1.6 Hz), 7.06–6.91 (m, 4H), 5.96 (dd, 1H, J = 16.4, 6.0 Hz), 5.36–5.30 (m, 1H), 4.36–4.34 (m, 1H), 2.86–2.81 (m, 1H), 2.80–2.61 (m, 2H), 2.52–2.45 (m, 1H), 1.96–1.74 (m, 3H, changed to 2H by addition of D$_2$O), 1.38–1.34 (m, 2H), 1.20 (d, 6H, J = 6.4 Hz), 1.08–1.04 (m,2H)
1d	+3.3, *c* 1, CH$_2$Cl$_2$	68	152–154	454	7.94–7.90 (m, 2H), 7.40–7.35 (m, 1H), 7.07 (dd, 1H, J = 16.0, 2.4 Hz), 7.00–6.87 (m, 4H), 5.95 (dd, 1H, J = 16.0, 6.0 Hz) 5.37–5.32 (m, 1H), 4.40–4.38 (m, 1H), 2.80–2.62 (m, 2H), 2.44–2.39 (m, 1H), 2.03–1.78 (m , 3H, changed to 2H by addition of D$_2$O), 1.31–1.25 (m, 2H), 1.04–1.00 (m, 2H)
1e	−4.9, *c* 1, CH$_2$Cl$_2$	65	155–157	466	7.94–7.90 (m, 2H), 7.39–7.34 (m, 1H), 7.11–6.38 (m, 5H), 5.92 (dd, 1H, J = 16.0, 6.0 Hz), 5.31–5.28 (m, 1H), 4.29–4.27 (m, 1H), 3.92 (s,3H), 2.77–2.55 (m, 2H), 2.46–2.41 (m, 1H), 1.95–1.73 (m, 3H, changed to 2H by addition of D$_2$O), 1.32–1.27 (m, 2H), 1.05–1.00 (m, 2H)
1f	+3.5, *c* 1, CH$_2$Cl$_2$	70	50–53	466	7.96–7.90 (m, 2H), 7.40–7.35 (m, 1H), 7.10–6.49 (m, 5H), 5.94 (dd, 1H, J = 16.0, 6.0 Hz), 5.34–5.29 (m, 1H), 4.32 (br, 1H), 3.69 (s, 3H), 2.77–2.58 (m, 2H), 2.46–2.40 (m, 1H), 1.96–1.74 (m, 3H, changed to 2H by addition of D$_2$O), 1.31–1.24 (m, 2H), 1.04–1.00 (m, 2H)
1g	+2.8, *c* 1, CH$_2$Cl$_2$	46	106–108	466	7.98 (dd, 1H, J = 10.4, 2.8 Hz), 7.90 (dd, 1H, J = 9.2, 5.2), 7.37–7.35 (m, 1H), 7.06 (dd, 1H, J = 16.4, 1.6), 7.00–6.72 (m, 4H), 5.95 (dd, 1H, J = 16.4, 6.0 Hz), 5.36–5.32 (m, 1H), 4.39–4.36 (m, 1H), 3.74 (s, 3H), 2.81–2.65 (m, 2H), 2.44–2.39 (m, 1H), 2.04–1.84 (m, 3H, changed to 2H by addition of D$_2$O), 1.30–1.27 (m, 2H), 1.03–0.99 (m, 2H)
1h	−9.5, *c* 1, CH$_2$Cl$_2$	58	111–113	500 (M+Na)	7.98–7.89 (m, 2H), 7.39–7.34 (m, 1H), 7.07–6.88 (m, 5H), 5.94 (dd, 1H, J = 16.0, 6.0), 5.32–5.28 (m, 1H), 4.33–4.31 (m, 1H), 2.84–2.77 (m, 1H), 2.77–2.58 (m, 2H), 2.46–2.40 (m, 1H), 1.94–1.71 (m, 3H, changed to 2H by addition of D$_2$O), 1.33–1.25 (m, 2H), 1.17 (d, 1H, J = 7.2, 6H), 1.04–1.00 (m, 2H)
1i	−26.2, *c* 1, CHCl$_3$	57	131–133	466	7.88 (d, 1H, J = 8.0 Hz), 7.57 (d, 1H, J = 2.8), 7.29 (dd, 1H, J = 8.0, 2.8 Hz), 7.11 (dd, 1H, J = 16.0, 1.2 Hz), 7.05–6.86 (m, 4H), 5.97 (dd, 1H, J = 16.0, 6.0 Hz), 5.40–5.35 (m, 1H), 4.42 (br, 1H), 3.79 (s, 3H), 2.84–2.65 (m, 2H), 2.45–2.38 (m, 1H), 2.06–1.83 (m, 3H, changed to 2H by addition of D$_2$O), 1.32–1.26 (m, 2H), 1.04–1.00 (m, 2H)
1j	−34.6, *c* 1, CHCl$_3$	60	132–134	478	7.86 (d, 1H, J = 9.2 Hz), 7.61 (s, 1H), 7.29 (dd, 1H, J = 8.0, 2.0), 7.12–6.58 (m, 5H), 5.96 (dd, 1H, J = 16.0, 6.0 Hz), 5.36–5.33 (m, 1H), 4.36–4.34 (m, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 2.82–2.61 (m, 2H), 2.45–2.41 (m, 1H), 1.99–1.84 (m, 3H, changed to 2H by addition of D$_2$O), 1.32–1.30 (m, 2H), 1.04–1.00 (m,2H)
1k	−33.6, *c* 1, CHCl$_3$	63	135–137	490	7.94 (br, 1H), 7.59 (d, 1H, J = 2.8 Hz), 7.29 (dd, 1H, J = 8.0, 2.8 Hz), 7.12–6.97 (m, 5H), 5.96 (dd, 1H, J = 16.4, 6.0 Hz), 5.38–5.33 (m, 1H), 4.38–4.35 (m, 1H), 3.75 (s, 3H), 2.87–2.79 (m, 1H), 2.76–2.63 (m, 2H), 2.46–2.42 (m, 1H), 2.02–1.76 (m, 3H, changed to 2H by addition of D$_2$O), 1.37–1.33 (m, 2H), 1.20 (d, 6H, J = 7.2 Hz), 1.07–1.02 (m, 2H)
1l	−11.4, *c* 1, CHCl$_3$	81	158–160	472	8.04 (dd, 1H, J = 11.6, 8.8 Hz), 7.66 (dd, 1H, J = 10.8, 7.6 Hz), 7.00–6.88 (m, 4H), 7.04 (dd, 1H, J = 16.0, 0.9 Hz), 5.94 (dd, 1H, J = 16.4, 6.0 Hz), 5.37–5.31 (m, 1H), 4.41–4.38 (m, 1H), 2.81–2.62 (m, 2H), 2.44–2.38 (m, 1H), 2.03–1.78 (m, 3H, changed to 2H by addition of D$_2$O), 1.30–1.24 (m, 2H), 1.05–1.02 (m, 2H)
1m	−22.6, *c* 1, CHCl$_3$	62	50–53	484	8.07 (dd, 1H, J = 11.6, 8.4 Hz), 7.67 (dd, 1H, J = 10.8, 7.6 Hz), 7.11–6.49 (m, 4H), 7.04 (dd, 1H, J = 16.4, 0.9 Hz), 5.93 (dd, 1H, J = 16.4, 5.6 Hz), 5.34–5.30 (m, 1H), 4.33 (br, 1H), 3.71 (s, 3H), 2.78–2.59 (m, 2H), 2.44–2.40 (m, 1H), 1.96–1.74 (m, 3H, changed to 2H by addition of D$_2$O), 1.31–1.25 (m, 2H), 1.05–1.02 (m, 2H)
1n	−4.1, *c* 1, CHCl$_3$	59	83–85	484	8.10 (dd, 1H, J = 11.6, 8.8 Hz), 7.65 (dd, 1H, J = 11.2, 8.0 Hz), 7.02–6.74 (m, 4H), 7.04 (d, 1H, J = 16.4), 5.94 (dd, 1H, J = 16.4, 5.6), 5.37–5.32 (m, 1H), 4.41–4.38 (m, 1H), 3.75 (s, 3H), 2.82–2.63 (m, 2H), 2.04–1.81 (m, 3H, changed to 2H by addition of D$_2$O), 2.43–2.39 (m, 1H), 1.30–1.24 (m, 2H), 1.04–1.00 (m, 2H)
1o	−12.2, *c* 1, CHCl$_3$	67	132–134	496	8.09 (dd, 1H, J = 11.6, 8.4 Hz), 7.68 (dd, 1H, J = 11.2, 7.6 Hz), 7.06–6.88 (m, 5H), 5.93 (dd, 1H, J = 16.4, 5.6 Hz), 5.33–5.30 (m, 1H), 4.34–4.32 (m, 1H), 2.84–2.76 (m, 1H), 1.18 (d, 6H, J = 6.8 Hz), 2.77–2.59 (m, 2H), 1.94–1.71 (m, 3H, changed to 2H by addition of D$_2$O), 2.45–2.41 (m, 1H), 1.33–1.29 (m, 2H), 1.06–1.02 (m, 2H)
1p	−2.3, *c* 1, CHCl$_3$	68	206–208	580	7.92 (d, 1H, J = 11.2 Hz), 7.46 (d, 1H, J = 7.2 Hz), 7.55–6.88 (m, 8H), 7.03 (dd, 1H, J = 16.0, 1.2 Hz), 5.93 (dd, 1H, J = 16.4, 6.0 Hz), 5.35–5.31 (m, 1H), 4.39 (br, 1H), 2.80–2.62 (m, 2H), 2.01v1.77 (m, 3H, changed to 2H by addition of D$_2$O), 2.39–2.35 (m, 1H), 1.28–1.20 (m, 2H), 1.01–0.97 (m, 2H)
1q	−5.6, *c* 1, CHCl$_3$	54	122–124	604	7.95 (d, 1H, J = 11.2 Hz), 7.63 (d, 1H, J = 7.6 Hz), 7.32–6.50 (m, 9H), 5.93 (dd, 1H, J = 16.4, 5.6 Hz), 5.31–5.28 (m, 1H), 4.32–4.30 (m, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 2.77–2.58 (m, 2H), 2.41–2.37 (m, 1H), 1.94–1.76 (m, 3H, changed to 2H by addition of D$_2$O), 1.24–1.21 (m, 2H), 1.00–0.97 (m,2H)
1r	−3.5, *c* 1, CHCl$_3$	60	123–125	628	7.95 (d, 1H, J = 11.2 Hz), 7.52 (d, 1H, J = 7.2 Hz), 7.47–6.88 (m, 9H), 5.92 (dd, 1H, J = 16.4, 6.0 Hz), 5.30–5.27 (m, 1H), 4.31 (br, 1H), 2.97–2.94 (m, 1H), 2.83–2.80 (m, 1H), 2.76–2.58 (m, 2H), 2.40–2.36 (m, 1H), 1.91–1.70 (m, 3H, changed to 2H by addition of D$_2$O), 1.30–1.17 (m, 14H), 0.99–0.95 (m, 2H)

[a] The definition of R, R_1 and R_2 is the same as Table 1.

Table 3
Inhibition of HMG-CoA reductase in vitro



Compound	R	R_1	R_2	IC_{50} (μM)
1a	4-F	H	H	62.4
1c	4-$CH(CH_3)_2$	H	H	11.3
1d	4-F	F	H	6.93
1f	3-OCH_3	F	H	5.61
1i	4-F	OCH_3	H	25.7
1k	4-$CH(CH_3)_2$	OCH_3	H	41.3
1m	3-OCH_3	F	F	359.6
1o	4-$CH(CH_3)_2$	F	F	759
1p	4-F	F	SC_6H_4-4-F	45.7
1q	3-OCH_3	F	SC_6H_4-3-OCH_3	7.1
Pitavastatin calcium				8.9

at 100 °C (oil bath temperature) for 16 h. When it was cooled to room temperature, the inorganic material was removed by filtration and washed with ethyl acetate. The resulting solution was transferred to a separatory funnel, and ethyl acetate and water were added. The organic layer was separated, washed with brine (200 mL), dried over Na_2SO_4, and concentrated to give yellow oil (29.64 g, 98%) which was used for the next step without further purification. It was purified by silica gel chromatography (petroleum ether–ethyl acetate, 10:1) to provide **3a** as an analytical sample: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.08 (s, 1H, NH), 7.33–7.13 (m, 5H, ArH), 4.25–4.20 (m, 4H, 2 × CH_2), 1.98–1.91 (m, 1H, CH_{CH}), 1.32–1.29 (m, 6H, 2 × CH_3), 0.72–0.67 (m, 2H, 2 × CH_{CH2}), 0.46–0.42 (m, 2H, 2 × CH_{CH2}).

6.2. Ethyl 2-cyclopropyl-4-hydroxyquinoline-3-carboxylate (4a)

The crude **3a** (29.0 g, 0.96 mol) was added to diphenyl ether (400 mL) and heated at 220 °C for 0.5 h. After the solution cooled, the precipitate was filtered off, washed with petroleum ether (4 × 100 mL), and dried. The obtained solid was recrystallized from 95% ethanol to give the colorless needle-like crystals **4a** (21.3 g, 87%): mp 248–250 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.88 (s, 1H, OH), 8.03 (d, 1H, J = 8.4 Hz, ArH), 7.69 (d, 1H, J = 8.4 Hz, ArH), 7.64 (dd, 1H, J = 6.8, 1.6 Hz, ArH), 7.32 (t, 1H, J = 7.2 Hz, ArH), 4.25 (q, 2H, J = 6.8 Hz, CH_2), 2.08–2.06 (m, 1H, CH_{CH}), 1.28 (t, 3H, J = 7.2 Hz, CH_3), 1.08–1.05 (m, 4H, 4 × CH_{CH2}).

Compounds **4b–d** were prepared in the manner analogous to the method described above when 4-fluoroaniline, 4-methoxyaniline or 3,4-difluoroaniline was used instead of aniline. Some physical properties are included in Table 4.

6.3. Ethyl 4-chloro-2-cyclopropyl-quinoline-3-carboxylate (5a)

Phosphorus oxychloride (15 mL, 0.16 mol) was added to a suspension of **4a** (20.5 g, 0.08 mol) in acetonitrile (150 mL) and the mixture was heated at 75 °C for 6 h. The resulting light brown solution was poured into the aqueous solution saturated with sodium bicarbonate (300 mL); the suspension was extracted with ethyl acetate twice. The organic extracts were washed with water, dried over Na_2SO_4 and concentrated to give **5a** as a lightly yellow oil (19.4 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, 1H, J = 8.4 Hz, ArH), 7.93 (d, 1H, J = 8.4 Hz, ArH), 7.72–7.52 (m, 2H, ArH), 4.53 (q, 2H, J = 7.2 Hz, CH_2), 2.13–2.09 (m, 1H, CH_{CH}), 1.46 (t, 3H, J = 7.2 Hz, CH_3), 1.34–1.30 (m, 2H, 2 × CH_{CH2}), 1.07–1.02 (m, 2H, 2 × CH_{CH2}). MS (ESI): m/z = 276, 278 $(M+H)^+$.

Compounds **5b–d** were prepared in the manner analogous to the method described above. But the **5d** was purified by silica gel chromatography (petroleum ether–ethyl acetate, 100:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, 1H, J = 10.8, 8.4 Hz, ArH), 7.68 (dd, 1H, J = 11.2, 7.6 Hz, ArH), 4.53 (q, 2H, J = 7.2 Hz, CH_2), 2.10–2.06 (m, 1H, 2 × CH_{CH}), 1.45 (t, 3H, J = 7.2 Hz, CH_3), 1.31–1.27 (m, 2H, 2 × CH_{CH2}), 1.09–1.04 (m, 2H, 2 × CH_{CH2}). MS (ESI): m/z = 312, 314 $(M+H)^+$.

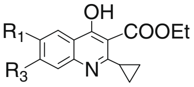
The physical properties of **5a–d** are shown in Table 5.

6.4. Ethyl 2-cyclopropyl-4-(4-fluorothiophenyl)-quinoline-3-carboxylate (6a)

A mixture of 4-fluorothiophenol (1.13 g, 8.8 mmol), **5a** (2.0 g, 7.25 mmol), anhydrous K_2CO_3 (1.22 g, 8.8 mmol), and DMF (20 mL) was stirred for 20 h at room temperature. The inorganic material was removed by filtration and washed with ethyl acetate. The resulting mixture was transferred to a separatory funnel, and ethyl acetate and water were added. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated to dryness to give an yellow solid, which was recrystallized from n-hexane to give **6a** (2.31 g, 87%) as a lightly yellow powder: mp 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, 1H, J = 8.4 Hz), 7.97 (d, 1H, J = 8.8 Hz), 7.66 (t, 1H, J = 7.6 Hz), 7.43 (t, 1H, J = 7.6 Hz), 7.28–6.90 (m, 4H), 4.47 (q, 2H, J = 7.2 Hz), 2.18–2.13 (m, 1H), 1.40–1.36 (m, 5H), 1.12–1.07 (m, 2H).

Compounds **6b–k** were prepared in manner analogous to the method described above. Some physical properties are included in Table 1.

Table 4
Physical properties and yield of **4a–d**



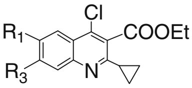
Compound	R_1	R_3	Formula	Reaction temp. (°C)	Yield* (%)	Mp (°C)	^{1}H NMR δ ppm in DMSO-d_6
4a	H	H	$C_{15}H_{15}NO_3$	190–220	85	248–250	10.88 (s, 1H), 8.03 (d, 1H, J = 8.4 Hz), 7.69 (d, 1H, J = 8.4 Hz), 7.64 (dd, 1H, J = 6.8, 1.6 Hz), 7.32 (t, 1H, J = 7.2 Hz), 4.25 (q, 2H, J = 6.8 Hz), 2.08–2.06 (m, 1H), 1.28 (t, 3H, J = 7.2 Hz), 1.08–1.05 (m, 4H)
4b	F	H	$C_{15}H_{14}FNO_3$	200–220	83	279–280	10.67 (s, 1H), 7.87 (dd, 1H, J = 8.8, 2.8 Hz), 7.68 (dd, 1H, J = 9.2, 5.2 Hz), 7.31–7.25 (m, 1H), 4.36 (q, 2H, J = 7.2 Hz), 2.25–2.20 (m, 1H), 1.37 (t, 3H, J = 7.2 Hz), 1.11–1.05 (m, 4H)
4c	OCH_3	H	$C_{16}H_{17}NO_4$	170–200	84	256–258	10.88 (s, 1H), 7.66 (d, 1H, J = 9.2 Hz), 7.45 (d, 1H, J = 2.8 Hz), 7.29 (dd, 1H, J = 9.2, 2.8 Hz), 4.25 (q, 2H, J = 7.2 Hz), 3.83 (s, 3H), 2.10–2.06 (m, 1H), 1.28 (t, 3H, J = 7.2 Hz), 1.06–1.04 (m, 4H)
4d	F	F	$C_{15}H_{13}F_2NO_3$	200–230	71	280–282	10.63 (s, 1H), 7.99 (dd, 1H, J = 10.8, 8.8 Hz), 7.53 (dd, 1H, J = 10.8, 6.8 Hz), 4.36 (q, 2H, J = 7.2 Hz), 2.23–2.18 (m, 1H), 1.37 (t, 3H, J = 7.2 Hz), 1.10–1.06 (m, 4H)

* The yields were calculated from **2**.

6.5. Ethyl 2-cyclopropyl-6,7-difluoro-4-(4-fluorothiophenyl) quinoline-3-carboxylate (6l)

4-Fluorothiophenol (0.678 g, 5.29 mmol) was added to a mixture of NaH (0.127 g, 5.29 mmol, 60%) in THF (15 mL) at 0 °C. The resulting mixture was stirred for 0.5 h, and then **5d** (1.5 g, 4.81 mmol) was added. The mixture was stirred at ice bath for 4 h. After completion the reaction mixture was transferred to a separatory funnel, then ethyl acetate and water were added. The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated to dryness. The residue was recrystallized from *n*-hexane to give **6l** (1.73 g, 89%) as a lightly yellow powder: mp

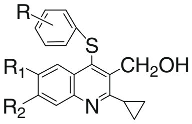
Table 5
Physical properties and yield of **5a–d**



Compound	R_1	R_3	Formula	Yield (%)	Mp (°C)	MS (M+H)	^{1}H NMR δ ppm in $CDCl_3$
5a	H	H	$C_{15}H_{14}ClNO_2$	89	Oil	276, 278	8.16 (d, 1H, *J* = 8.4 Hz), 7.93 (d, 1H, *J* = 8.4 Hz), 7.72–7.52 (m, 2H), 4.53 (q, 2H, *J* = 7.2 Hz), 2.13–2.09 (m, 1H), 1.46 (t, 3H, *J* = 7.2 Hz), 1.34–1.30 (m, 2H), 1.07–1.02 (m, 2H)
5b	F	H	$C_{15}H_{13}ClFNO_2$	94	65–67	294, 296	7.93 (dd, 1H, *J* = 8.8, 5.2 Hz), 7.68 (dd, 1H, *J* = 9.2, 2.8 Hz), 7.49–7.44 (m, 1H), 4.53 (q, 2H, *J* = 7.2 Hz), 2.12–2.07 (m, 1H), 1.46 (t, 3H, *J* = 7.2 Hz), 1.32–1.28 (m, 2H), 1.07–1.02 (m, 2H)
5c	OCH_3	H	$C_{16}H_{16}ClNO_3$	86	85–87	306, 308	7.88 (d, 1H, *J* = 8.8 Hz), 7.43–7.37 (m, 2H), 4.55 (q, 2H, *J* = 7.2 Hz), 3.97 (s, 3H), 2.13–2.09 (m, 1H), 1.48 (t, 3H, *J* = 7.2 Hz), 1.32–1.28 (m, 2H), 1.06–1.01 (m, 2H)
5d	F	F	$C_{15}H_{12}ClF_2NO_2$	67[a]	68–70	312, 314	7.90 (dd, 1H, *J* = 10.8, 8.4 Hz), 7.68 (dd, 1H, *J* = 11.2, 7.6 Hz), 4.53 (q, 2H, *J* = 7.2 Hz), 2.10–2.06 (m, 1H), 1.45 (t, 3H, *J* = 7.2 Hz), 1.31–1.27 (m, 2H), 1.09–1.04 (m, 2H)

[a] Purified by silica gel column chromatography (petroleum ether–ethyl acetate, 100:1).

Table 6
Physical properties and yield of 2-cyclopropyl-4-substituted-thiophenyl-quinoline-3-methanol (**7a–r**)[a]



Compound	Formula	Yield (%)	Mp (°C)	^{1}H NMR δ ppm in $CDCl_3$
7a	$C_{19}H_{16}FNOS$	98	137–139	8.35 (d, 1H, *J* = 8.4 Hz), 8.09 (d, 1H, *J* = 8.4 Hz), 7.67 (t, 1H, *J* = 8.0 Hz), 7.47 (t, 1H, *J* = 8.0 Hz), 7.11–6.90 (m, 4H), 5.36 (s, 2H), 2.66–2.60 (m, 1H), 1.84 (s, 1H), 1.44–1.42 (m, 2H), 1.18–1.13 (m, 2H)
7b	$C_{20}H_{19}NO_3$	90	154–156	8.38 (d, 1H, *J* = 8.4 Hz), 8.01 (d, 1H, *J* = 8.4 Hz), 7.66 (t, 1H, *J* = 8.0 Hz), 7.46 (t, 1H, *J* = 8.0 Hz), 7.13–6.60 (m, 4H), 5.34 (d, 2H, *J* = 6.4 Hz), 3.70 (s, 1H), 2.66–2.60 (m, 1H), 1.83 (br, 1H), 1.42–1.38 (m, 2H), 1.16–1.11 (m, 2H)
7c	$C_{22}H_{23}NOS$	88	108–110	8.43 (d, 1H, *J* = 8.4 Hz), 8.01 (d, 1H, *J* = 7.6 Hz), 7.66 (t, 1H, *J* = 8.0 Hz), 7.46 (t, 1H, *J* = 8.0 Hz), 7.09–7.01 (m, 4H), 5.34 (d, 2H, *J* = 6.4 Hz), 2.87–2.81 (m, 1H), 1.74 (br, 1H), 2.65–2.59 (m, 1H), 1.40–1.39 (m, 2H), 1.23 (d, 6H, *J* = 6.8 Hz), 1.14–1.10 (m, 2H)
7d	$C_{19}H_{15}F_2NOS$	94	150–152	7.96–7.92 (m, 2H), 7.41–7.36 (m, 1H), 7.08–6.88 (m, 4H), 5.32 (d, 2H, *J* = 6.4 Hz), 2.59–2.54 (m, 1H), 1.81 (t, 1H, *J* = 6.4 Hz), 1.34–1.30 (m, 2H), 1.11–1.07 (m, 2H)
7e	$C_{20}H_{18}FNO_2S$	64	168–170	7.96–7.92 (m, 2H), 7.39–7.34 (m, 1H), 7.15–6.54 (m, 4H), 5.29 (d, 2H, *J* = 6.4 Hz), 3.89 (s, 3H), 2.62–2.57 (m, 1H), 1.98 (t, 1H, *J* = 6.4 Hz), 1.34–1.30 (m, 2H), 1.11–1.06 (m, 2H)
7f	$C_{20}H_{18}FNO_2S$	92	170–172	7.99-7.92 (m, 2H), 7.41–7.36 (m, 1H), 7.12–6.57 (m, 4H), 5.30 (d, 2H, *J* = 6.4 Hz), 3.69 (s, 3H), 2.59–2.56 (m, 1H), 1.82 (br, 1H), 1.34–1.30 (m, 2H), 1.11–1.06 (m, 2H)
7g	$C_{20}H_{18}FNO_2S$	81	128–130	8.04 (dd, 1H, *J* = 10.4, 2.8 Hz), 7.92 (dd, 1H, *J* = 9.2, 5.6 Hz), 7.40–7.35 (m, 1H), 7.11–6.74 (m, 4H), 5.32 (d, 2H, *J* = 6.4 Hz), 3.73 (s, 3H), 2.59–2.53 (m, 1H), 1.74 (t, 1H, *J* = 6.4 Hz), 1.32–1.28 (m, 2H), 1.09–1.05 (m, 2H)
7h	$C_{22}H_{22}FNOS$	82	132–134	8.04–7.92 (m, 2H), 7.41–7.37 (m, 1H), 7.08–6.99 (m, 4H), 5.31 (s, 2H), 2.84–2.80 (m, 1H), 2.58 (br, 1H), 1.72 (br, 1H), 1.32 (br, 2H), 1.17 (d, 6H, *J* = 6.4 Hz), 1.10–1.08 (m, 2H)
7i	$C_{20}H_{18}FNO_2S$	97	116–118	7.88 (d, 1H, *J* = 9.2 Hz), 7.59 (d, 1H, *J* = 2.8 Hz), 7.29 (d, 1H, *J* = 9.2 Hz), 7.12–6.90 (m, 4H), 5.35 (s, 2H), 3.79 (s, 3H), 2.61–2.54 (m, 1H), 1.94 (br, 1H), 1.36–1.32 (m, 2H), 1.12–1.08 (m, 2H)
7j	$C_{21}H_{21}NO_3S$	89	97–99	7.91 (d, 1H, *J* = 8.4 Hz), 7.63 (d, 1H, *J* = 2.8 Hz), 7.29 (d, 1H, *J* = 9.2 Hz), 7.14–6.64 (m, 4H), 5.33 (d, 2H,*J* = 6.0 Hz), 3.79 (s, 3H), 3.70 (s, 3H), 2.55–2.51 (m, 1H), 1.88 (br, 1H), 1.35–1.32 (m, 2H), 1.11–1.07 (m, 2H)
7k	$C_{23}H_{25}NO_2S$	87	105–107	7.88 (d, 1H, *J* = 9.2 Hz), 7.65 (d, 1H, *J* = 2.4 Hz), 7.28 (d, 1H, *J* = 9.2 Hz), 7.09–7.04 (m, 4H), 5.33 (d, 2H, *J* = 6.0 Hz), 3.78 (s, 3H), 2.87–2.80 (m, 1H), 2.55–2.55 (m, 1H), 1.83 (br, 1H), 1.34 (br, 2H), 1.20 (d, 6H, *J* = 7.2 Hz), 1.12–1.07 (m, 2H)
7l	$C_{19}H_{14}F_3NOS$	98	117–119	8.08 (dd, 1H, *J* = 11.8, 8.6 Hz), 7.74 (dd, 1H, *J* = 11.2, 8.0 Hz), 7.08–6.90 (m, 4H), 5.31 (s, 2H), 1.81 (br, 1H), 2.60–2.54 (m, 1H), 1.36–1.32 (m, 2H), 1.14–1.10 (m, 2H)
7m	$C_{20}H_{17}F_2NO_2S$	94	144–146	8.09 (dd, 1H, *J* = 11.6, 8.8 Hz), 7.71 (dd, 1H, *J* = 10.8, 7.6 Hz), 7.13–6.56 (m, 4H), 5.28 (s, 2H), 3.70 (s, 3H), 2.60–2.56 (m, 1H), 1.76 (br, 1H), 1.35–1.31 (m, 2H), 1.13–1.08 (m, 2H)
7n	$C_{20}H_{17}F_2NO_2S$	59	118–119	8.16 (dd, 1H, *J* = 12.0, 8.8 Hz), 7.66 (dd, 1H, *J* = 11.2, 8.0 Hz), 7.10–6.75 (m, 4H), 5.31 (d, 2H, *J* = 6.4 Hz), 3.74 (s, 3H), 2.57–2.53 (m, 1H), 1.72 (t, 1H, *J* = 6.4 Hz), 1.32–1.27 (m, 2H), 1.10–1.06 (m, 2H)
7o	$C_{22}H_{21}F_2NOS$	81	90–92	8.16 (dd, 1H, *J* = 11.4, 9.0 Hz), 7.70 (dd, 1H, *J* = 10.8, 7.6 Hz), 7.28–7.00 (m, 4H), 5.31 (s, 2H), 2.86–2.82 (m, 1H), 2.60–2.57 (m, 1H), 1.72 (s, 1H), 1.34–1.28 (m, 2H), 1.20 (d, 6H, *J* = 7.2 Hz), 1.13–1.10 (m, 2H)
7p	$C_{25}H_{18}F_3NOS_2$	82	143–145	7.93 (d, 1H, *J* = 10.8 Hz), 7.55–6.89 (m, 8H), 7.45 (d, 1H, *J* = 7.2 Hz), 5.28 (s, 2H), 2.55–2.51 (m, 1H), 1. 85 (s, 1H), 1.25–1.21 (m, 2H), 1.07–1.02 (m, 2H)
7q	$C_{27}H_{24}FNO_3S_2$	82	141–143	7.97 (d, 1H, *J* = 10.8 Hz), 7.63 (d, 1H, *J* = 7.2 Hz), 7.33–6.57 (m, 8H), 5.26 (d,2H, *J* = 6.4 Hz), 3.79 (s, 3H), 3.70 (s, 3H), 2.56–2.52 (m,1H), 1.75 (t, 1H, *J* = 6.4 Hz), 1.27–1.23 (m, 2H), 1.07–1.02 (m, 2H)
7r	$C_{31}H_{32}FNOS_2$	92	102–104	8.00 (d, 1H, *J* = 10.8 Hz), 7.53 (d, 1H, *J* = 7.6 Hz), 7.48–6.98 (m, 8H), 5.26 (d, 2H, *J* = 4.8 Hz), 2.98–2.94 (m, 1H), 2.84–2.80 (m, 1H), 2.55–2.50 (m, 1H), 1.68 (br, 1H), 1.31–1.16 (m, 14H), 1.05–1.01 (m, 2H)

[a] The definition of R, R_1 and R_2 is the same as Table 1.

114–116 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.96 (dd, 1H, J = 11.6, 8.4 Hz), 7.69 (dd, 1H, J = 11.2, 8.0 Hz), 7.26–6.92 (m, 4H), 4.46 (q, 2H, J = 7.2 Hz), 2.12–2.08 (m, 1H), 1.36 (t, 3H, J = 7.2 Hz), 1.34–1.31 (m, 2H), 1.11–1.07 (m, 2H).

Compounds **6m**–**o** were prepared in the manner analogous to the method described above. Some physical properties are included in Table 1.

6.6. Ethyl 2-cyclopropyl-6-fluoro-4,7-di(4-fluorothiophenyl) quinoline-3-carboxylate (6p)

A mixture of 4-fluorothiophenol (1.30 g, 10.1 mmol), **5d** (1.5 g, 4.81 mmol), anhydrous K$_2$CO$_3$ (1.39 g, 10.1 mmol), and DMF (15 mL) was stirred at 50 °C for 20 h. When it was cooled to room temperature, the inorganic material was removed by filtration and washed with ethyl acetate. The resulting mixture was transferred to a separatory funnel, and ethyl acetate and water were added. The organic layer was separated, washed with brine, dried over Na$_2$SO$_4$, and concentrated to dryness. The residue was purified by silica gel column chromatography (petroleum ether–ethyl acetate, 60:1) to provide **6p** (2.06 g, 84%) as a yellow solid: mp 93–95 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.81 (d, 1H, J = 10.8 Hz), 7.55–6.90 (m, 9H), 4.43 (q, 2H, J = 7.2 Hz), 2.08–2.04 (m, 1H), 1.34 (t, 3H, J = 7.2 Hz), 1.25–1.21 (m, 2H), 1.04–0.99 (m, 2H).

Compounds **6q** and **6r** were prepared in the manner analogous to the method described above. Some physical properties are included in Table 1.

6.7. 2-Cyclopropyl-4-(4-fluorothiophenyl)quinoline-3-methanol (7a)

To a solution of **6a** (2.0 g, 5.44 mmol) in toluene (5 mL), at 0 °C under an atmosphere of nitrogen, was added DIBAL-H (13.6 mL, 13.6 mmol, 1 mol/L) in toluene. The resulting solution was stirred for 2 h at ice bath before quenching with 6 M HCl. The mixture was added to EtOAc and the organic layer was separated, washed with water, dried over Na$_2$SO$_4$ and concentrated to give the title compound as a white solid **7a** (1.73 g, 98%), mp: 137–139 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.35 (d, 1H, J = 8.4 Hz), 8.09 (d, 1H, J = 8.4 Hz), 7.67 (t, 1H, J = 8.0 Hz), 7.47 (t, 1H, J = 8.0 Hz), 7.11–6.90 (m, 4H), 5.36 (s, 2H), 2.66–2.60 (m, 1H), 1.84 (s, 1H, disappeared by addition of D$_2$O), 1.44–1.42 (m, 2H), 1.18–1.13 (m, 2H).

Compounds **7b**–**r** were prepared in the manner analogous to the method described above. Some physical properties are included in Table 6.

6.8. 2-Cyclopropyl-4-(4-fluorothiophenyl)-3-bromomethyl-quinoline (8a)

A solution of PBr$_3$ (0.95 mL, 10.1 mmol) in CH$_2$Cl$_2$ (6 mL) was added to the mixture of **7a** (1.65 g, 5.07 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C. The resulting mixture was stirred for 3 h at room temperature before quenching with saturated aqueous NaHCO$_3$ solution to pH 8. The mixture was added to CH$_2$Cl$_2$ and the organic layer was separated, washed with water, dried over Na$_2$SO$_4$, concentrated to give the title compound as an off-white solid (1.83 g, 93%), mp: 128–130 °C.

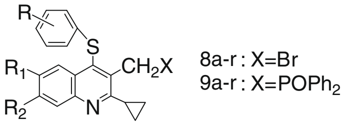
Compounds **8b**–**r** were prepared in the manner analogous to the method described above. Some physical properties are included in Table 7.

6.9. 2-Cyclopropyl-4-(4-fluorothiophenyl)-3-(diphenyl-oxo-phosphonyl-methyl)-quinoline (9a)

A solution of **8a** (1.70 g, 4.38 mmol) and ethyl diphenylphosphinite (1.2 mL, 5.69 mmol) in toluene (20 mL) was refluxed for 2 h during which time the precipitated solid developed. After cooling to room temperature, the solid was isolated by filtration and washed with petroleum ether. The product was then dried to afford the title compound (1.84 g, 82%), mp: 215–217 °C.

Table 7

Physical properties and yield of yield of 2-cyclopropyl-4-substituted-thiophenyl-3-bromomethyl (or 3-diphenyl-oxo-phosphonyl-methyl)-quinolines (**8a**–**r** or **9a**–**r**)[a]



Compound	Formula	Yield (%)	Mp (°C)
8a	$C_{19}H_{15}BrFNS$	93	128–130
8b	$C_{20}H_{18}BrNOS$	93	131–133
8c	$C_{22}H_{22}BrNS$	97	Oil
8d	$C_{19}H_{14}BrF_2NS$	97	146–148
8e	$C_{20}H_{17}BrFNOS$	81	174–176
8f	$C_{20}H_{17}BrFNOS$	91	102–104
8g	$C_{20}H_{17}BrFNOS$	91	135–137
8h	$C_{22}H_{21}BrFNS$	98	116–118
8i	$C_{20}H_{17}BrFNOS$	93	122–124
8j	$C_{21}H_{20}BrNO_2S$	97	122–124
8k	$C_{23}H_{24}BrNOS$	96	Oil
8l	$C_{19}H_{13}BrF_3NS$	93	105–107
8m	$C_{20}H_{16}BrF_2NOS$	93	99–101
8n	$C_{20}H_{16}BrF_2NOS$	94	129–131
8o	$C_{22}H_{20}BrF_2NS$	83	97–99
8p	$C_{25}H_{17}BrF_3NS_2$	91	152–154
8q	$C_{27}H_{23}BrFNO_2S_2$	79	103–105
8r	$C_{31}H_{31}BrFNS_2$	96	137–139
9a	$C_{31}H_{25}FNOPS$	82	215–217
9b	$C_{32}H_{28}NO_2PS$	95	238–240
9c	$C_{34}H_{32}NOPS$	81	217–219
9d	$C_{31}H_{24}F_2NOPS$	91	244–246
9e	$C_{32}H_{27}FNO_2PS$	94	204–206
9f	$C_{32}H_{27}FNO_2PS$	93	240–242
9g	$C_{32}H_{27}FNO_2PS$	84	259–261
9h	$C_{34}H_{31}FNOPS$	88	253–255
9i	$C_{32}H_{27}FNO_2PS$	91	236–238
9j	$C_{33}H_{30}NO_3PS$	96	201–202
9k	$C_{35}H_{34}NO_2PS$	88	243–245
9l	$C_{31}H_{23}F_3NOPS$	91	266–267
9m	$C_{32}H_{26}F_2NO_2PS$	86	239–241
9n	$C_{32}H_{26}F_2NO_2PS$	88	277–279
9o	$C_{34}H_{30}F_2NOPS$	87	267–269
9p	$C_{37}H_{27}F_3NOPS_2$	89	251–253
9q	$C_{39}H_{33}FNO_3PS_2$	93	226–228
9r	$C_{43}H_{41}FNOPS_2$	85	276–278

[a] The definition of R, R$_1$ and R$_2$ is the same as Table 1.

Compounds **9b**–**r** were prepared in the manner analogous to the method described above. Some physical properties are included in Table 7.

6.10. *tert*-Butyl (3*R*,5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorothiophenyl)-quinoline-3-yl]-3,5-*O*-isoproylidene-6-heptenoate (11a)

A hexane solution of *n*-BuLi (1.6 mL, 4.29 mmol, 2.7 M) was added to a solution **9a** (1.82 g, 3.57 mmol) in anhydrous THF (50 mL) at 0 °C and stirred for 0.5 h under an atmosphere of nitrogen. **10** (1.11 g, 4.29 mmol) in anhydrous THF (5 mL) was added to the solution and stirred for 10 h at room temperature, and then quenched with 2 M HCl solution at 0 °C. The resulting mixture was added to EtOAc and the organic layer was separated, washed with brine, dried over Na$_2$SO$_4$, concentrated to dryness. The residue was purified by silica gel column chromatography (petroleum ether–ethyl acetate, 20:1) to give **11a** (0.98 g, 50%) as a lightly yellow powder: mp 103–105 °C; $[\alpha]_D^{25}$ = +8.9 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, 1H, *J* = 8.4 Hz), 7.96 (d, 1H, *J* = 8.8 Hz), 7.63 (t, 1H, *J* = 7.6 Hz), 7.44 (t, 1H, *J* = 7.6 Hz), 7.05–6.86 (m, 5H), 5.91 (dd, 1H, *J* = 16.4, 5.6 Hz), 4.57–4.53 (m, 1H), 4.36–4.32 (m, 1H), 2.52–2.31 (m, 3H), 1.63–1.02 (m, 21H).

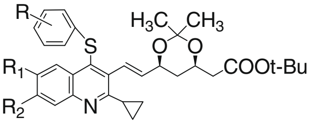
Compounds **11b**–**r** were prepared in the manner analogous to the method described above. Their physical properties are included in Table 8.

6.11. (4*R*,6*S*)-6-[(*E*)-2-[2-Cyclopropyl-4-(4-fluorothiophenyl)-quinoline-3-yl]-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (1a)

A solution of **11a** (0.95 g, 1.73 mmol) and CF_3COOH (2.6 mL, 34.6 mmol) in CH_2Cl_2 (13 mL) was stirred at 0 °C for 2 h before quenching with a saturated aqueous $NaHCO_3$ solution. The mixture was added to EtOAc and the organic layer was separated, washed

Table 8

Physical properties and yield of yield of (3*R*,5*S*, 6*E*)-*tert*-butyl-7-(2-cyclopropyl-4-substituted-thiophenyl-quinoline-3-yl)-3,5-dihydroxy-3,5-*O*-isoproylidene-6-heptenoates (**11a**–**r**)[a]



Compound	Formula	$[\alpha]_D^{25}$	Yield (%)	Mp (°C)	^1H NMR δ ppm in $CDCl_3$
11a	$C_{32}H_{36}FNO_4S$	+8.9, *c* 1, $CHCl_3$	50	103–105	8.36 (d, 1H, *J* = 8.4 Hz), 7.96 (d, 1H, *J* = 8.8 Hz), 7.63 (t, 1H, *J* = 7.6 Hz), 7.44 (t, 1H, *J* = 7.6 Hz), 7.05–6.86 (m, 5H), 5.91 (dd, 1H, *J* = 16.4, 5.6 Hz), 4.57–4.53 (m, 1H), 4.36–4.32 (m, 1H), 2.52–2.31 (m, 3H), 1.63–1.02 (m, 21H)
11b	$C_{33}H_{39}NO_5S$	+7.0, *c* 1, $CHCl_3$	25	35–36	8.34 (d, 1H, *J* = 8.4 Hz), 7.96 (d, 1H, *J* = 8.0 Hz), 7.62 (t, 1H, *J* = 7.6 Hz), 7.42 (t, 1H, *J* = 7.6 Hz), 7.10–6.57 (m, 5H), 5.94 (dd, 1H, *J* = 16.4, 5.6 Hz), 4.57–4.52 (m, 1H), 4.34–4.31 (m, 1H), 3.69 (s, 3H), 2.54–2.29 (m, 3H), 1.62–1.03 (m, 21H)
11c	$C_{35}H_{43}NO_4S$	+1.5, *c* 1, $CHCl_3$	64	40– 42	8.38 (d, 1H, *J* = 8.4 Hz), 7.96 (br, 1H), 7.62 (t, 1H, *J* = 7.6 Hz), 7.42 (t, 1H, *J* = 7.6 Hz), 7.05– 6.95 (m, 5H), 5.92 (dd, 1H, *J* = 16.4, 5.6 Hz), 4.56–4.52 (m, 1H), 4.36–4.32 (m, 1H), 2.85–2.81 (m, 1H), 2.54–2.29 (m, 3H), 1.64–1.03 (m, 27H)
11d	$C_{32}H_{35}F_2NO_4S$	+11.4, *c* 1, CH_2Cl_2	47	Oil	7.96 (dd, 1H, *J* = 10.4, 2.8 Hz), 7.90 (dd, 1H, *J* = 9.2, 5.6 Hz), 7.38–7.33 (m, 1H), 7.02–6.85 (m, 5H), 5.90 (dd, 1H, *J* = 16.4, 5.2 Hz), 4.54–4.50 (m, 1H), 4.33–4.29 (m, 1H), 2.47–2.27 (m, 3H), 1.64–0.99 (m, 21H)
11e	$C_{33}H_{38}FNO_5S$	+4.1, *c* 1, CH_2Cl_2	29	Oil	7.93 (dd, 1H, *J* = 10.4, 2.8 Hz), 7.89 (dd, 1H, *J* = 9.2,5.6 Hz), 7.36–7.31 (m, 1H), 7.10–6.43 (m, 5H), 5.91 (dd, 1H, *J* = 16.4, 5.2 Hz), 4.53–4.48 (m, 1H), 4.29–4.24 (m, 1H), 3.89 (s, 3H), 2.51–2.24 (m, 3H), 1.54–0.98 (m, 21H)
11f	$C_{33}H_{38}FNO_5S$	+13.0, *c* 1, CH_2Cl_2	17	Oil	7.94 (dd, 1H, *J* = 10.4, 2.8 Hz), 7.90 (dd, 1H, *J* = 9.2, 5.2 Hz), 7.37–7.32 (m, 1H), 7.08–6.54 (m, 5H), 5.92 (dd, 1H, *J* = 16.4, 5.2 Hz), 4.54–4.49 (m, 1H), 4.31–4.28 (m, 1), 3.67 (s, 3H), 2.49–2.26 (m, 3H), 1.60–0.98 (m, 21H)
11g	$C_{33}H_{38}FNO_5S$	+14.1, *c* 1, CH_2Cl_2	23	Oil	8.01 (dd, *J* = 10.4, 2.8 Hz), 7.88 (dd, 1H, *J* = 9.2,5.6 Hz), 7.36–7.31 (m, 1H), 7.03–6.71 (m, 5H), 5.91 (dd, 1H, *J* = 16.4, 5.2 Hz), 4.56–4.52 (m, 1H), 4.33–4.29 (m, 1H), 3.73 (s, 3H), 2.47–2.28 (m, 3H), 1.66–0.86 (m, 21H)
11h	$C_{35}H_{42}FNO_4S$	+10.5, *c* 1, CH_2Cl_2	31	Oil	7.98 (dd, 1H, *J* = 10.4, 2.8 Hz), 7.89 (dd, 1H, *J* = 9.2, 5.6 Hz), 7.36–7.32 (m, 1H), 7.03–6.84 (m, 5H), 5.91 (dd, 1H, *J* = 16.4, 5.2 Hz), 4.54–4.50 (m, 1H), 4.34–4.28 (m, 1H), 2.84–2.77 (m, 1H), 2.50–2.27 (m, 3H), 1.62–0.96 (m, 27H)
11i	$C_{33}H_{38}FNO_5S$	+8.9, *c* 1, $CHCl_3$	55	47–49	7.86 (d, 1H, *J* = 8.4 Hz), 7.61 (d, 1H, *J* = 2.8 Hz), 7.28 (dd, 1H, *J* = 8.4, 2.8 Hz), 7.07–6.87 (m, 5H), 5.92 (dd, 1H, *J* = 16.4, 5.6 Hz), 4.58–4.54 (m, 1H), 4.36–4.33 (m, 1H), 3.80 (s, 3H), 2.51–2.31 (m, 3H), 1.67–0.99 (m, 21H)
11j	$C_{34}H_{41}NO_6S$	+1.6, *c* 1, $CHCl_3$	58	Oil	7.85 (br, 1H), 7.60 (d, 1H, *J* = 2.8 Hz), 7.26 (dd, *J* = 9.2, 3.2), 7.11–6.59 (m, 5H), 5.94 (dd, 1H, *J* = 16.4, 5.2), 4.58–4.54 (m, 1H), 4.34–4.32 (m, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 2.49–2.29 (m, 3H), 1.64–0.99 (m, 21H)
11k	$C_{36}H_{45}NO_5S$	+1.0, *c* 1, $CHCl_3$	69	50–51	7.84 (br, 1H), 7.60 (d, 1H, *J* = 2.8 Hz), 7.25 (dd, 1H, *J* = 9.2, 2.8 Hz), 7.04–6.99 (m, 5H), 5.93 (dd, 1H, *J* = 16.4, 5.2 Hz), 4.58–4.54 (m, 1H), 4.35–4.31 (m, 1H), 3.75 (s, 3H), 2.85–2.80 (m, 1H), 2.49–2.30 (m, 3H), 1.66–1.00 (m, 27H)
11l	$C_{32}H_{34}F_3NO_4S$	+10.8, *c* 1, $CHCl_3$	75	107–109	8.08 (dd, 1H, *J* = 11.6, 8.4 Hz), 7.65 (dd, 1H, *J* = 10.8, 7.6 Hz), 7.02–6.86 (m, 5H), 5.87 (dd, 1H, *J* = 16.4, 5.2 Hz), 4.52–4.49 (m, 1H), 4.32–4.29 (m, 1H), 2.47–2.27 (m, 3H), 1.62–0.99 (m, 21H)
11m	$C_{33}H_{37}F_2NO_5S$	+5.8, *c* 1, $CHCl_3$	31	94–96	8.06 (dd, 1H, *J* = 12.0, 8.8 Hz), 7.67 (dd, 1H, *J* = 11.2, 7.6 Hz), 7.10–6.52 (m, 5H), 5.90 (dd, 1H, *J* = 16.4, 5.2 Hz), 4.54–4.48 (m, 1H), 4.31–4.26 (m, 1H), 3.67 (s, 3H), 2.48–2.25 (m, 3H), 1.59–1.01 (m, 21H)
11n	$C_{33}H_{37}F_2NO_5S$	+7.7, *c* 1, $CHCl_3$	34	132–134	8.13 (dd, 1H, *J* = 12.0, 8.8 Hz), 7.65 (dd, 1H, *J* = 11.2, 7.6 Hz), 7.04–6.72 (m, 5H), 5.89 (dd, 1H, *J* = 16.4, 5.2 Hz), 4.56–4.52 (m, 1H), 4.34–4.30 (m, 1H), 3.73 (s, 3H), 2.48–2.29 (m, 3H), 1.66–0.99 (m, 21H)
11o	$C_{35}H_{41}F_2NO_4S$	−4.0, *c* 1, $CHCl_3$	54	119–121	8.10 (dd, 1H, *J* = 12.0, 8.4 Hz), 7.64 (dd, 1H, *J* = 10.8, 7.6 Hz), 7.05–6.91 (m, 5H), 5.90 (dd, 1H, *J* = 16.0, 5.2 Hz), 4.54–4.50 (m, 1H), 4.33–4.29 (m, 1H), 2.84–2.80 (m, 1H), 2.48–2.70 (m, 3H), 1.63–1.00 (m, 27H)
11p	$C_{38}H_{38}F_3NO_4S_2$	+7.1, *c* 1, $CHCl_3$	24	120–122	7.96 (d, 1H, *J* = 10.8 Hz), 7.54–6.85 (m, 10H), 5.88 (dd, 1H, *J* = 16.4, 5.6 Hz), 4.52–4.48 (m, 1H), 4.32–4.28 (m, 1H), 2.47–2.27 (m, 3H), 1.62–0.95 (m, 21H)
11q	$C_{40}H_{44}FNO_6S_2$	+11.2, *c* 1, $CHCl_3$	13	Oil	7.95 (d, 1H, *J* = 11.2 Hz), 7.65 (d, 1H, *J* = 7.2 Hz), 7.31–6.53 (m, 9H), 5.91 (dd, 1H, *J* = 16.4, 5.2 Hz), 4.53–4.48 (m, 1H), 4.30–4.27 (m, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 2.45–2.25 (m, 3H), 1.59–0.96 (m, 21H)
11r	$C_{44}H_{52}FNO_4S_2$	+17.5, *c* 1.2, $CHCl_3$	26	Oil	7.92 (d, 1H, *J* = 11.6 Hz), 7.49–6.97 (m, 9H), 6.88 (d, 1H, *J* = 16.4 Hz), 5.87 (dd, 1H, *J* = 16.0, 5.2 Hz), 4.62–4.59 (m, 1H), 4.27–4.24 (m, 1H), 2.98–2.95 (m, 1H), 2.82–2.79 (m, 1H), 2.41–2.20 (m, 3H), 1.61–0.95 (m, 33H)

[a] The definition of R, R_1 and R_2 is the same as Table 1.

with water, dried over Na_2SO_4, concentrated to dryness. The residue was purified by silica gel column chromatography (petroleum ether–ethyl acetate, 1:1) to give **1a** (0.46 g, 61%) as a lightly yellow powder: mp 150–152 °C; $[\alpha]_D^{25} = -15.7$ (c 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, 1H, $J = 8.4$ Hz), 7.98 (d, 1H, $J = 8.4$ Hz), 7.65 (t, 1H, $J = 8.0$ Hz), 7.44 (t, 1H, $J = 8.0$ Hz), 7.10 (dd, 1H, $J = 16.4$, 1.6 Hz), 7.02–6.88 (m, 4H), 5.97 (dd, 1H, $J = 16.0$, 6.0 Hz), 5.40–5.35 (m, 1H), 4.44–4.39 (m, 1H), 2.83–2.65 (m, 2H), 2.49–2.43 (m, 1H), 2.06–1.81 (m, 3H, changed to 2H by addition of D_2O), 1.39–1.33 (m, 2H), 1.08–1.04 (m, 2H).

The other 3,5-dihydroxy-3,5-*O*-isopropylidene-6-heptenoates were converted to the corresponding pyran-2-ones in the similar method. The physical properties of **1a**–**r** are shown in Table 2.

6.12. HMG-CoA reductase inhibition assay in vitro

The HMG-CoA reductase inhibitory activity was assayed spectrophotometrically, following the method of Kleinsek et al.[7] whereby the rate of decrease in absorbance at 340 nm due to the oxidation of NADPH was measured. The standard assay mixture contained 0.1 mM HMG-CoA, 0.2 mM NADPH, 0.2 mM KCl, 4 mM EDTA, 10 mM dithiothreitol, and 160 mM potassium phosphate buffer (pH 7.0) in a total volume of 140 μL.

The reaction mixture containing the enzyme (100–150 μL) and all components except HMG-CoA were prior monitored to detect any HMG-CoA independent oxidation of NADPH.

Before bioassay, the test compounds were dissolved in 0.1 mol/L NaOH/THF (1/1) (during the process, the lactone was hydrolyzed into the sodium salt of dihydroxy acid) and diluted with the buffer. The solution obtained was added to the assay system at multiconcentration levels. The enzymatic reaction was initiated by addition of HMG-CoA. After the solution was incubated for 30 min at 37 °C, the reaction was terminated and the rate of decreased absorbance at 340 nm was measured.

Acknowledgments

The work was supported by “New Drug Innovation 2009X09301-007” by Ministry of Science and Technology of China.

References and notes

1. (a) Watanabe, M.; Koike, H.; Ishiba, T.; Okade, T.; Seo, S.; Hiri, K. *Bioorg. Med. Chem.* **1997**, *5*, 437; (b) Bratton, L. D.; Auerbach, B.; Choi, C.; Dillon, L.; Hanselman, J. C.; Larsen, S. D.; Lu, G.; Olsen, K.; Pfeferkorn, J. A.; Robertson, A.; Sekerke, C.; Unangst, P. C.; Trivedi, B. K. *Bioorg. Med. Chem.* **2007**, *15*, 5576.
2. Saito, Y.; Yamada, N.; Teramoto, T.; Itakura, H.; Hata, Y.; Nakaya, N.; Mabuchi, H.; Tushima, M.; Sasaki, J.; Ogawa, N.; Goto, Y. *Atherosclerosis* **2002**, *162*, 373.
3. (a) Sliskovic, D. R.; Picard, J. A.; Roark, W. H.; Roth, B. D.; Ferguson, E.; Krause, B. R.; Newton, R. S.; Sekerke, C.; Shaw, M. K. *J. Med. Chem.* **1991**, *34*, 367; (b) Suzuki, M.; Iwasaki, H.; Fujikawa, Y.; Sakashita, M.; Kitahara, M.; Sakoda, R. *Bioorg. Med. Chem.* **2001**, *9*, 2727.
4. (a) Zhang, Z.; Zhou, W. *Tetrahedron Lett.* **2007**, *46*, 3855; (b) Zhang, Z.; Yu, A.; Zhou, W. *Bioorg. Med. Chem.* **2007**, *15*, 7274; (c) Ma, X.; Zhou, W.; Brun, R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 986.
5. Cai, Z.; Zhou, W.; Sun, L. *Bioorg. Med. Chem.* **2007**, *15*, 7809.
6. Hormi, O. *Org. Synth.* **1993**, *Coll. Vol. 8*, 247.
7. Kleinsek, D. A.; Dugan, R. E.; Baker, T. A.; Porter, J. W. *Methods Enzymol.* **1981**, *71*, 462.
8. (a) Kuroda, M.; Endo, A. *Biochem. Biophys. Acta* **1977**, *486*, 70; (b) Kleinsek, D. A.; Ranfanathan, S.; Porter, J. W. *Proc. Natl. Acad. Sci.* **1977**, *74*, 1431; (c) Heller, R. A.; Shrewsbury, M. A. *J. Biol. Chem.* **1976**, *251*, 3815; (d) Kim, H.-J.; Lee, D.-H.; Hwang, Y.-Y.; Lee, K.-S.; Lee, J.-S. *J. Agric. Food. Chem.* **2005**, *53*, 5882.