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Synthesis and HMG CoA reductase inhibition of 4-thiophenyl quinolines as potential hypocholesterolemic agents

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Abstract—A series of novel 4-thiophenyl quinoline-based mevalonolactone derivatives were synthesized from ethyl 6,7,8-trisubstituted-4-chloro-quinoline-3-carboxylates by several reactions and evaluated for their ability to inhibit the rat 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-isopropyl-thiophenyl and 3-methoxy-thiophenyl. (4*R*,6*S*)-6-[(*E*)-2-(6,7,8-trifluoro-4-isopropylthiophenyl-quinoline-3-yl)-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (**A16**) and (4*R*, 6*S*)-6-[(*E*)-2-(6-fluoro-4,7-di-(3-methoxy-thiophenyl)-quinoline-3-yl)-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (**A23**) were approximately three times more potent than rosuvastatin or pitavastatin in inhibiting HMG CoA reductase and selected as the hypocholesterolemic candidates for further evaluation.

1. Introduction

Hypercholesterolemia is well recognized as a primary risk factor in atherosclerotic diseases and coronary heart disease. Clinical studies with lipid-lowering agents have demonstrated that decreasing elevated serum cholesterol levels reduces the incidence of cardiovascular mortality.[1] The class of drugs called statins are currently potent hepocholesterolemic agents for reducing low-density lipoprotein (LDL) particle concentration in the bloodstream by competitive inhibiting 3-hydroxy-3-methylglutaryl CoA reductase (HMG CoA reductase), a major rate-limiting enzyme in cholesterol biosynthesis.[2] Currently available statins include lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, and pitavastatin.

The structure of statins is characterized by desmethylmevalonic acid or the lactone, the pharmacophore which is connected to a lipophilic ring, such as hexahydronaphthalene, indole, pyrrole, pyrimidine, or quinoline, by a linking element (a two-carbon spacer).[3] Numerous attempts to find new potent compounds and systematical QSAR study on heteroaromatic motifs have been undertaken.[4,5] Sliskovic[6] and Suzuki[3] et al. found that some quinoline derivatives had potent inhibition on HMG CoA reductase. They disclosed the active compounds such as pitavastatin in which the desmethylmevalonic acid portion was linked through a *trans*-ethylene group to position 3 in quinoline, and a 4-fluorophenyl and 2-cyclopropyl groups were preferable substituents. 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 investigations on quinoline derivatives with pharmacological interests,[7] we made our efforts toward optimization of the inhibition on HMG CoA reductase using a quinoline as the central ring. And herein, we describe the preparation of quinoline-containing mevalonolactones (compounds **A**), 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 4 by substituted thiophenyl as a lipophilic group, and at position 6, 7, 8 by different groups, such an H, F, Cl substituted thiophenyl (see Fig. 1). The inhibition on HMG CoA reductase of these novel 4-thiophenyl quinoline derivatives will also be reported.

Keywords: HMG CoA reductase inhibitors; 4-Thiophenyl quinolines; Synthesis.
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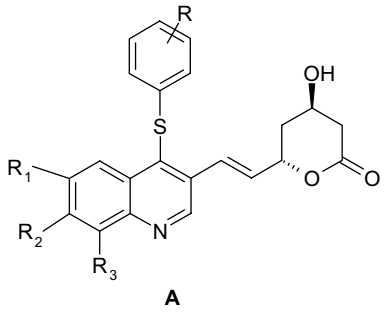


A

Figure 1.

2. Chemistry

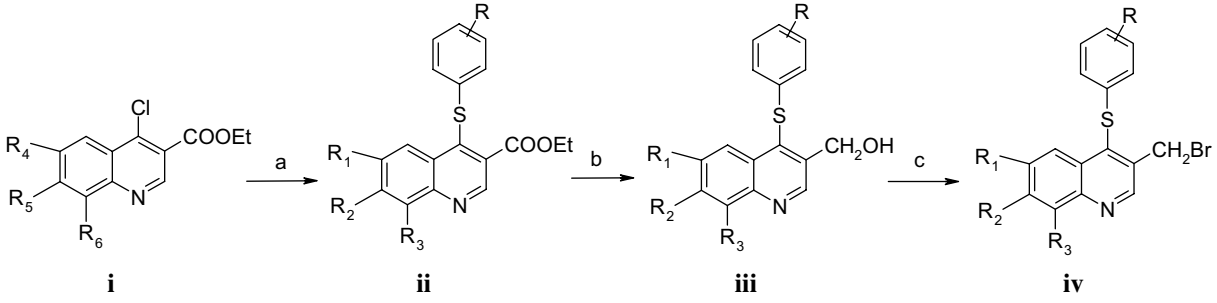
The new 4-thiophenyl quinoline derivatives (**A**) were synthesized in optically pure forms by the general method shown in Scheme 1.

The aromatic nucleophilic substitution (S_NAr) reaction of ethyl halo-quinoline-3-carboxylates (**i1**–**i4**) with thiophenol, 4-fluorothiophenol, 3-methoxythiophenol, or 4-isopropylthiophenol was highly regiospecific to afford the 4-monosubstituted (**ii1**–**ii16**), 4,7-disubstituted (**ii17**–**ii28**), 4,7,8-trisubstituted (**ii29**–**ii36**) or 4,6,7,8-tetrasubstituted (**ii36**–**ii40**) products by controlling the reaction temperature, the type and concentration of the base, the solvents as well as the ratio of the substrate to the nucleophile.[8] Characterizations of **ii1**–**ii40** are shown in Table 1.

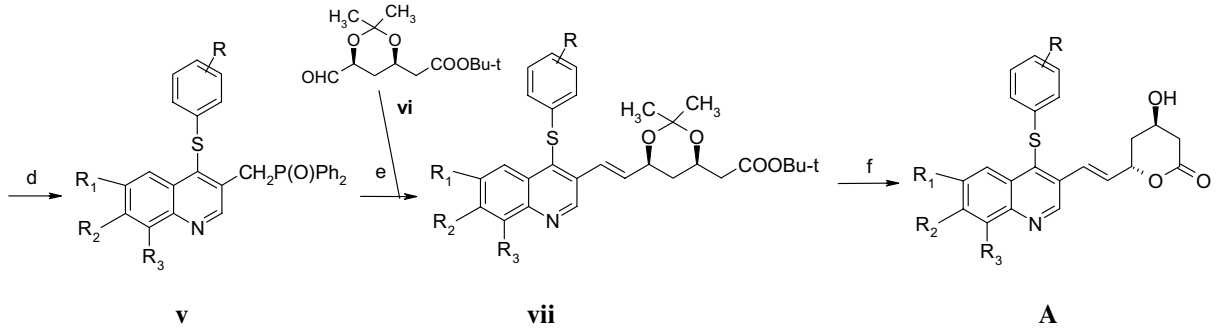
Subsequently, reduction of compounds **ii** to the alcohols **iii** was accomplished with diisobutylaluminum hydride (DIBAL-H). Bromination of the alcohols **iii** with PBr_3 afforded the bromides **iv**, which were converted to the corresponding phosphorus compounds **v** with Ph_2POEt in toluene. The olefins **vii** were generated by Wittig–Horner reaction of **v** with *tert*-butyl (3*R*,5*S*)-6-oxo-3,5-dihydroxy-3,5-*O*-isopropylidene-hexanoate (**vi**) under basic condition. The olefins **vii** were deprotected and lactonized with CF_3COOH in CH_2Cl_2 to give the target compounds **A**. Characterizations of **A1**–**A40** are shown in Table 2.

3. Bioassay

The inhibitory activity of compounds **A**, with rosuvastatin, pitavastatin, atorvastatin, and fluvastatin as the references on rat liver HMG CoA reductase, was assayed spectrophotometrically, following the method of Kleinsek[9] whereby the rate of decrease in absorbance

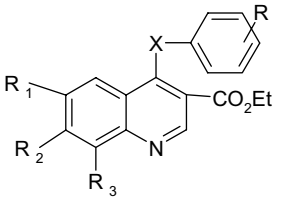


i1, R_4 = H, R_5 = H, R_6 = H
i2, R_4 = H, R_5 = Cl, R_6 = H
i3, R_4 = F, R_5 = Cl, R_6 = H
i4, R_4 = F, R_5 = F, R_6 = F



Scheme 1. Reagents and conditions: (a) substituted thiophenols, Et_3N/THF or K_2CO_3/DMF. (b) DIBAL-H, toluene, 0 (°C); (c) PBr_3, CH_2Cl_2; (d) Ph_2POEt, toluene, reflux; (e) *n*-BuLi, 2,2,6,6-tetramethyl-piperlidine, 0 (°C) rt; (f) CF_3COOH, CH_2Cl_2, 0 (°C).

Table 1. Characterization of the ethyl ester **ii1**–**ii40**



Compound	R	R_1	R_2	R_3	Yield (%)	Mp (°C)	^{1}H NMR δ ppm in $CDCl_3$
ii1	H	H	H	H	88.9	Oil	9.07 (s,1H), 8.43 (dd, 1H, *J* = 8.4, 1.2 Hz), 8.14 (d, 1H, *J* = 8.4 Hz), 7.76–7.72 (m, 1H), 7.55–7.51 (m, 1H), 7.20–7.14 (m, 5H), 4.25 (q, 2H, *J* = 7.2 Hz), 1.28 (t, 3H, *J* = 7.2 Hz)
ii2	*p*-F	H	H	H	89.9	52–4	9.05 (s,1H), 8.43 (dd, 1H, *J* = 8.6, 0.8 Hz), 8.14 (d, 1H, *J* = 8.4 Hz), 7.79–7.75 (m, 1H), 7.59–7.55 (m, 1H), 7.21 (dd, 2H,*J* = 11.8, 5.0 Hz), 6.93 (t, 2H, *J* = 6.4 Hz), 4.30 (q, 2H, *J* = 7.6 Hz), 1.33 (t, 3H, *J* = 7.2 Hz)
ii3	*m*-OCH_3	H	H	H	90.2	Oil	9.06 (s,1H), 8.43 (dd, 1H, *J* = 8.4, 1.2 Hz), 8.13 (dd, 1H, *J* = 8.8, 1.2 Hz), 7.77–7.73 (m, 1H), 7.57–7.52 (m, 1H), 7.10 (t, 1H, *J* = 8.0 Hz), 6.75–6.67 (m, 3H), 3.66 (s, 3H), 4.29 (q, 2H, *J* = 7.2 Hz), 1.31 (t, 3H, *J* = 7.2 Hz)
ii4	*p*-$CH(CH_3)_2$	H	H	H	98.0	44–6	9.03 (s,1H), 8.19 (dd, 1H, *J* = 8.4, 0.8 Hz), 8.13 (d, 1H, *J* = 8.4 Hz), 7.76–7.72 (m, 1H), 7.56–7.52 (m, 1H), 7.16–7.06 (m, 4H), 2.82 (t, 1H, *J* = 7.2 Hz), 1.18 (d, 6H, *J* = 6.8 Hz), 4.21 (q, 2H, *J* = 6.8 Hz), 1.27 (t, 3H, *J* = 6.8 Hz)
ii5	H	H	Cl	H	79.6	82–4	9.06 (s, 1H), 8.37 (d, 1H, *J* = 9.2 Hz), 8.14, (d, 1H, *J* = 2.0 Hz), 7.48 (dd, 1H, *J* = 9.2, 2.0 Hz), 7.22–7.16 (m, 5H), 4.26 (q, 2H, *J* = 7.2 Hz), 1.30 (t, 3H, *J* = 6.8 Hz)
ii6	*p*-F	H	Cl	H	97.1	91–4	9.04 (s, 1H), 8.36 (d, 1H,*J* = 9.2 Hz), 8.13 (d, 1H, *J* = 2.0 Hz), 7.50 (dd, 1H, *J* = 9.2, 2.0 Hz), 7.21–7.18 (m, 2H), 6.95–6.91 (m, 2H), 4.29 (q, 2H, *J* = 7.2 Hz), 1.32 (t, 3H, *J* = 7.2 Hz)
ii7	*m*-OCH_3	H	Cl	H	95.8	76–8	9.06 (s, 1H), 8.35 (d, 1H, *J* = 9.2 Hz), 8.12 (d, 1H, *J* = 2.0 Hz), 7.47 (dd, 1H, *J* = 9.2, 2.0 Hz), 7.11–7.09 (m, 1H), 6.74–6.70 (m, 3H), 3.68 (s, 3H), 4.29 (q, 2H, *J* = 6.8 Hz), 1.31 (t, 3H, *J* = 6.8 Hz)
ii8	*p*-$CH(CH_3)_2$	H	Cl	H	85.8	108–10	9.01 (s, 1H), 8.40 (d, 1H, *J* = 9.2 Hz), 8.11 (d, 1H, *J* = 2.0 Hz), 7.47 (dd, 1H, *J* = 9.2, 2.0 Hz), 7.14–7.07 (m,4H), 2.85–2.81 (m,1H), 1.18 (d, 6H, *J* = 6.8 Hz), 4.22 (q, 2H, *J* = 7.6 Hz), 1.28 (t, 3H, *J* = 7.2 Hz)
ii9	H	F	Cl	H	91.7	94–6	9.02 (s, 1H), 8.22 (d, 1H, *J* = 7.6 Hz), 8.14 (d, 1H, *J* = 10.4 Hz), 7.26–7.17 (m, 5H), 4.28 (q, 2H, *J* = 7.2 Hz), 1.33 (t, 3H, *J* = 7.6 Hz)
ii10	*p*-F	F	Cl	H	88.5	100–2	9.00 (s, 1H), 8.22 (d, 1H, *J* = 6.8 Hz), 8.13 (d, 1H, *J* = 10.4 Hz), 7.21 (dd, 2H, *J* = 11.8, 5.0 Hz), 6.95 (t, 2H, *J* = 7.6 Hz), 4.31 (q, 2H, *J* = 7.2 Hz), 1.33 (t, 3H, *J* = 7.6 Hz)

(*continued on next page*)

Table 1 (*continued*)

Compound	R	R_1	R_2	R_3	Yield (%)	Mp (°C)	^{1}H NMR δ ppm in $CDCl_3$
ii11	*m*-OCH_3	F	Cl	H	98.0	50–2	9.01 (s, 1H), 8.20 (d, 1H, *J* = 7.2 Hz), 8.12 (d, 1H, *J* = 10.4 Hz), 7.15–7.11 (m, 1H), 6.74–6.71 (m, 3H), 3.69 (s, 3H), 4.29 (q, 2H, *J* = 7.2 Hz), 1.28 (t, 3H, *J* = 7.6 Hz)
ii12	*p*-$CH(CH_3)_2$	F	Cl	H	89.2	116–8	8.98 (s, 1H), 8.20 (d, 1H, *J* = 7.2 Hz), 8.17 (d, 1H, *J* = 10.4 Hz), 7.15–7.09 (m, 4H), 2.84–2.86 (m, 1H), 1.20 (d, 6H, *J* = 6.8 Hz), 4.24 (q, 2H, *J* = 7.6 Hz), 1.29 (t, 3H, *J* = 7.2 Hz)
ii13	H	F	F	F	59.6	92–4	9.04 (s, 1H), 8.05–7.99 (m, 1H), 7.26–7.17 (m, 5H), 4.27 (q, 2H, *J* = 7.2 Hz), 1.29 (t, 3H, *J* = 6.4 Hz)
ii14	*p*-F	F	F	F	60.0	126–8	9.04 (s, 1H), 8.05–8.00 (m, 1H), 7.24–7.20 (m, 2H), 6.99–6.94 (m, 2H), 4.30 (q, 2H, *J* = 7.2 Hz), 1.32 (t, 3H, *J* = 7.2 Hz)
ii15	*m*-OCH_3	F	F	F	55.8	70–2	9.07 (s, 1H), 8.06–8.01 (m, 1H), 7.16 (t, 1H, *J* = 8.0 Hz), 6.77–6.72 (m, 3H), 3.72 (s, 3H), 4.31 (q, 2H, *J* = 7.2 Hz), 1.32 (t, 3H, *J* = 6.8 Hz)
ii16	*p*-$CH(CH_3)_2$	F	F	F	52.4	86–8	9.01 (s,1H), 8.08–8.03 (m, 1H), 7.15–7.10 (m,4H), 2.86–2.83 (m,1H), 1.19 (d, 6H, *J* = 6.8 Hz), 4.23 (q, 2H, *J* = 7.2 Hz), 1.28 (t, 3H, *J* = 7.2 Hz)
ii17	H	H	SC_6H_5	H	80.0	98–100	8.98 (s,1H), 8.29 (d, 1H, *J* = 9.2 Hz), 7.76 (d, 1H, *J* = 1.6 Hz), 7.34 (dd, 1H, *J* = 8.8, 1.6 Hz), 7.56–7.54 (m, 2H), 7.42–7.40 (m, 3H), 7.22–7.15 (m, 5H), 4.24 (q, 2H, *J* = 7.2 Hz), 1.28 (t, 3H, *J* = 7.6 Hz)
ii18	*p*-F	H	SC_6H_4-4-F	H	91.2	68–70	8.96 (s, 1H), 8.28 (d, 1H, *J* = 9.2 Hz), 7.66 (s, 1H), 7.56 (dd, 1H, *J* = 8.8, 5.6 Hz), 7.56 (dd, 2H, *J* = 10.0, 5.2 Hz), 7.20–7.10 (m, 4H), 6.91 (t, 2H, *J* = 7.4 Hz), 4.27 (q, 2H, *J* = 7.2 Hz), 1.30 (t, 3H, *J* = 7.2 Hz)
ii19	*m*-OCH_3	H	SC_6H_4-3-OCH_3	H	88.1	Oil	8.99 (s, 1H), 8.29 (d, 1H, *J* = 9.2 Hz), 7.80 (d, 1H, *J* = 2.0 Hz), 7.36 (dd, 1H, *J* = 8.8, 2.0 Hz), 7.31 (t, 1H, *J* = 8.0 Hz),7.14–7.07 (m, 3H), 6.95–6.92 (m,1H), 6.73–6.68 (m,3H), 3.78 (s, 3H), 3.68 (s, 3H), 4.27 (q, 2H, *J* = 7.2 Hz), 1.30 (t, 3H, *J* = 7.2 Hz)
ii20	*p*-$CH(CH_3)_2$	H	SC_6H_4-4-$CH(CH_3)_2$	H	93.0	Oil	8.93 (s, 1H), 8.32 (d, 1H, *J* = 8.8 Hz), 7.71 (s, 1H), 7.34 (dd, 1H, *J* = 9.2, 1.6 Hz), 7.49 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.4 Hz), 7.12–7.06 (m, 4H), 4.11 (q, 2H, *J* = 6.8), 2.95 (m,1H), 2.83 (m, 1H), 1.31–1.14 (m, 15H)
ii21	H	F	SC_6H_5	H	65.3	Oil	8.90 (s, 1H), 8.02 (d, 1H, *J* = 11.2 Hz), 7.53 (d, 1H, *J* = 8.0 Hz), 7.60–7.57 (m, 2H), 7.46–7.44 (m, 3H), 7.25–7.15 (m, 5H), 4.25 (q, 2H, *J* = 6.8 Hz), 1.27 (t, 3H, *J* = 7.2 Hz)
ii22	*p*-F	F	SC_6H_4-4-F	H	89.0	146–8	8.89 (s, 1H), 8.02 (d, 1H, *J* = 10.8 Hz), 7.45 (d, 1H, *J* = 7.2 Hz), 7.59 (dd, 2H, *J* = 7.0, 5.2 Hz), 7.22–7.15 (m, 4H), 6.94 (t, 2H, *J* = 7.6 Hz), 4.28 (q, 2H, *J* = 7.2 Hz), 1.31 (t, 3H, *J* = 6.8 Hz)

ii23	*m*-OCH_3	F	SC_6H_4-3-OCH_3	H	60.0	Oil	8.92 (s, 1H), 8.02 (d, 1H, *J* = 11.2 Hz), 7.56 (d, 1H, *J* = 7.6 Hz), 7.36 (t, 1H, *J* = 8.0 Hz), 7.17–7.01 (m, 3H), 7.00–6.97 (m, 1H), 6.74–6.70 (m, 3H), 3.80 (s, 3H), 3.69 (s, 3H), 4.27 (q, 2H, *J* = 7.2 Hz), 1.27 (t, 3H, *J* = 6.8 Hz)
ii24	*p*-$CH(CH_3)_2$	F	SC_6H_4-4-$CH(CH_3)_2$	H	77.7	88–90	8.86 (s, 1H), 8.05 (d, 1H, *J* = 11.2 Hz), 7.53–7.50 (m, 3H), 7.32 (d, 2H, *J* = 8.0 Hz), 7.13–7.08 (m, 4H), 2.97 (t, 1H, *J* = 6.8 Hz), 2.84 (t, 1H, *J* = 6.8 Hz), 1.30 (d, 6H, *J* = 7.2 Hz),1.20 (d, 6H, *J* = 6.8 Hz), 4.22 (q, 2H, *J* = 7.2 Hz), 1.26 (t, 3H, *J* = 7.2 Hz)
ii25	H	F	SC_6H_5	F	65.3	82–4	9.01 (s, 1H), 7.93 (dd, 1H, *J* = 10.2, 2.0 Hz), 7.39–7.37 (m, 2H), 7.28–7.19 (m, 8H), 4.25 (q, 2H, *J* = 7.2 Hz), 1.29 (t, 3H, *J* = 6.8 Hz)
ii26	*p*-F	F	SC_6H_4-4-F	F	52.6	114–6	8.99 (s, 1H), 7.91 (dd, 1H, *J* = 9.0, 2.0 Hz), 7.46 (dd, 2H, *J* = 8.6, 5.2 Hz), 7.23 (dd, 2H, *J* = 8.6, 4.8 Hz), 7.00–6.94 (m, 4H), 4.28 (q, 2H, *J* = 7.2 Hz), 1.31 (t, 3H, *J* = 6.8 Hz)
ii27	*m*-OCH_3	F	SC_6H_4-3-OCH_3	F	60.0	Oil	9.02 (s, 1H), 7.93 (dd, 1H, *J* = 10.2, 1.2 Hz), 7.18–7.13 (m, 2H), 6.94–6.91 (m, 2H), 6.78–6.73 (m, 4H), 3.73 (s, 3H), 3.71 (s, 3H), 4.28 (q, 2H, *J* = 7.6), 1.31 (t, 3H, *J* = 7.2)
ii28	*p*-$CH(CH_3)_2$	F	SC_6H_4-4-$CH(CH_3)_2$	F	50.0	75–7	8.97 (s, 1H), 7.94 (dd, 1H, *J* = 10.4, 2.0 Hz), 7.35 (d, 2H, *J* = 8.0), 7.16–7.09 (m, 6H), 4.21 (q, 2H, *J* = 7.6), 2.88–2.83 (m, 2H), 1.29–1.19 (m, 15H)
ii29	H	SC_6H_5	SC_6H_5	H	90.2	110–3	9.10 (s, 1H), 7.92 (s, 1H), 7.88 (s, 1H), 7.59–7.53 (m, 5H), 7.43–7.40 (m, 5H), 7.18 (d, 3H, *J* = 7.6 Hz), 6.88 (d, 2H, *J* = 7.6 Hz), 4.29 (q, 2H, *J* = 6.8 Hz), 1.27 (t, 3H, *J* = 7.2 Hz)
ii30	*p*-F	SC_6H_4-4-F	SC_6H_4-4-F	H	88.0	118–22	8.87 (s, 1H), 7.97 (s, 1H), 7.44 (s, 1H), 7.55 (dd, 2H, *J* = 7.0, 5.2 Hz), 7.34 (dd, 2H, *J* = 6.8, 5.2 Hz), 7.15 (t, 2H, *J* = 6.8 Hz), 7.04 (t, 2H, *J* = 8.4 Hz), 6.94 (dd, 2H, *J* = 7.0, 4.4 Hz), 6.85 (t, 2H, *J* = 8.4 Hz), 4.30 (q, 2H, *J* = 6.8 Hz), 1.31 (t, 3H, *J* = 7.2 Hz)
ii31	*m*-OCH_3	SC_6H_4-3-OCH_3	SC_6H_4-3-OCH_3	H	62.0	Oil	8.89 (s, 1H), 8.18 (s, 1H), 7.57 (s, 1H), 7.34 (t, 1H, *J* = 8.0 Hz), 7.24–7.20 (m, 1H), 7.15–7.12 (m, 1H), 7.09 (t, 1H, *J* = 2.0 Hz), 7.03 (t, 1H, *J* = 8.0 Hz), 7.00–6.95 (m, 1H), 6.88–6.85 (m, 3H), 6.66–6.63 (m, 1H), 6.56 (t, 1H, *J* = 1.6 Hz), 6.53–6.50 (m, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.66 (s, 3H), 4.30 (q, 2H, *J* = 6.8 Hz), 1.31 (t, 3H, *J* = 7.2 Hz)
ii32	*p*-$CH(CH_3)_2$	SC_6H_4-4-$CH(CH_3)_2$	SC_6H_4-4-$CH(CH_3)_2$	H	83.5	Oil	8.74 (s, 1H), 7.98 (s, 1H), 7.58 (s, 1H), 7.51 (d, 2H, *J* = 8.0 Hz), 7.30 (d, 4H, *J* = 8.4 Hz), 7.19 (d, 2H, *J* = 8.4 Hz), 7.01 (d, 2H, *J* = 8.4 Hz), 7.76 (d, 2H, *J* = 8.0 Hz), 2.97–2.92 (m, 2H), 2.84–2.81 (m, 1H), 4.27 (q, 2H, *J* = 7.2 Hz), 1.27 (t, 3H, *J* = 6.8 Hz)
ii33	H	F	SC_6H_5	SC_6H_5	69.1	128–30	9.05 (s, 1H), 8.14 (d, 1H, *J* = 10.8 Hz), 7.26–7.11 (m, 15H), 4.23 (q, 2H, *J* = 6.8 Hz), 1.26 (t, 3H, *J* = 7.2 Hz)
ii34	*p*-F	F	SC_6H_4-4-F	SC_6H_4-4-F	89.3	80–3	9.03 (s, 1H), 8.11 (d, 1H, *J* = 10.4 Hz), 7.28–7.21 (m, 6H), 6.97–6.87 (m, 6H), 4.26 (q, 2H, *J* = 6.8 Hz), 1.26 (t, 3H, *J* = 7.2 Hz)
ii35	*m*-OCH_3	F	SC_6H_4-3-OCH_3	SC_6H_4-3-OCH_3	60.3	104–6	9.07 (s, 1H), 8.14 (d, 1H, *J* = 10.4 Hz), 7.17 (m, 3H), 6.82–6.64 (m, 9H), 3.72 (s, 3H), 3.70 (s, 3H), 3.69 (s, 3H), 4.27 (q, 2H, *J* = 6.8 Hz), 1.29 (t, 3H, *J* = 6.8 Hz)

(*continued on next page*)

Table 1 (*continued*)

Compound	R	R_1	R_2	R_3	Yield (%)	Mp (°C)	^{1}H NMR δ ppm in $CDCl_3$
ii36	*p*-$CH(CH_3)_2$	F	SC_6H_4-4-$CH(CH_3)_2$	SC_6H_4-4-$CH(CH_3)_2$	65.8	Oil	9.04 (s, 1H), 8.14 (d, 1H, *J* = 11.2 Hz), 7.18–7.02 (m, 12H), 4.20 (q, 2H, *J* = 6.8 Hz), 2.88–2.81 (m,3H), 1.33–1.15 (m, 21H)
ii37	H	SC_6H_5	SC_6H_5	SC_6H_5	98.0	91–3	8.90 (s, 1H), 7.88 (s, 1H), 7.52–7.40 (m, 5H), 7.30–7.04 (m, 13H), 6.85–6.83 (m, 2H), 4.25 (q, 2H, *J* = 6.8 Hz), 1.27 (t, 3H, *J* = 6.8 Hz)
ii38	*p*-F	SC_6H_4-4-F	SC_6H_4-4-F	SC_6H_4-4-F	90.2	126–8	8.87 (s, 1H), 7.72 (s, 1H), 7.40 (dd, 2H, *J* = 9.8, 5.2 Hz), 7.19 (dd, 2H, *J* = 8.4, 5.2 Hz), 7.14–7.10 (m, 4H), 6.93–6.80 (m, 8H), 4.27 (q, 2H, *J* = 7.6 Hz), 1.27 (t, 3H, *J* = 7.2 Hz)
ii39	*m*-OCH_3	SC_6H_4-3-OCH_3	SC_6H_4-3-OCH_3	SC_6H_4-3-OCH_3	76.9	Oil	8.92 (s, 1H), 7.95 (s, 1H), 7.29 (t, 1H, *J* = 8.0 Hz), 7.09 (t, 1H, *J* = 7.6 Hz), 7.05–6.94 (m, 5H),6.73–6.58 (m, 7H), 6.44–6.37 (m, 2H), 3.76 (m, 3H), 3.67 (s, 3H), 3.65 (s, 3H), 3.64 (s, 3H), 4.26 (q, 2H, *J* = 6.8 Hz), 1.27 (t, 3H, *J* = 7.2 Hz)
ii40	*p*-$CH(CH_3)_2$	SC_6H_4-4-$CH(CH_3)_2$	SC_6H_4-4-$CH(CH_3)_2$	SC_6H_4-4-$CH(CH_3)_2$	84.3	Oil	8.86 (s,1H), 7.82 (s, 1H), 7.34–7.25 (m, 4H), 7.13–7.10 (m, 2H), 7.06–6.95 (m, 8H), 6.77–6.75 (m, 2H), 3.00–2.97 (m, 1H), 2.85–2.76 (m, 3H), 1.34–1.16 (m, 24H), 4.20 (q, 2H, *J* = 6.8 Hz), 0.86 (t, 3H, *J* = 5.2 Hz)

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.[10–13]

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 19 compounds **A**) giving less than 80% of decreased absorbance would go to the secondary screening (IC_{50} determination).

3.2. IC_{50} determination

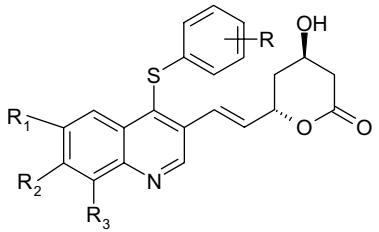
The concentration of an inhibitor required to inhibit 50% of the HMG CoA reductase under the above assay conditions was defined as IC_{50}. The UV absorbance was measured in eight levels (5×10^{-4} M, 1×10^{-4} M, 5×10^{-5} M, 1×10^{-5} M, 5×10^{-6}M, 1×10^{-6} M, 5×10^{-7} M and 1×10^{-7} M at final 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

(1) Effects of modification of 4-position. For known pitavastatin analogues, a phenyl group is connected at position 4 in the quinoline and it is located in the *ortho* to the pharmacophore group at position 3. This substitution pattern is also found in other artificial HMG CoA inhibitors such as fluvastatin, atorvastatin, and rosuvastatin which belong to the indole, pyrrole and pyrimidine derivatives, respectively. The 4-thiophenyl, 4-(4-fluoro-thiophenyl), 4-(3-methoxy-thiophenyl) or 4-(4-isopropyl-thiophenyl)-quinolines were first disclosed in this paper and among them, 19 novel compounds were found to possess good or moderate inhibition on HMG CoA reductase. In particular, 14 compounds displayed the activity better than or equivalent to that of fluvastatin. And the inhibition of five compounds: **A16**, **A23**, **A40**, **A21**, and **A14** was more potent than that of rosuvastatin.
It was known that the preferable group at position 4 in pitavastatin analogues was 4-fluorophenyl. Surprisingly, 4-isopropyl-thiophenyl or 3-methoxy-thiophenyl group was found to be superior to 4-fluorothiophenyl (**A16** vs **A14**, **A4** vs **A2**, and **A12** vs **A10**; **A11** vs **A10**, **A23** vs **A22**, **A27** vs **A26** and **A31** vs **A30**) in the thiophenyl quinolines.

(2) Effects of modification of R_2. The early report showed that replacement of H by some small groups, e.g. Cl or OCH_3, might enhance the activity in the 4-fluorophenyl-quinolines.[3] The present work demonstrated that introduction of the bulky group

Table 2. Characterization of the target compounds A1–40[a]



Compound	$[a]_D^{25}$	Yield (%)	Mp (°C)	Formula MS EI^+ (M+1)	^1H NMR δ ppm in $CDCl_3$
A1	+26.7, *c* 0.94, CH_2Cl_2	91.7	102–4	$C_{22}H_{19}NO_3S$ 378	9.29 (s, 1H), 8.38 (d, 1H, *J* = 8.4 Hz), 8.09 (d, 1H, *J* = 7.6 Hz), 7.80–7.75 (m, 1H), 7.67–7.63 (m, 1H), 7.32 (dd, 1H, *J* = 16.4, 1.2 Hz), 7.24 (t, 2H, *J* = 7.6 Hz), 7.17 (t, 1H, *J* = 7.2 Hz), 7.08–7.06 (m, 2H), 6.75 (dd, 1H, *J* = 16.0, 6.0 Hz), 5.31–5.26 (m, 1H), 4.15–4.12 (m, 1H), 2.71–2.42 (m, 2H), 1.95–1.77 (m, 2H)
A2	+28.9, *c* 0.47, CH_2Cl_2	82.2	130–2	$C_{22}H_{18}FNO_3S$ 396	9.08 (s, 1H), 8.46 (d, 1H, *J* = 8.0 Hz), 8.11 (d, 1H, *J* = 8.4 Hz), 7.73–7.69 (m, 1H), 7.76 (t, 1H, *J* = 7.2 Hz), 7.40 (dd, 1H, *J* = 16.2, 1.2 Hz), 7.08–7.04 (m, 2H), 6.91–6.87 (m, 2H), 6.34, (dd, 1H, *J* = 16.0, 6.0 Hz), 5.38–5.34 (m, 1H), 4.42–4.39 (m, 1H), 2.80–2.63 (m, 2H), 2.07–1.83 (m, 2H)
A3	+24.2, *c* 0.88, CH_2Cl_2	95.6	132–5	$C_{23}H_{21}NO_4S$ 408	9.09 (s, 1H), 8.47 (d, 1H, *J* = 8.4 Hz), 8.11 (d, 1H, *J* = 8.8 Hz), 7.71 (t, 1H, *J* = 7.6 Hz), 7.56 (t, 1H, *J* = 8.0 Hz), 7.37 (d, 1H, *J* = 16.4 Hz), 7.07 (t, 1H, *J* = 8.0 Hz), 6.67–6.57 (m, 3H), 6.34, (dd, 1H, *J* = 16.2, 5.6 Hz), 5.36–5.33 (m, 1H), 4.35–4.33 (m, 1H), 3.68 (s, 3H), 2.77–2.61 (m, 2H), 2.03–1.82 (m, 2H)
A4	+28.9, *c* 0.84, CH_2Cl_2	37.8	147–8	$C_{25}H_{25}NO_3S$ 420	9.09 (s, 1H), 8.51 (d, 1H, *J* = 8.4 Hz), 8.12 (d, 1H, *J* = 8.0 Hz), 7.71 (t, 1H, *J* = 8.0 Hz), 7.56 (t, 1H, *J* = 8.0 Hz), 7.41 (d, 1H, *J* = 16.8 Hz), 7.06–7.00 (m, 4H), 6.33 (dd, 1H, *J* = 16.4, 6.0 Hz), 5.34 (s, 1H), 4.36 (s, 1H), 2.85–2.74 (m, 1H), 2.72–2.63 (m, 2H), 2.02–1.82 (m, 2H), 1.18 (d, 6H, *J* = 6.8 Hz)
A5	+25.0, *c* 1, CH_2Cl_2	48.7	158–9	$C_{22}H_{18}ClNO_3S$ 412	9.07 (s, 1H), 8.38 (d, 1H, *J* = 9.2 Hz), 8.09 (d, 1H, *J* = 2.0 Hz), 7.48 (dd, 1H, *J* = 9.2, 2.4 Hz), 7.34 (dd, 1H, *J* = 16.4, 1.6 Hz), 7.20–7.01 (m, 5H),6.34 (dd, 1H, *J* = 16.4, 6.0 Hz), 5.37–5.32 (m, 1H), 4.37–4.33 (m, 1H), 2.76–2.62 (m, 2H), 2.05–1.78 (m, 2H)
A6	+21.1, *c* 1, CH_2Cl_2	48.7	179–81	$C_{22}H_{17}ClFNO_3S$ 430	9.06 (s, 1H), 8.38 (d, 1H, *J* = 8.8 Hz), 8.09 (d, 1H, *J* = 2.0 Hz), 7.50 (dd, 1H, *J* = 9.2, 2.0 Hz), 7.37 (dd, 1H, *J* = 16.0, 0.8 Hz), 7.07–7.03 (m, 2H),6.93–6.88 (m, 2H), 6.34 (dd, 1H, *J* = 15.8, 5.6 Hz), 5.39–5.34 (m, 1H), 4.42–4.38 (m, 1H), 2.79–2.64 (m, 2H), 2.09–1.81 (m, 2H)
A7	+22.3, *c* 1, CH_2Cl_2	57.5	140–2	$C_{23}H_{20}ClNO_4S$ 442	9.07 (s, 1H), 8.38 (d, 1H, *J* = 9.2 Hz), 8.09 (d, 1H, *J* = 1.6 Hz), 7.49 (dd, 1H, *J* = 9.2, 2.0 Hz), 7.34 (dd, 1H, *J* = 16.0, 0.8 Hz), 7.08 (t, 1H, *J* = 8.0 Hz), 6.68–6.55 (m, 3H), 6.34 (dd, 1H, *J* = 16.4, 6.0 Hz), 5.37–5.32 (m, 1H), 4.34–4.32 (m, 1H), 3.69 (s, 3H), 2.76–2.62 (m, 2H), 2.05–1.79 (m, 2H)
A8	+14.1, *c* 1, CH_2Cl_2	41.0	170	$C_{25}H_{24}ClNO_3S$ 454	9.07 (s, 1H), 8.42 (d, 1H, *J* = 8.8 Hz), 8.10 (d, 1H, *J* = 2.0 Hz), 7.49 (dd, 1H, *J* = 8.8, 2.0 Hz), 7.37 (dd, 1H, *J* = 16.0, 0.8 Hz), 7.06–6.96 (m,4H), 6.33 (dd, 1H, *J* = 16.4, 6.0 Hz), 5.36–5.32 (m, 1H), 4.38–4.35 (m, 1H), 2.85–2.80 (m,1H), 2.78–2.62 (m, 2H), 2.04–1.79 (m, 2H), 1.18 (d, 6H, *J* = 6.8 Hz)
A9	+18.3, *c* 1, $CHCl_3$	63.0	172–4	$C_{22}H_{17}ClFNO_3S$ 430	9.05 (s, 1H), 8.19–8.15 (m, 2H), 7.35 (dd, 1H, *J* = 16.0, 1.2 Hz), 7.22–7.15 (m, 3H), 7.05–7.02 (m, 2H), 6.36 (dd, 1H, *J* = 16.2, 6.0 Hz), 5.37–5.32 (m, 1H), 4.37–4.33 (m, 1H), 2.77–2.61 (m, 2H), 2.05–1.79 (m, 2H)

(*continued on next page*)

Table 2 (*continued*)

Compound	$[a]_D^{25}$	Yield (%)	Mp (°C)	Formula MS EI^+ (M+1)	^1H NMR δ ppm in $CDCl_3$
A10	+25.1, *c* 1, CH_2Cl_2	75.0	192–4	$C_{22}H_{16}ClF_2NO_3S$ 448	9.03 (s, 1H), 8.19–8.15 (m, 2H), 7.37 (dd, 1H, *J* = 16.6, 0.8 Hz), 7.08–7.03 (m, 2H), 6.95–6.90 (m, 2H), 6.36 (dd, 1H, *J* = 16.2, 5.6 Hz), 5.39–5.35 (m, 1H), 4.42–4.40 (m, 1H), 2.79–2.64 (m, 2H), 2.09–1.80 (m, 2H)
A11	+21.1, *c* 1, CH_2Cl_2	62.2	150–3	$C_{23}H_{19}ClFNO_4S$ 460	9.04 (s, 1H), 8.19–8.15 (m, 2H), 7.34 (dd, 1H, *J* = 16.4, 1.2 Hz), 7.10 (t, 1H, *J* = 8.0 Hz), 6.70–6.67 (m, 1H), 6.61–6.56 (m, 2H), 6.36 (dd, 1H, *J* = 16.2, 5.6 Hz), 5.37–5.33 (m, 1H), 4.37–4.33 (m, 1H), 3.71 (s, 3H), 2.77–2.61 (m, 2H), 2.05–1.80 (m, 2H)
A12	+16.2, *c* 1, CH_2Cl_2	63.7	175–7	$C_{25}H_{23}ClFNO_3S$ 472	9.02 (s, 1H), 8.19–8.15 (m, 2H), 7.37 (d, 1H, *J* = 16.8 Hz), 7.06 (d,2H, *J* = 8.4 Hz), 6.96 (d,2H, *J* = 8.8 Hz), 6.35 (dd, 1H, *J* = 16.4, 6.0 Hz), 5.38–5.33 (m, 1H), 4.39–4.36 (m, 1H), 2.85–2.78 (m,1H), 2.72–2.62 (m, 2H), 2.04–1.78 (m, 2H), 1.18 (d, 6H, *J* = 7.2 Hz)
A13	+27.7, *c* 1, CH_2Cl_2	81.4	177–8	$C_{22}H_{16}F_3NO_3S$ 432	9.08 (s, 1H), 8.08–8.03 (m, 1H), 7.35 (dd, 1H, *J* = 16.4, 1.6 Hz), 7.23–7.14 (m, 3H), 7.04–7.02 (m, 2H), 6.36 (dd, 1H, *J* = 16.0, 5.6 Hz), 5.37–5.32 (m, 1H), 4.37–4.35 (m, 1H), 2.76–2.62 (m, 2H), 2.05–1.77 (m, 2H)
A14	+26.2, *c* 1, CH_2Cl_2	50.9	183–5	$C_{22}H_{15}F_4NO_3S$ 450	9.07 (s, 1H), 8.08–8.03 (m, 1H), 7.36 (d, 1H, *J* = 16.4 Hz), 7.09–7.05 (m,2H), 6.95–6.91 (m,2H), 6.36 (dd, 1H, *J* = 16.4, 6.0 Hz), 5.40–5.35 (m, 1H), 4.41 (s, 1H), 2.79–2.65 (m, 2H), 2.08–1.79 (m, 2H)
A15	+25.5, *c* 0.6, CH_2Cl_2	54.7	168–70	$C_{23}H_{18}F_3NO_4S$ 462	9.08 (s, 1H), 8.08–8.03 (m, 1H),7.33 (dd, 1H, *J* = 16.0, 1.2 Hz), 7.11 (t, 1H, *J* = 8.0 Hz), 6.72–6.55 (m, 3H), 6.36 (dd, 1H, *J* = 16.4, 6.0 Hz), 5.38–5.33 (m, 1H), 4.37–4.35 (m, 1H), 3.71 (s, 3H), 2.77–2.62 (m, 2H), 2.06–1.79 (m, 2H)
A16	+18.7, *c* 1, CH_2Cl_2	62.0	169–71	$C_{25}H_{22}F_3NO_3S$ 474	9.08 (s, 1H), 8.11–8.06 (m, 1H), 7.37 (d, 1H, *J* = 16.4 Hz), 7.09–7.00 (m,4H), 6.35, (dd, 1H, *J* = 16.0, 5.6 Hz), 5.37–5.32 (m, 1H), 4.39–4.36 (m, 1H), 2.86–2.79 (m,1H), 2.78–2.62 (m, 2H), 2.03–2.78 (m, 2H), 1.22–1.18 (m, 6H)
A17	+17.8, *c* 0.8, CH_2Cl_2	64.6	138–40	$C_{28}H_{23}NO_3S_2$ 486	9.00 (s, 1H), 8.32 (d, 1H, *J* = 8.8 Hz), 7.80 (s, 1H), 7.55–7.52 (m, 1H), 7.41–7.31 (m, 6H), 7.19–7.01 (m, 5H), 6.29 (dd, 1H, *J* = 16.2, 6.4 Hz), 5.33–5.29 (m, 1H), 4.33–4.31 (m, 1H), 2.75–2.59 (m, 2H), 2.01–1.78 (m, 2H)
A18	+12.2, *c* 0.97, CH_2Cl_2	75.9	140–2	$C_{30}H_{27}NO_5S_2$ 522	9.00 (s, 1H), 8.31 (d, 1H, *J* = 9.2 Hz), 7.69 (d, 1H, *J* = 1.6 Hz), 7.56–7.53 (m, 2H),7.36–7.32 (m, 2H), 7.13–7.19 (m, 2H), 7.05–7.02 (m, 2H), 6.91–6.86 (m, 2H), 6.29 (dd, 1H, *J* = 16.2, 6.4 Hz), 5.36–5.32 (m, 1H), 4.383 (m, 1H), 2.78–2.62 (m, 2H), 2.08–1.80 (m, 2H)
A19	+15.9, *c* 1, CH_2Cl_2	52.8	48–51	$C_{30}H_{27}NO_5S_2$ 546	9.01 (s, 1H), 8.33 (d, 1H, *J* = 8.8 Hz), 7.84 (d, 1H, *J* = 2.0 Hz), 7.40 (dd, 1H, *J* = 8.8, 2.0 Hz), 7.34–7.26 (m, 2H), 7.12–7.05 (m, 3H), 6.93–6.90 (m, 1H), 6.68–6.56 (m, 3H), 6.30 (dd, 1H, *J* = 16.2, 6.0 Hz),5.35–5.30 (m, 1H), 4.34–4.323 (m, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 2.76–2.60 (m, 2H), 2.03–1.80 (m, 2H)

A20	+7.4, *c* 1, CH_2Cl_2	66.5	109–12	$C_{34}H_{35}NO_3S_2$ 570	9.01 (s, 1H), 8.37 (d, 1H, *J* = 8.8 Hz), 7.78 (d, 1H, *J* = 1.6 Hz), 7.40 (dd, 1H, *J* = 6.6, 2.0 Hz), 7.51 (d, 2H, *J* = 8.4 Hz), 7.35–7.28 (m, 2H), 7.08–6.98 (m, 4H), 6.31 (dd, 1H, *J* = 16.2, 6.0 Hz), 5.35–5.32 (m, 1H), 4.373 (s, 1H), 2.99–2.95 (m,1H), 2.85–2.80 (m, 1H), 2.79–2.62 (m, 2H), 2.03–1.82 (m, 2H), 1.31 (d, 6H, *J* = 7.2 Hz), 1.20 (d, 6H, *J* = 7.2 Hz)
A21	+8.0, *c* 0.8, CH_2Cl_2	82.2	92–4	$C_{28}H_{22}FNO_3S_2$ 504	8.93 (s, 1H),8.06 (d, 1H, *J* = 11.2 Hz), 7.60–7.56 (m, 3H), 7.45–7.42 (m, 2H), 7.32 (dd, 1H, *J* = 16.8, 1.6 Hz), 7.21–7.11 (m, 3H), 7.04–7.01 (m, 2H), 6.30 (dd, 1H, *J* = 16.4, 6.0 Hz), 5.34–5.29 (m, 1H), 4.33–4.31 (m, 1H), 2.74–2.59 (m, 2H), 2.05–1.77 (m, 2H)
A22	+2.4, *c* 1, CH_2Cl_2	67.0	128–30	$C_{28}H_{20}F_3NO_3S_2$ 540	8.92 (s, 1H), 8.04 (d, 1H, *J* = 11.2 Hz), 7.49 (d, 1H, *J* = 7.6 Hz), 7.33 (dd, 1H, *J* = 16.0, 0.8 Hz), 7.60–7.56 (m, 2H), 7.17–7.13 (m, 2H), 7.07–7.03 (m, 2H), 6.93–6.88 (m, 2H), 6.30 (dd, 1H, *J* = 16.0, 5.6 Hz), 5.36–5.32 (m, 1H), 4.38–4.36 (m, 1H), 2.77–2.67 (m, 2H), 2.05–1.79 (m, 2H)
A23	+6.0, *c* 1, CH_2Cl_2	67.9	133–4	$C_{30}H_{26}FNO_5S_2$ 564	8.93 (s, 1H), 8.06 (d, 1H, *J* = 11.2 Hz), 7.36–7.29 (m, 2H), 7.16–7.07 (m, 3H), 6.98–6.95 (m, 1H), 6.69–6.67 (m, 1H), 6.60–6.56 (m, 2H), 6.30 (dd, 1H, *J* = 16.0, 5.6 Hz), 5.34–5.30 (m, 1H), 4.33–4.31 (m, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 2.75–2.59 (m, 2H), 2.02–1.79 (m, 2H)
A24	+2.9, *c* 1, CH_2Cl_2	45.8	134–6	$C_{34}H_{34}FNO_3S_2$ 588	8.91 (s, 1H), 8.06 (d, 1H, *J* = 11.2 Hz),7.55–7.50 (m, 3H), 7.36–7.25 (m, 3H),7.07–6.95 (m, 4H), 6.29 (dd, 1H, *J* = 16.4, 6.4 Hz),5.34–5.29 (m, 1H), 4.35–4.33 (m, 1H),2.75–2.59 (m, 2H), 3.00–2.93 (m, 1H), 2.85–2.78 (m, 1H), 2.03–1.78 (m, 2H), 1.30 (d, 6H, *J* = 6.4 Hz), 1.18 (d, 6H, *J* = 6.4 Hz)
A25	+ 23.7, *c* 1, CH_2Cl_2	59.8	186–8	$C_{28}H_{21}F_2NO_3S_2$ 522	9.06 (s, 1H), 7 .98 (dd, 1H, *J* = 10.0, 1.2 Hz), 7.39–7.32 (m, 3H), 7.28–7.14 (m, 6H), 7.06–7.04 (m, 2H), 6.38 (dd, 1H, *J* = 16.0, 5.6 Hz), 5.37–5.32 (m, 1H), 4.36–4.34 (m, 1H), 2.76–2.61 (m, 2H), 2.06–1.76 (m, 2H)
A26	+ 20.4, *c* 1, CH_2Cl_2	64.2	156–8	$C_{28}H_{19}F_4NO_3S_2$ 558	9.04 (s, 1H), 7.95 (dd, 1H, *J* = 10.0, 2.0 Hz), 7.35 (dd, 1H, *J* = 16.4, 1.2 Hz), 7.47–7.44 (m, 2H), 7.09–7.05 (m, 2H), 7.00–6.90 (m, 4H), 7.37 (dd, 1H, *J* = 16.4, 5.6 Hz), 5.39–5.34 (m, 1H), 4.40–4.39 (m, 1H), 2.78–2.64 (m, 2H), 2.08–1.78 (m, 2H)
A27	+21.4, *c* 1, CH_2Cl_2	53.2	140–2	$C_{30}H_{25}F_2NO_5S_2$ 582	9.06 (s, 1H), 7.97 (dd, 1H, *J* = 10.0, 0.8 Hz), 7.33 (d, 1H, *J* = 16.0 Hz), 7.18–7.08 (m, 2H), 6.93–6.90 (m, 2H), 6.77–6.57 (m, 4H), 6.38 (dd, 1H, *J* = 16.4, 5.6 Hz), 5.37–5.34 (m, 1H), 4.36–4.34 (m, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 2.76–2.61 (m, 2H), 2.04–1.77 (m, 2H)
A28	+ 17.4, *c* 1, CH_2Cl_2	96.8	145–7	$C_{34}H_{33}F_2NO_3S_2$ 606	9.04 (s, 1H), 7.99 (dd, 1H, *J* = 10.4,1.2 Hz), 7.38–7.34 (m, 3H), 7.13–7.06 (m, 4H), 6.99–6.97 (m, 2H), 6.36 (dd, 1H, *J* = 16.4, 6.0 Hz), 5.35–5.32 (m, 1H), 4.36–4.35 (m, 1H), 2.87–2.80 (m, 2H), 2.77–2.61 (m, 2H), 2.02–1.78 (m, 2H), 1.21–1.17 (m, 12H)

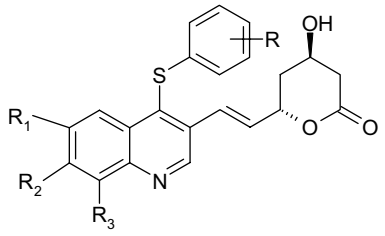
(*continued on next page*)

Table 2 (*continued*)

Compound	$[a]_D^{25}$	Yield (%)	Mp (°C)	Formula MS EI^+ (M+1)	^1H NMR δ ppm in $CDCl_3$
A29	+19.7, *c* 1, CH_2Cl_2	81.5	190–2	$C_{34}H_{27}NO_3S_3$ 594	8.91 (s, 1H), 8.12 (s, 1H), 7.57 (s, 1H), 7.55–7.53 (m, 2H), 7.43–7.40 (m, 3H), 7.35–7.27 (m, 6H), 7.14–7.10 (m, 3H), 6.85–6.83 (m, 2H), 6.29 (dd, 1H, *J* = 16.0, 6.0 Hz), 5.32 (m, 1H), 4.34–4.33 (m, 1H), 2.75–2.63 (m, 2H), 2.03–1.80 (m, 2H)
A30	+18.0, *c* 1, CH_2Cl_2	84.2	180–1	$C_{34}H_{24}F_3NO_3S_3$ 648	8.91 (s, 1H), 7.96 (s, 1H), 7.50 (s, 1H), 7.57–5.73 (m, 2H), 7.38–7.33 (m, 3H), 7.16–7.12 (m, 2H), 7.05–7.00 (m, 2H), 6.87–6.80 (m, 4H), 6.29 (dd, 1H, *J* = 16.0, 6.0 Hz), 5.38–5.33 (m, 1H), 4.41–4.39 (m, 1H), 2.79–2.62 (m, 2H), 2.09–1.84 (m, 2H)
A31	+21.4, *c* 1, CH_2Cl_2	67.7	57–59	$C_{37}H_{33}NO_6S_3$ 684	8.91 (s, 1H),8.19 (s, 1H), 7.61 (s, 1H), 7.34–7.28 (m, 2H), 7.21–6.83 (m, 8H), 6.64–6.61 (m, 1H), 6.46–6.38 (m, 2H), 6.28 (dd, 1H, *J* = 16.0,6.0 Hz), 5.33–5.29 (m,1H), 4.33–4.31 (m,1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.67 (s, 3H), 2.75–2.58 (m, 2H), 2.03–1.80 (m, 2H)
A32	+21.4, *c* 0.73, CH_2Cl_2	50.3	182–4	$C_{43}H_{45}NO_3S_3$ 720	8.88 (s, 1H),8.04 (s, 1H),7.54–7.49 (m, 3H), 7.37–7.26 (m, 5H), 7.20 (d, 2H, *J* = 8.0 Hz), 6.79 (d, 2H, *J* = 8.0 Hz), 6.75 (d, 2H, *J* = 8.4 Hz), 6.27 (dd, 1H, *J* = 16.4, 6.0 Hz), 5.34–5.29 (m, 1H), 4.36–4.34 (m, 1H), 2.98–2.91 (m, 2H), 2.84–2.81 (m, 1H), 2.76–2.59 (m, 2H), 2.04–1.82 (m, 2H), 1.31–1.26 (m, 12H), 1.20 (d, 6H, *J* = 7.2 Hz)
A33	+ 15.4, *c* 0.9, CH_2Cl_2	65.7	138–9	$C_{34}H_{26}FNO_3S_3$ 612	9.10 (s, 1H), 8.19 (d, 1H, *J* = 10.8 Hz), 7.32 (dd, 1H, *J* = 16.2, 1.2 Hz), 7.22–7.04 (m, 15H), 6.33 (dd, 1H, *J* = 16.4, 5.6 Hz), 5.34–5.29 (m, 1H), 4.34–4.30 (m, 1H), 2.74–2.59 (m, 2H), 2.04–1.74 (m, 2H)
A34	+ 14.3, *c* 1, CH_2Cl_2	52.4	194–6	$C_{34}H_{23}F_4NO_3S_3$ 665	9.09 (s, 1H), 8.16 (d, 1H, *J* = 10.8 Hz), 7.33 (dd, 1H, *J* = 16.0, 1.2 Hz), 7.27–7.20 (m, 4H), 7.09–7.06 (m, 2H), 6.95–6.87 (m, 6H), 7.34 (dd, 1H, *J* = 16.4, 5.6 Hz), 5.37–5.32 (m, 1H), 4.39–4.38 (m, 1H), 2.78–2.63 (m, 2H), 2.06–1.77 (m, 2H)
A35	+17.9, *c* 0.94, CH_2Cl_2	41.4	oil	$C_{37}H_{32}FNO_6S_3$ 702	9.11 (s, 1H), 8.20 (d, 1H, *J* = 10.4 Hz), 7.32 (dd, 1H, *J* = 16.4, 1.2 Hz), 7.13–7.05 (m, 3H), 6.81–6.58 (m, 9H), 6.34 (dd, 1H, *J* = 16.0, 6.0 Hz), 5.34–5.29 (m, 1H), 4.34–4.32 (m, 1H), 3.71–3.69 (m, 9H), 2.76–2.60 (m, 2H), 2.02–1.77 (m, 2H)
A36	+16.6, *c* 1, CH_2Cl_2	69.1	156–8	$C_{43}H_{44}FNO_3S_3$ 738	9.11 (s, 1H), 8.17 (d, 1H, *J* = 10.8 Hz), 7.34 (d, 1H, *J* = 16.4 Hz), 7.14 (t, 4H, *J* = 8.4 Hz), 7.08–7.02 (m, 6H), 6.98 (d, 2H, *J* = 8.0 Hz), 6.33 (dd, 1H, *J* = 16.0, 5.6 Hz), 5.35–5.32 (m, 1H), 4.35–4.33 (m, 1H), 2.85–2.80 (m, 3H), 1.20–1.18 (m, 18H), 2.80–2.64 (m, 2H), 1.99–1.79 (m, 2H)
A37	+ 31.1, *c* 0.92, THF	69.6	200–3	$C_{40}H_{31}NO_3S_4$ 702	8.98 (s, 1H), 7.87 (s, 1H), 7.43–7.25 (m, 6H), 7.19–7.04 (m, 13H), 6.74–6.72 (m, 2H), 6.30 (dd, 1H, *J* = 16.4, 6.0 Hz), 5.33–5.29 (m, 1H), 4.35–4.34 (m, 1H), 2.75–2.59 (m, 2H), 2.03–1.79 (m, 2H)
A38	+ 25.5, *c* 1, THF	75.5	218–20	$C_{40}H_{27}F_4NO_3S_4$ 774	9.17 (s, 1H), 7.73 (s, 1H), 7.51–7.48 (m, 2H), 7.33–7.27 (m, 2H), 7.23–7.17 (m, 3H), 7.14–6.97 (m,8H), 6.84–6.75 (m, 3H), 5.31–5.23 (m, 1H), 5.14 (s, 1H), 2.71–2.42 (m, 2H), 1.94–1.75 (m, 2H)
A39	+28.2, *c* 1, CH_2Cl_2	80.0	oil	$C_{44}H_{39}NO_7S_4$ 822	9.00 (s, 1H), 7.95 (s, 1H), 7.32 (dd, 1H, *J* = 16.4, 1.2 Hz), 7.26–7.22 (m, 2H), 7.11–6.94 (m, 6H), 6.74–6.57 (m, 6H), 6.34–6.27 (m, 3H), 5.32 (s, 1H), 4.35–4.33 (m, 1H), 3.72–3.66 (m, 12H), 2.75–2.63 (m, 2H), 2.03–1.83 (m, 2H)
A40	+ 21.9, *c* 1, Acetone	81.5	162–4	$C_{52}H_{55}NO_3S_4$ 870	8.97 (s, 1H), 7.84 (s, 1H), 7.37–7.31 (m, 3H), 7.22 (d, 2H, *J* = 8.0 Hz), 7.13 (d, 2H,*J* = 7.2 Hz), 7.06–6.95 (m, 8H), 6.66 (d, 2H, *J* = 8.0 Hz), 6.29 (dd, 1H, *J* = 16.0, 5.6 Hz), 5.31 (s, 1H), 4.35 (s, 1H), 2.97–2.94 (m, 1H), 2.85–2.77 (m, 3H), 2.75–2.59 (m, 2H), 2.02–1.79 (m, 2H), 1.29–1.16 (m, 24H)

[a] The definition of R, R_1, R_2, and R_3 is the same as Table 1.

Table 3. Inhibition of HMG CoA reductase in vitro[a]



Compound	R	R_1	R_2	R_3	IC_{50}[a] (μM)
A2	4-F	H	H	H	18.56
A4	4-$CH(CH_3)_2$	H	H	H	12.65
A8	4-$CH(CH_3)_2$	H	SC_6H_4-4-$CH(CH_3)_2$	H	15.75
A11	3-OCH_3	F	Cl	H	9.24
A12	4-$CH(CH_3)_2$	F	Cl	H	22.05
A13	H	F	F	F	10.67
A14	4-F	F	F	F	7.93
A16	4-$CH(CH_3)_2$	F	F	F	3.21
A21	H	F	SC_6H_5	H	4.41
A22	4-F	F	SC_6H_4-4-F	H	38.93
A23	3-OCH_3	F	SC_6H_4-3-OCH_3	H	3.64
A24	4-$CH(CH_3)_2$	F	SC_6H_4-4-$CH(CH_3)_2$	H	10.60
A27	3-OCH_3	F	SC_6H_4-3-OCH_3	F	49.67
A29	H	SC_6H_5	SC_6H_5	H	32.55
A31	3-OCH_3	SC_6H_4-3-OCH_3	SC_6H_4-3-OCH_3	H	15.37
A32	4-$CH(CH_3)_2$	SC_6H_4-4-$CH(CH_3)_2$	SC_6H_4-4-$CH(CH_3)_2$	H	14.15
A34	4-F	F	SC_6H_4-4-F	SC_6H_4-4-F	11.94
A35	3-OCH_3	F	SC_6H_4-3-OCH_3	SC_6H_4-3-OCH_3	74.55
A40	4-$CH(CH_3)_2$	SC_6H_4-4-$CH(CH_3)_2$	SC_6H_4-4-$CH(CH_3)_2$	SC_6H_4-4-$CH(CH_3)_2$	4.35
Rosuvastatin Calcium					9.03
Pitavastatin Calcium					10.55
Atorvastatin Calcium					13.22
Fluvastatin Sodium					21.21

[a] see Section 6 for protocol.

(substituted thiophenyl) to 7-position might generally give more potency than the halogen (F, Cl) or hydrogen counterparts (**A23** vs **A11**, **A21** vs **A13**, and **A34** vs **A2**). It suggested that a lipophilic interaction, other than a steric effect between R_2 and the domain of the enzyme, would be predominated.

(3) Effects of modification of R_1 and R_3. It is difficult to conclude the structure–activity relationship on the substituents at position 6 and position 8 in the quinoline. It seems that a variety of groups including H, halogen or substituted thiophenyl flanked at these positions are acceptable for the enzyme.

5. Conclusion

A series of 4-thiophenyl quinoline-based mevalonolactones was synthesized to evaluate their ability to inhibit 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-isopropylthiophenyl and 3-methoxy-thiophenyl. Secondly, in agreement with the previous literature, substitution at positions 6, 7, and 8 of the quinoline nucleus moderately increased the potency. (4*R*, 6*S*)-6-[(*E*)-2-(6,7,8-trifluoro-4-isopropylthiophenyl-quinoline-3-yl)-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (**A16**) and (4*R*, 6*S*)-6-[(*E*)-2-(6-fluoro-4,7-di-(3-methoxy-thiophenyl)-quinoline-3-yl)-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (**A23**) were approximately three times more potent than rosuvastatin or pitavastatin in HMG CoA reductase inhibition and selected as the hypocholesterolemic candidates for further evaluation.

6. Experimental

Melting points were determined on an Electrothermal Melting Point Apparatus and were uncorrected. Samples were characterized on a 400 MHz Nuclear Magnetic Resonance Spectrometer with either deuterated dimethylsulfoxide or deuterated chloroform as solvent. Mass spectra were recorded by an LC–Platform Mass Spectrometer using Electrospray Ionization.

6.1. Ethyl 4-(4-fluorothiophenyl)-quinoline-3-carboxylate (ii2)

A mixture of ethyl 4-chloro-quinoline-3-carboxylate **1a** (8.0 g, 34 mmol), 4-fluoro thiophenol (5.2 g, 41 mmol), triethylamine (6.9 g, 68 mmol), and THF (80 mL) was stirred at 25 °C for 1 h and then the reaction mixture was filtered. Upon concentration, the crude product solidified to give the title compound as a off-white solid

(10.0 g, 89.9%), which was used without further purification. mp: 52–4 °C, ^{1}H NMR δ ppm in $CDCl_3$: 9.05 (s,1H), 8.43 (dd, 1H, J = 8.6, 0.8 Hz), 8.14 (d, 1H, J = 8.4 Hz), 7.79–7.75 (m, 1H), 7.59–7.55 (m, 1H), 7.21 (dd, 2H, J = 11.8, 5.0 Hz), 6.93 (t, 2H, J = 6.4 Hz), 4.30 (q, 2H, J = 7.6 Hz), 1.33 (t, 3H, J = 7.2 Hz).

Compounds ii1 and **ii3–12** were prepared in manner analogous to the method described above.

6.2. Ethyl 4-(4-fluorothiophenyl)-6,7,8-trifluoro-quinoline-3-carboxylate (ii14)

A solution of triethylamine (0.9 g, 8.6 mmol) in THF (60 ml) was dropped into a mixture of ethyl 4-chloro-6,7,8-trifluoro-quinoline-3-carboxylate, **i4** (5.0 g, 17.3 mmol), and 4-fluoro-thiophenol (2.2 g, 17.3 mmol) in THF (50 ml) at −15 °C. The mixture was stirred for 1 h at this temperature before quenching with water and ethyl acetate. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, petroleum ether–EtOAc, 10:1) to provide the title compound as a yellow solid (4.0 g, 60.0%). mp: 126–8 °C, ^{1}H NMR δ ppm in $CDCl_3$: 9.04 (s, 1H), 8.05–8.00 (m, 1H), 7.24–7.20 (m, 2H), 6.99–6.94 (m, 2H), 4.30 (q, 2H, J = 7.2 Hz), 1.32 (t, 3H, J = 7.2 Hz).

Compounds ii13, **ii15**, and **ii16** were prepared in manner analogous to the method described above.

6.3. Ethyl 4,7-di-(3-methoxythiophenyl)-quinoline-3-carboxylate (ii19)

3-Methoxythiophenol (10.8 g, 77 mmol) was added to a mixture of NaH (60%, 3.0 g, 75 mmol) in DMF (30 ml) at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 h after which, 4,7-dichloro-quinoline-3-carboxylate, **ii2** (7.0 g, 25.9 mmol) was added. The mixture was stirred at 60 °C for 0.5 h. When TLC indicated that the reaction was complete, 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. The resulting oil was purified by silica gel chromatography (petroleum ether–EtOAc, 6:1) to provide the title compound (10.9 g, 88.1%) as an oil. ^{1}H NMR δ ppm in $CDCl_3$: 8.99 (s, 1H), 8.29 (d, 1H, J = 9.2 Hz), 7.80 (d, 1H, J = 2.0 Hz), 7.36 (dd, 1H, J = 8.8, 2.0 Hz), 7.31 (t, 1H, J = 8.0 Hz),7.14–7.07 (m, 3H), 6.95–6.92 (m,1H), 6.73–6.68 (m,3H), 3.78 (s, 3H), 3.68 (s, 3H), 4.27 (q, 2H, J = 7.2 Hz), 1.30 (t, 3H, J = 7.2 Hz).

Compounds ii17, **ii18**, and **ii20** were prepared in manner analogous to the method described above.

6.4. Ethyl 4,7-di-(3-methoxythiophenyl)-6-fluoro-quinoline-3-carboxylate (ii23)

A mixture of **i3** (6.0 g, 20.8 mmol), 3-methoxythiophenol (5.8 g, 41.6 mmol) in DMF (20 ml) was stirred at room temperature for 0.5 h before cooling to 0 °C. Anhydrous K_2CO_3 (20.0 g, 145 mmol) was added into the mixture and stirred for 1 h below 10 °C. The solid was isolated by filtration and washed with EtOAc. 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. The resulting oil was purified by silica gel chromatography (petroleum ether–EtOAc, 6:1) to provide the title compound (6.2 g, 60.0%) as an oil. ^{1}H NMR δ ppm in $CDCl_3$: 8.92 (s, 1H), 8.02 (d, 1H, J = 11.2 Hz), 7.56 (d, 1H, J = 7.6 Hz), 7.36 (t, 1H, J = 8.0 Hz), 7.17–7.01 (m, 3H), 7.00–6.97 (m, 1H), 6.74–6.70 (m, 3H), 3.80 (s, 3H), 3.69 (s, 3H), 4.27 (q, 2H, J = 7.2 Hz), 1.27 (t, 3H, J = 6.8 Hz).

Compounds ii21, **ii22**, and **ii24** were prepared in manner analogous to the method described above.

6.5. Ethyl 4,7-di-(4-isopropylthiophenyl)-6,8-difluoro-quinoline-3-carboxylate (ii28)

About 7.7 ml Et_3N was added to a solution of **i4** (8.0 g, 27.4 mmol) and 4-isopropylthiophenol (8.4 g, 55 mmol) in THF (80 ml) at room temperature and stirred for 1 h. The insoluble materials were filtered off, and the filtrate was evaporated in vacuo to give the crude product. Recrystallization from petroleum ether gave the title compound as a yellow solid (7.4 g, 50.0%), mp: 75–77 °C. ^{1}H NMR δ ppm in $CDCl_3$: 8.97 (s, 1H), 7.94 (dd, 1H, J = 10.4, 2.0 Hz), 7.35 (d, 2H, J = 8.0), 7.16–7.09 (m, 6H), 4.21 (q, 2H, J = 7.6), 2.88–2.83 (m, 2H), 1.29–1.19 (m, 15H).

Compounds ii25–ii27 were prepared in manner analogous to the method described above.

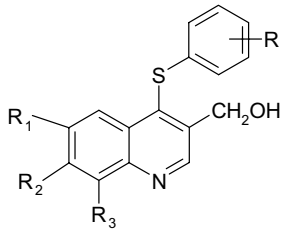
6.6. Ethyl 4,7,8-tri-(4-isopropylthiophenyl)-6-fluoro-quinoline-3-carboxylate (ii36)

Anhydrous K_2CO_3 (37.8 g, 274 mmol) was added to a mixture of **i4** (8.0 g, 27.4 mmol) and 4-isopropylthiophenol (13.7 g, 90.1 mmol) in DMF (80 ml) at 25 °C and stirred for 1 h. The insoluble materials were filtered off, and the filtrate 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. The resulting oil was purified by silica gel chromatography (petroleum ether–EtOAc, 6:1) to provide the title compound (13.0 g, 65.8%) as yellow oil. ^{1}H NMR δ ppm in $CDCl_3$: 9.04 (s, 1H), 8.14 (d, 1H, J = 11.2 Hz), 7.18–7.02 (m, 12H), 4.20 (q, 2H, J = 6.8 Hz), 2.88–2.81 (m,3H), 1.33–1.15 (m, 21H).

Compounds ii33–ii35 were prepared in manner analogous to the method described above.

Except for shifting reaction temperature from room temperature to 60 °C, **ii29–ii32** were prepared in manner analogous to the method described above.

Table 4. Physical properties and yield of 4-substituted thiophenyl quinoline-3-methanol (**iii1**–**40**)[a]



Compound	Formula	Yield (%)	Mp (°C)	^{1}H NMR δ ppm in $CDCl_3$
iii1	$C_{16}H_{13}NOS$	64.6	144–6	9.09 (s, 1H), 8.43 (d, 1H, *J* = 8.4 Hz), 8.14 (d, 1H, *J* = 8.4 Hz), 7.73–7.67 (m, 1H), 7.56–7.52 (m, 1H), 7.04–6.89 (m, 5H), 5.03 (s, 2H)
iii2	$C_{16}H_{12}FNOS$	76.5	130–2	9.10 (s, 1H), 8.43 (d, 1H, *J* = 8.4 Hz), 8.12 (dd, 1H, *J* = 8.6, 0.8 Hz), 7.72–7.67 (m, 1H), 7.56–7.52 (m, 1H), 7.05–7.01 (m, 2H), 6.90–6.85 (m, 2H), 5.04 (s, 2H)
iii3	$C_{17}H_{15}NO_2S$	61.5	122–4	9.10 (s, 1H), 8.38 (d, 1H, *J* = 8.4 Hz), 8.11 (d, 1H, *J* = 8.0 Hz), 7.70–7.66 (m, 1H), 7.54–7.50 (m, 1H), 7.04 (t, 1H, *J* = 8.0 Hz), 6.65–6.54 (m, 3H), 5.02 (s, 2H), 3.63 (s, 3H)
iii4	$C_{19}H_{19}NOS$	63.9	100–2	9.09 (s, 1H), 8.45 (d, 1H, *J* = 8.4 Hz), 8.14 (d, 1H, *J* = 8.0 Hz), 7.72–7.68 (m, 1H), 7.56–7.52 (m, 1H), 7.05–6.96 (m,4H), 5.02 (s, 2H), 2.82–2.78 (m, 1H), 1.17 (d, 6H, *J* = 7.2 Hz)
iii5	$C_{16}H_{11}ClNOS$	52.8	122	9.11 (s, 1H), 8.34 (d, 1H, *J* = 9.2 Hz), 8.13 (d, 1H, *J* = 2.0 Hz), 7.48 (dd, 1H, *J* = 8.8, 2.0 Hz), 7.21–7.14 (m, 3H), 7.03–7.09 (m, 2H), 5.01 (s, 2H)
iii6	$C_{16}H_{11}ClFNOS$	63.6	142–6	9.09 (s, 1H), 8.31 (d, 1H, *J* = 9.2 Hz), 8.11 (d, 1H, *J* = 2.0 Hz), 7.48 (dd, 1H, *J* = 8.8, 2.0 Hz), 7.05–7.02 (m, 2H), 6.92–6.88 (m, 2H), 5.02 (s, 2H)
iii7	$C_{17}H_{14}ClNO_2S$	69.8	118	9.10 (s, 1H), 8.33 (d, 1H, *J* = 8.8 Hz), 8.12 (d, 1H, *J* = 2.0 Hz), 7.48 (dd, 1H, *J* = 8.8, 2.0 Hz), 7.09 (t, 1H, *J* = 8.0), 6.69–6.66 (m, 1H), 6.59–6.54 (m, 2H), 5.02 (s, 2H), 3.67 (s, 3H)
iii8	$C_{19}H_{18}ClNOS$	53.3	88–90	9.09 (s, 1H), 8.38 (d, 1H, *J* = 9.2 Hz), 8.12 (d, 1H, *J* = 2.0 Hz), 7.47 (dd, 1H, *J* = 8.8, 2.0 Hz), 7.06–6.96 (m,4H), 5.00 (s, 2H), 2.82–2.79 (m,1H), 1.17 (d, 6H, *J* = 7.2)
iii9	$C_{16}H_{11}ClFNOS$	61.8	120–4	9.12 (s, 1H), 8.25 (d, 1H, *J* = 6.8 Hz), 8.12 (d, *J* = 10.0 Hz), 7.25–7.18 (m, 3H), 7.06–7.03 (m, 2H), 5.02 (s, 2H)
iii10	$C_{16}H_{10}ClF_2NOS$	62.2	154–6	9.09 (s, 1H), 8.23 (d, 1H, *J* = 7.6 Hz), 8.11 (d, 1H, *J* = 10.4 Hz), 7.07–7.04 (m, 2H), 6.95–6.91 (m, 2H), 5.03 (s, 2H)
iii11	$C_{17}H_{13}ClFNO_2S$	75.6	117–8	9.11 (s, 1H), 8.24 (d, 1H, *J* = 7.6 Hz), 8.14 (d, 1H, *J* = 10.4 Hz), 7.15–7.11 (m, 1H), 6.73–6.70 (m, 1H), 6.60–6.57 (m, 2H), 5.04 (s, 2H), 3.71 (s, 3H)
iii12	$C_{19}H_{17}ClFNOS$	73.9	132–4	9.06 (s, 1H), 8.19 (d, 1H, *J* = 6.8 Hz), 8.13 (d, 1H, *J* = 10.8 Hz), 7.06 (dd, 2H, *J* = 6.4, 2.0 Hz), 6.96 (dd, 2H, *J* = 6.8, 2.0 Hz), 5.00 (s, 2H), 2.81 (m, 1H), 1.17 (d, 6H, *J* = 6.8 Hz)
iii13	$C_{16}H_{10}F_3NOS$	70.6	126–8	9.15 (s, 1H), 8.02–7.97 (m, 1H), 7.24–7.17 (m, 3H), 7.03–7.01 (m, 2H), 5.03 (s, 2H)
iii14	$C_{16}H_9F_4NOS$	63.2	140–2	9.13 (s, 1H), 8.00–7.95 (m, 1H), 7.06–7.02 (m, 2H), 6.92 (t, 2H, *J* = 7.2 Hz), 5.03 (s, 2H)
iii15	$C_{17}H_{12}F_3NO_2S$	63.2	100–2	9.16 (s, 1H), 8.03–7.98 (m, 1H), 7.13 (t, 1H, *J* = 8.4 Hz), 6.73–6.70 (m, 1H), 6.58–6.55 (m, 2H), 5.04 (s, 2H), 3.70 (s, 3H)
iii16	$C_{19}H_{16}F_3NOS$	76.7	99–102	9.13 (s, 1H), 8.05–8.00 (m, 1H), 7.10–7.06 (m, 2H), 6.99–6.96 (m, 2H), 5.02 (s, 2H), 2.84–2.81 (m,1H), 1.20–1.17 (m, 6H)
iii17	$C_{22}H_{17}NOS_2$	53.1	104	9.00 (s, 1H), 8.27 (d, 1H, *J* = 8.8 Hz), 7.83 (d, 1H, *J* = 1.6 Hz), 7.54–7.52 (m, 2H), 7.13–7.08 (m, 4H), 7.19–7.12 (m, 3H), 6.91–6.87 (m, 2H), 4.97 (s, 2H)

(*continued on next page*)

Table 4 (*continued*)

Compound	Formula	Yield (%)	Mp (°C)	^{1}H NMR δ ppm in $CDCl_3$
iii18	$C_{22}H_{15}F_2NOS_2$	66.6	106–8	9.00 (s, 1H), 8.25 (d, 1H, *J* = 9.2 Hz), 7.73 (d, 1H, *J* = 1.6 Hz), 7.34 (dd, 1H, *J* = 9.2, 2.4 Hz), 7.56–7.52 (m, 2H), 7.13–7.08 (m, 2H), 7.05–7.01 (m, 2H), 6.91–6.87 (m, 2H), 4.98 (s, 2H)
iii19	$C_{24}H_{2321}NO_3S_2$	49.4	82–4	9.02 (s, 1H), 8.28 (d, 1H, *J* = 8.8 Hz), 7.88 (d, 1H, *J* = 1.6 Hz), 7.39 (dd, 1H, *J* = 8.8, 2.0 Hz), 7.29 (t, 1H, *J* = 8.0 Hz), 7.12–7.06 (m, 3H), 6.92–6.89 (m,1H), 6.68–6.65 (m,1H), 6.60–6.55 (m, 2H), 4.98 (s, 2H), 3.78 (s, 3H), 3.68 (s, 3H)
iii20	$C_{28}H_{29}NOS_2$	63.5	114	8.97 (s, 1H), 8.30 (d, 1H, *J* = 9.2 Hz), 7.77 (s, 1H), 7.36 (dd, 1H, *J* = 8.8, 1.6 Hz), 7.48 (d, 2H, *J* = 8.4 Hz), 7.26 (d, 2H, *J* = 8.0 Hz), 7.04 (d, 2H, *J* = 8.0 Hz), 6.95 (d, 2H, *J* = 8.0 Hz), 4.96 (s, 2H), 2.95–2.92 (m,1H), 2.83–2.79 (m, 1H), 1.28 (d, 6H, *J* = 6.8 Hz), 1.17 (d, 6H, *J* = 7.2 Hz)
iii21	$C_{22}H_{16}FNOS_2$	50.6	88–90	8.91 (s, 1H), 7.97 (d, 1H, *J* = 11.2 Hz), 7.60 (d, 1H, *J* = 7.2 Hz), 7.54–7.53 (m, 2H), 7.40–7.39 (m, 3H), 7.18–7.11 (m, 3H), 6.99 (d, 2H, *J* = 7.2 Hz), 4.92 (s, 2H)
iii22	$C_{22}H_{14}F_3NOS_2$	87.5	108–10	8.95 (s, 1H), 7.99 (d, 1H, *J* = 11.2 Hz), 7.52 (d, 1H, *J* = 7.6 Hz), 7.60–7.59 (m, 2H), 7.15 (t, 2H, *J* = 8.0 Hz), 7.06–7.03 (m, 2H), 6.92 (t, 2H, *J* = 8.0 Hz), 4.98 (s, 2H)
iii23	$C_{24}H_{20}FNO_3S_2$	45.9	93–5	8.95 (s, 1H), 8.01 (d, 1H, *J* = 11.2 Hz), 7.67 (d, 1H, *J* = 6.8 Hz), 7.33 (t, 1H, *J* = 8.0 Hz), 7.15–7.08 (m, 3H), 6.97–6.94 (m, 1H), 6.70–6.67 (m, 1H), 6.58–6.56 (m, 2H), 4.96 (s, 2H), 3.79 (s, 3H), 3.69 (s, 3H)
iii24	$C_{28}H_{28}FNOS_2$	59.8	126–8	8.91 (s, 1H), 8.03 (d, 1H, *J* = 11.2 Hz), 7.55 (d, 1H, *J* = 8.0 Hz), 7.53–7.50 (m, 2H), 7.31 (d, 2H, *J* = 8.4 Hz), 7.06 (d, 2H, *J* = 8.4 Hz), 6.97–6.95 (m, 2H), 4.95 (s, 2H), 2.98–2.94 (m, 1H), 2.83–2.78 (m, 1H), 1.30–1.27 (m, 6H), 1.18 (d, 6H, *J* = 6.8 Hz)
iii25	$C_{22}H_{15}F_2NOS_2$	73.7	134–6	9.14 (s, 1H), 7.92 (dd, 1H, *J* = 9.6, 2.0 Hz), 7.38–7.25 (m, 2H), 7.25–7.14 (m, 6H), 7.04–7.02 (m, 2H), 5.02 (s, 2H)
iii26	$C_{22}H_{13}F_4NOS_2$	75.7	149–50	9.12 (s, 1H), 7.88 (d, 1H, *J* = 10.0 Hz), 7.45 (dd, 2H, *J* = 7.6, 5.2 Hz), 7.06 (dd, 2H, *J* = 8.0, 5.2 Hz), 6.98–6.90 (m, 4H), 5.03 (s, 2H)
iii27	$C_{24}H_{19}F_2NO_3S_2$	57.2	122–4	9.14 (s, 1H), 7.93 (dd, 1H, *J* = 10.0, 1.6 hz), 7.18–7.10 (m, 2H), 6.93–6.89 (m, 2H), 6.77–6.74 (m, 2H), 6.59–6.57 (m, 2H), 5.03 (s, 2H), 3.73 (s, 3H), 3.70 (s, 3H)
iii28	$C_{28}H_{27}F_2NOS_2$	71.8	152–4	9.10 (s, 1H), 7.95 (dd, 1H, *J* = 10.4, 2.5 Hz), 7.35 (d, 2H, *J* = 7.4 Hz), 7.13–7.07 (m, 4H), 7.00–6.97 (m, 2H), 5.01 (s, 2H), 2.87–2.81 (m, 2H), 1.21–1.18 (m, 12H)
iii29	$C_{28}H_{21}NOS_3$	60.9	190–3	9.13 (s, 1H), 7.93 (s, 1H), 7.88 (s, 1H), 7.60–7.54 (m, 5H), 7.44–7.40 (m, 5H), 7.19–7.17 (m, 3H), 6.88–6.87 (m, 2H), 4.88 (s, 2H)
iii30	$C_{28}H_{18}F_3NOS_3$	74.1	174–6	8.91 (s, 1H), 7.87 (s, 1H), 7.52 (s, 1H), 7.57–7.52 (m, 2H), 7.34–7.30 (m, 2H), 7.14 (t, 2H, *J* = 8.0), 7.01 (t, 2H, *J* = 8.4), 6.88–6.87 (m, 4H), 4.98 (s, 2H)
iii31	$C_{31}H_{27}NO_4S_3$	68.7	112–5	8.90 (s, 1H), 8.12 (s, 1H), 7.64 (s, 1H), 7.32 (t, 1H, *J* = 8.0), 7.19–6.82 (m, 8H), 6.64–6.62 (m, 1H), 6.43 (t, 1H, *J* = 2.0), 6.39–6.36 (m, 1H), 4.94 (s, 2H), 3.78 (s, 3H), 3.71 (s, 3H), 3.66 (s, 3H)
iii32	$C_{37}H_{39}NOS_3$	71.8	96–8	8.84 (s, 1H), 7.99 (s, 1H), 7.57 (s, 1H), 7.50 (d, 2H, *J* = 8.0), 7.29 (d, 2H, *J* = 8.4), 7.18 (d, 2H, *J* = 8.4), 6.99 (d, 2H, *J* = 8.4), 6.74 (d, 2H, *J* = 8.0), 5.97–5.92 (m, 2H), 4.93 (s, 2H), 2.84–2.81 (m, 2H), 1.30–1.20 (m, 18H)
iii33	$C_{28}H_{20}FNOS_3$	65.0	154–6	9.17 (s, 1H), 8.15 (d, 1H, *J* = 10.8 Hz), 7.26–7.04 (m, 15H), 5.00 (s, 2H)
iii34	$C_{28}H_{17}F_4NOS_3$	78.5	200–3	9.15 (s, 1H), 8.10 (d, 1H, *J* = 10.8), 7.26–7.21 (m, 5H), 7.08–7.04 (m, 2H), 6.95–6.86 (m, 5H), 5.00 (s, 2H)
iii35	$C_{31}H_{26}FNO_4S_3$	66.9	110–2	9.17 (s, 1H), 8.15 (d, 1H, *J* = 10.4 Hz), 7.14–7.04 (m, 3H), 6.80–6.78 (d, 1H, *J* = 8.0 Hz), 6.75–6.67 (m, 5H), 6.64–6.61 (m, 1H), 6.59–6.57 (m, 2H), 5.00 (s, 2H), 3.73–3.68 (m, 9H)
iii36	$C_{37}H_{38}FNOS_3$	41.3	140–2	9.20 (s, 1H), 8.19 (d, 1H, *J* = 10.8 Hz), 7.21–7.02 (m, 12H), 5.03 (s, 2H), 2.91–2.82 (m, 3H), 1.25–1.18 (m, 18H)
iii37	$C_{34}H_{25}NOS_4$	46.8	163–5	8.98 (s, 1H), 7.81 (s, 1H), 7.39–7.28 (m, 5H), 7.20–7.03 (m, 13H), 6.72–6.69 (m, 2H), 4.94 (s, 2H)

Table 4 (*continued*)

Compound	Formula	Yield (%)	Mp (°C)	^{1}H NMR δ ppm in $CDCl_3$
iii38	$C_{34}H_{21}F_4NOS_4$	87.2	190–2	9.00 (s, 1H), 7.61 (s, 1H), 7.37–7.34 (m, 2H), 7.20–7.16 (m, 2H), 7.13–7.09 (m, 2H), 7.07–7.02 (m, 2H), 6.93–6.79 (m, 6H), 6.69–6.65 (m, 2H), 4.96 (s, 2H)
iii39	$C_{38}H_{33}NO_5S_4$	55.4	116–8	9.01 (s, 1H), 7.87 (s, 1H), 7.22 (t, 1H, J = 8.0 Hz), 7.09 (t, 1H, J = 8.4 Hz), 7.04–6.92 (m, 5H), 6.73–6.55 (m, 7H), 6.30–6.24 (m, 2H), 3.70 (s, 3H), 3.67 (s, 3H), 3.66 (s, 3H), 3.64 (s, 3H), 4.94 (s, 2H)
iii40	$C_{46}H_{49}NOS_4$	55.0	170–3	8.96 (s, 1H), 7.78 (s, 1H), 7.30 (d, 2H, J = 7.0 Hz), 7.19 (d, 2H, J = 8.0 Hz), 7.12 (d, 2H, J = 7.4 Hz), 7.06–6.94 (m, 8H), 6.65 (d, 2H, J = 7.4), 4.93 (s, 2H), 2.96–2.93 (m, 1H), 2.86–2.76 (m, 3H), 1.29–1.14 (m, 24H)

[a] The definition of R, R_1, R_2, and R_3 is the same as Table 1.

6.7. Ethyl 4,6,7,8-tetra-(4-isopropylthiophenyl)-quinoline-3-carboxylate (ii40)

A mixture of **i4** (8.0 g, 27.4 mmol), 4-isopropylthiophenol (18.7 g, 123.3 mmol), anhydrous K_2CO_3 (37.8 g, 274 mmol) in DMSO (80 ml) was stirred at 60 °C for 1 h. The insoluble materials were filtered off, and the filtrate 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. The resulting oil was purified by silica gel chromatography (petroleum ether–EtOAc, 6:1) to provide the title compound (19.4 g, 84.3%) as yellow oil. ^{1}H NMR δ ppm in $CDCl_3$: 8.86 (s, 1H), 7.82 (s, 1H), 7.34–7.25 (m, 4H), 7.13–7.10 (m, 2H), 7.06–6.95 (m, 8H), 6.77–6.75 (m, 2H), 3.00–2.97 (m, 1H), 2.85–2.76 (m, 3H), 1.34–1.16 (m, 24H), 4.20 (q, 2H, J = 6.8 Hz), 0.86 (t, 3H, J = 5.2 Hz).

Compounds **ii37**–**ii39** were prepared in manner analogous to the method described above. The ^{1}HNMR data of all compounds **ii** were seen in Table 1.

6.8. 6,7,8-Trifluoro-4-thiophenyl-quinoline-3-methanol (iii13)

About 22 ml (55 mmol) of a 2.5 M DIBAL-H in toluene was added to a solution of **ii13** (8.0 g, 21.9 mmol) in anhydrous toluene (80 ml) at 0 °C under an atmosphere of nitrogen. The resulting solution was stirred for 2 h at 0 °C before quenching with 6 M HCl. The mixture was added to EtOAc and the organic layer was separated, washed with water, dried over Na_2SO_4 and concentration. Recrystallization from 95% ethanol to give the title compound as a yellow solid (5.0 g, 70.6%), mp: 126–128 °C. ^{1}H NMR δ ppm in $CDCl_3$: 9.15 (s, 1H), 8.02–7.97 (m, 1H), 7.24–7.17 (m, 3H), 7.03–7.01 (m, 2H), 5.03 (s, 2H).

Compounds iii1–12, and **iii14–40** were prepared in manner analogous to the method described above. Some physical properties are included in Table 4.

6.9. 6,7,8-Trifluoro-4-thiophenyl-3-bromomethyl-quinoline (iv13)

A solution of PBr_3 (8.4 g, 31 mmol) in CH_2Cl_2 (40 ml) was added to the mixture of **iii13** (5.0 g, 15.5 mmol) in CH_2Cl_2 (30 ml) at 0 °C. The resulting mixture was stirred for 2 h at room temperature before quenching with a saturated aqueous $NaHCO_3$ solution to pH 8. The mixture was added to CH_2Cl_2 and the organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated to afforded the title compound (5.9 g, 98%), which was used without further purification.

Compounds iv1–12 and **iv14–40** were prepared in manner analogous to the method described above. Some physical properties are seen in Table 5.

6.10. 6,7,8-Trifluoro-4-thiophenyl-3 (diphenyl-oxo-phosphonyl-methyl)-quinoline (v13)

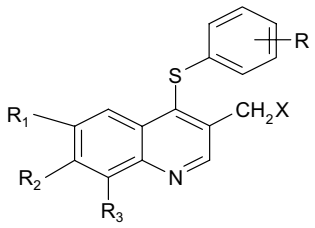
A solution of **iv13** (5.2 g, 13.4 mmol) and ethyl diphenylphosphinite (6.2 ml, 27 mmol) in toluene (25 ml) was refluxed for 2 h during which time the precipitated solid developed. After cooling to room temperature, the solid was isolated by filtration and washed with toluene. The product was then dried to afford the title compound (6.6 g, 75% yield of two steps), mp: 244–245 °C.

Compounds v1–12 and **v14–40** were prepared in manner analogous to the method described above. Some physical properties are seen in Table 5.

6.11. *tert*-Butyl (3*R*,5*S*,6*E*)-7-[6,7,8-trifluoro-4-thiophenyl-quinoline-3-yl]-3,5-dihydroxy-3,5-*O*-isopropylidene-6-heptenoate (vii13)

1.2 ml (3 mmol) of a 2.5 M hexane solution of *n*-BuLi was added to a solution of 2,2,6,6-tetramethylpiperidine (0.5 g, 3 mmol) in anhydrous THF (10 ml) at 0 °C and stirred for 15 min. under an atmosphere of nitrogen. **v13** (1.0 g, 2.0 mmol) was added to the resulting solution at 0 °C and stirred for 1 h at room temperature. **vi** (0.61 g, 2.4 mmol) in anhydrous THF (2 ml) was added to the solution and stirred for 2.5 h before quenching 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_2SO_4 and concentrated. The resulting oil was purified by silica gel chromatography (petroleum ether–EtOAc, 5:1) to provide the title compound (0.6 g, 55.8%) as white solid **vii13** (0.6 g, 55.8%), mp: 169–171 °C. $[\alpha]_D^{20} = +5.9$ (c 1, acetone). ^{1}H NMR δ ppm in $CDCl_3$:

Table 5. Physical properties and yield of 4-substituted-thiophenyl-3-bromomethyl (or 3-diphenyl-oxo-phosphonyl-methyl)-quinolines (**iv1**–**40** or **v1**–**40**)[a]



iv1~40 :X=Br and **v1~40** : X=$Ph_2P(O)$

Compound	Formula	Yield (%)	Mp (°C)	Compound	Formula	Yield (%)	Mp (°C)
iv1	$C_{16}H_{12}BrNS$	67.2	156–60	**V1**	$C_{28}H_{23}NOPS$	81.5	228–30
iv2	$C_{16}H_{11}BrFNS$	76.5	130–2	**V2**	$C_{28}H_{22}FNOPS$	100	184–5
iv3	$C_{17}H_{14}BrNOS$	85.4	100	**V3**	$C_{29}H_{25}NO_2PS$	100	197–8
iv4	$C_{19}H_{18}BrNS$	—	—	**V4**	$C_{31}H_{29}NOPS$	79.4[b]	190–2
iv5	$C_{16}H_{11}BrClNS$	87.0	104–6	**V5**	$C_{28}H_{21}ClNOPS$	98.7	210–2
iv6	$C_{16}H_{10}BrClFNS$	83.3	112–4	**V6**	$C_{28}H_{20}ClFNOPS$	100	192–4
iv7	$C_{17}H_{13}BrClNOS$	86.1	92–4	**V7**	$C_{29}H_{23}ClNO_2PS$	92.9	194–6
iv8	$C_{19}H_{17}BrClNS$	86.5	101–2	**V8**	$C_{31}H_{27}ClNOPS$	99.8	238–40
iv9	$C_{16}H_{10}BrClFNS$	85	130–2	**V9**	$C_{28}H_{20}ClFNOPS$	88.9	238–40
iv10	$C_{16}H_9BrClF_2NS$	84.5	156–7	**v10**	$C_{28}H_{19}ClF_2NOPS$	100	250–2
iv11	$C_{17}H_{12}BrClFNOS$	83	108–10	**v11**	$C_{29}H_{22}ClFNO_2PS$	87.8	216–8
iv12	$C_{19}H_{16}BrClFNS$	85.0	132–4	**v12**	$C_{31}H_{26}ClFNOPS$	100	234–6
iv13	$C_{16}H_9BrF_3NS$	86.8	98–100	**v13**	$C_{28}H_{19}F_3NOPS$	96.9	244–5
iv14	$C_{16}H_8BrF_4NS$	—	—	**v14**	$C_{28}H_{18}F_4NOPS$	84.2[b]	212–3
iv15	$C_{17}H_{11}BrF_3NOS$	80.3	112–4	**v15**	$C_{29}H_{21}F_3NO_2PS$	99.1	206–8
iv16	$C_{19}H_{15}BrF_3NS$	86.6	86–8	**v16**	$C_{31}H_{25}F_3NOPS$	87.9	236–8
iv17	$C_{22}H_{16}BrNS_2$	—	—	**v17**	$C_{34}H_{26}NOPS_2$	71.6[b]	238–40
iv18	$C_{22}H_{14}BrF_2NS_2$	—	—	**v18**	$C_{34}H_{24}F_2NOPS_2$	89.8[b]	213–5
iv19	$C_{24}H_{20}BrNO_2S_2$	—	—	**v19**	$C_{36}H_{30}NO_3PS_2$	87.8[b]	190–2
iv20	$C_{28}H_{28}BrNS_2$	81.9	87–90	**v20**	$C_{40}H_{38}NOPS_2$	100	200–2
iv21	$C_{22}H_{15}BrFNS_2$	—	104	**v21**	$C_{34}H_{25}FNOPS_2$	62.0[b]	238–41
iv22	$C_{22}H_{13}BrF_3NS_2$	89.8	150–2	**v22**	$C_{34}H_{23}F_3NOPS_2$	100	246–8
iv23	$C_{24}H_{19}BrFNO_2S_2$	—	oil	**v23**	$C_{36}H_{29}FNO_3PS_2$	84.0[b]	229–30
iv24	$C_{28}H_{27}BrFNS_2$	74.2	145–7	**v24**	$C_{40}H_{37}FNOPS_2$	96.3	250–1
iv25	$C_{22}H_{14}BrF_2NS_2$	76.6	120–2	**v25**	$C_{34}H_{24}F_2NOPS_2$	72.9	246–8
iv26	$C_{22}H_{12}BrF_4NS_2$	—	—	**v26**	$C_{34}H_{22}F_4NOPS_2$	72.4[b]	250–2
iv27	$C_{24}H_{18}BrF_2NO_2S_2$	—	—	**v27**	$C_{36}H_{28}F_2NO_3PS_2$	85.4[b]	184–5
iv28	$C_{28}H_{26}BrF_2NS_2$	80.3	116–7	**v28**	$C_{40}H_{36}F_2NOPS_2$	98.7	236–40
iv29	$C_{28}H_{20}BrNS_3$	88.9	140–2	**v29**	$C_{40}H_{30}NOPS_3$	94.2	246–8
iv30	$C_{28}H_{17}BrF_3NS_3$	82.2	156–8	**v30**	$C_{40}H_{27}F_3NOPS_3$	90.7	261–3
iv31	$C_{31}H_{26}BrNO_3S_3$	—	—	**v31**	$C_{43}H_{36}NO_4PS_3$	82.1[b]	156–8
iv32	$C_{37}H_{38}BrNS_3$	69.3	104–7	**v32**	$C_{49}H_{48}NOPS_3$	97.1	231–3
iv33	$C_{28}H_{19}BrFNS_3$	86.7	150–2	**v33**	$C_{40}H_{29}FNOPS_3$	86.2	238–40
iv34	$C_{28}H_{16}BrF_4NS_3$	90.5	141–2	**v34**	$C_{40}H_{26}F_4NOPS_3$	100	229–31
iv35	$C_{31}H_{25}BrFNO_3S_3$	—	—	**v35**	$C_{43}H_{35}FNO_4PS_3$	69.5[b]	178–80
iv36	$C_{37}H_{37}BrFNS_3$	82.0	135–8	**v36**	$C_{49}H_{47}FNOPS_3$	100	212–6
iv37	$C_{34}H_{24}BrNS_4$	100	139–41	**v37**	$C_{46}H_{34}NOPS_4$	95.4	222–4
iv38	$C_{34}H_{20}BrF_4NS_4$	87.8	173–5	**v38**	$C_{46}H_{30}F_4NOPS_4$	82.8	225–7
iv39	$C_{38}H_{32}BrNO_4S_4$	—	—	**v39**	$C_{50}H_{42}NO_5PS_4$	93.9[b]	104–6
iv40	$C_{46}H_{48}BrNS_4$	—	Oil	**v40**	$C_{58}H_{58}NOPS_4$	78.8	160–4

[a] The definition of R, R_1, R_2, and R_3 is the same as Table 1.
[b] Calculated on the two steps.

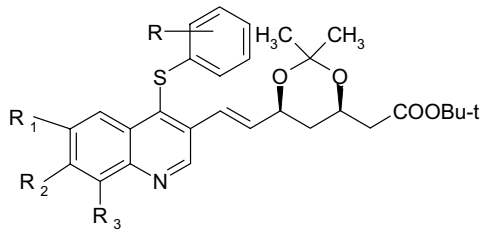
9.11 (s, 1H), 8.07–8.04 (m, 1H), 7.29–7.15 (m, 4H), 7.05–7.03 (m, 2H), 6.34 (dd, 1H, J = 16.8, 6.0 Hz), 4.56–4.52 (m, 1H), 4.32–4.29 (m, 1H), 2.47–2.27 (m, 2H), 1.64–1.21 (m, 17H).

Compounds vii1–12, vii14–40 were prepared in manner analogous to the method described above. Their physical properties are included in Table 6.

6.12. (4*R*, 6*S*)-6-[(*E*)-2-(6,7,8-Trifluoro-4-thiophenyl-quinoline-3-yl)-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (A13)

A solution of **vii13** (0.47 g, 0.86 mmol) and CF_3COOH (2 ml, 25.8 mmol) in CH_2Cl_2 (10 ml) was stirred at 0 °C for 2 h before quenching with a saturated aqueous $NaHCO_3$ solution. The mixture was added to EtOAc

Table 6. Physical properties and yield of (3*R*, 5*S*, 6*E*)-*tert*-butyl-7-(4-substituted-thiophenyl-quinoline-3-yl)-3,5-dihydroxy-3, 5-*O*-iso-propylidene-hept-6-enoates (vii1–40)[a]



Compound	Formula	$[a]_D^{25}$	Yield (%)	Mp (°C)	^{1}H NMR δ ppm in $CDCl_3$
vii1	$C_{30}H_{36}NO_4S$	−9.3, *c* 1, CH_2Cl_2	29.6	135–6	9.13 (s, 1H), 8.45 (d, 1H, *J* = 8.0 Hz), 8.10 (d, 1H, *J* = 8.4 Hz), 7.67 (t, 1H, *J* = 7.6 Hz), 7.53 (t, 1H, *J* = 8.0 Hz), 7.31 (d, 1H, *J* = 16.0 Hz), 7.19–7.04 (m, 5H), 6.32 (dd, 1H, *J* = 16.2, 6.0 Hz), 4.56–4.52 (m, 1H), 4.32–4.30 (m, 1H), 2.48–2.28 (m, 2H), 1.62–1.24 (m, 17H)
vii2	$C_{30}H_{35}FNO_4S$	−9.4, *c* 1, $CHCl_3$	26.7	110–2	9.10 (s, 1H), 8.45 (dd, 1H, *J* = 8.6, 1.2 Hz), 8.10 (d, 1H, *J* = 8.4 Hz), 7.70–7.66 (m, 1H), 7.57–7.52 (m, 1H), 7.30 (dd, 1H, *J* = 16.2, 0.8 Hz), 7.08–7.05 (m, 2H), 6.90–6.86 (m, 2H), 6.30 (dd, 1H, *J* = 16.4, 6.4 Hz), 4.57–4.53 (m, 1H), 4.34–4.30 (m, 1H), 2.49–2.29 (m, 2H), 1.67–1.62 (m, 1H), 1.34–1.25 (m, 1H), 1.54–1.44 (m, 15H)
vii3	$C_{31}H_{38}NO_5S$	−3.4, *c* 1, CH_2Cl_2	22.2	106–8	9.14 (s, 1H), 8.43 (d, 1H, *J* = 8.0 Hz), 8.10 (d, 1H, *J* = 8.4 Hz), 7.68 (t, 1H, *J* = 6.8 Hz), 7.53 (t, 1H, *J* = 8.0 Hz), 7.21 (d, 1H, *J* = 16.0 Hz), 7.08 (t, 1H, *J* = 8.0), 6.66–6.59 (m, 3H), 6.34 (dd, 1H, *J* = 16.4, 6.0 Hz), 4.59–4.54 (m, 1H), 4.33–4.31 (m, 1H), 3.67 (s, 3H), 2.48–2.29 (m, 2H), 1.65–1.64 (m, 1H), 1.35–1.27 (m, 1H), 1.51–1.43 (m, 15H)
vii4	$C_{33}H_{42}NO_4S$	+1.5, *c* 0.68, Acetone	28.5	107–8	9.12 (s, 1H), 8.49–8.47 (m, 1H), 8.09 (d, 1H, *J* = 8.0 Hz), 7.69–7.65 (m, 1H), 7.55–7.51 (m, 1H), 7.35 (d, 1H, *J* = 16.0 Hz), 7.04–6.98 (m, 4H), 6.32 (dd, 1H, *J* = 16.2, 6.4 Hz), 4.57–4.53 (m, 1H), 4.34–4.30 (m, 1H), 2.82–2.79 (m, 1H), 2.48–2.28 (m, 2H), 1.67–1.62 (m, 1H), 1.51–1.44 (m, 15H), 1.36–1.28 (m, 1H), 1.18 (d, 6H, *J* = 7.2)
vii5	$C_{30}H_{35}ClNO_4S$	+4.9, *c* 1, Acetone	31.9	130–2	9.11 (s, 1H), 8.38 (d, 1H, *J* = 9.2 Hz), 8.09 (d, 1H, *J* = 2.0 Hz), 7.46 (dd, 1H, *J* = 8.8, 2.0 Hz), 7.28 (d, 1H, *J* = 16.8 Hz), 7.20–7.02 (m, 5H), 6.32 (dd, 1H, *J* = 16.4, 5.6 Hz), 4.56–4.51 (m, 1H), 4.34–4.27 (m, 1H), 2.47–2.27 (m, 2H), 1.63–1.23 (m, 17H)
vii6	$C_{30}H_{34}ClFNO_4S$	+11.9, *c* 1, Acetone	20.3	151–3	9.09 (s, 1H), 8.39 (d, 1H, *J* = 8.8 Hz), 8.09 (d, 1H, *J* = 2.0 Hz), 7.50–7.47 (m, 1H), 7.26 (d, 1H, *J* = 16.4 Hz), 7.08–7.04 (m, 2H), 6.92–6.87 (m, 2H), 6.30 (dd, 1H, *J* = 16.0, 5.6 Hz), 4.57–4.53 (m, 1H), 4.35–4.29 (m, 1H), 2.49–2.29 (m, 2H), 1.67–1.24 (m, 17H)
vii7	$C_{31}H_{37}ClNO_5S$	+7.8, *c* 1, Acetone	25.0	96–8	9.12 (s, 1H), 8.36 (d, 1H, *J* = 9.2 Hz), 8.09 (d, 1H, *J* = 1.6 Hz), 7.46 (dd, 1H, *J* = 9.2, 2.4 Hz), 7.28 (dd, 1H, *J* = 16.0, 0.8 Hz), 7.10–7.06 (m, 1H), 6.68–6.58 (m, 3H), 6.33 (dd, 1H, *J* = 16.2, 6.0 Hz), 4.58–4.53 (m, 1H), 4.33–4.30 (m, 1H), 3.68 (s, 3H), 2.48–2.28 (m, 2H), 1.65–1.25, (m, 17H)
vii8	$C_{33}H_{41}ClNO_4S$	+1.9, *c* 1, CH_2Cl_2	33.6	oil	9.09 (s, 1H), 8.38 (d, 1H, *J* = 8.8 Hz), 8.06 (d, 1H, *J* = 2.0 Hz), 7.45 (dd, 1H, *J* = 9.0, 1.6 Hz), 7.30 (d, 1H, *J* = 16.0 Hz), 7.04–6.95 (m, 4H), 6.30 (dd, 1H, *J* = 16.0, 5.6 Hz), 4.56–4.52 (m, 1H), 4.32–4.29 (m, 1H), 2.81–2.78 (m,1H), 2.46–2.27 (m, 2H), 1.65–1.22 (m, 17H), 1.16 (d, 6H, *J* = 6.8 Hz)
vii9	$C_{30}H_{34}ClFNO_4S$	−17.7, *c* 1, $CHCl_3$	46.5	131–3	9.08 (s, 1H), 8.18–8.14 (m, 2H), 7.24 (dd, 1H, *J* = 15.8, 1.2 Hz), 7.22–7.12 (m, 3H), 7.05–7.03 (m, 2H), 6.34 (dd, 1H, *J* = 16.4, 5.6 Hz), 4.56–4.52 (m, 1H), 4.33–4.28 (m, 1H), 2.47–2.27 (m, 2H), 1.64–1.23 (m, 17H)

(*continued on next page*)

Table 6 (*continued*)

Compound	Formula	$[a]_D^{25}$	Yield (%)	Mp (°C)	^{1}H NMR δ ppm in $CDCl_3$
vii10	$C_{30}H_{33}ClF_2NO_4S$	+11.6, *c* 1, Acetone	69.5	120–1	9.06 (s, 1H), 8.18–8.16 (m, 2H), 7.28 (d, 1H, *J* = 15.2 Hz), 7.09–7.05 (m, 2H), 6.91–6.89 (m, 2H), 6.33 (dd, 1H, *J* = 16.4, 5.2 Hz), 4.57–4.53 (m, 1H), 4.34–4.31 (m, 1H), 2.49–2.29 (m, 2H), 1.67–1.26 (m, 17H)
vii11	$C_{31}H_{36}ClFNO_5S$	−11.3, *c* 1, $CHCl_3$	60.6	83–5	9.08 (s, 1H), 8.17–8.13 (m, 2H), 7.24 (dd, 1H, *J* = 17.2, 0.8 Hz), 7.10 (t, 1H, *J* = 8.4), 6.70–6.58 (m, 3H), 6.35 (dd, 1H, *J* = 16.4, 6.0 Hz), 4.58–4.54 (m, 1H), 4.33–4.29 (m, 1H), 3.69 (s, 3H), 2.48–2.28 (m, 2H), 1.66–1.24 (m, 17H)
vii12	$C_{33}H_{40}ClFNO_4S$	+7.1, *c* 1.1, Acetone	56.1	oil	9.07 (s, 1H), 8.18–8.14 (m, 2H), 7.31 (d, 1H, *J* = 16.4 Hz), 7.06–6.97 (m,4H), 6.35 (dd, 1H, *J* = 16.4, 5.6 Hz), 4.58–4.54 (m, 1H), 4.33–4.31 (m, 1H), 2.83–2.80 (m,1H), 2.48–2.28 (m, 2H), 1.66–1.24 (m, 17H), 1.18 (d, 6H, *J* = 6.8)
vii13	$C_{30}H_{33}F_3NO_4S$	+5.9, *c* 1, Acetone	55.8	169–71	9.11 (s, 1H), 8.07–8.04 (m, 1H), 7.29–7.15 (m, 4H), 7.05–7.03 (m, 2H), 6.34 (dd, 1H, *J* = 16.8, 6.0 Hz), 4.56–4.52 (m, 1H), 4.32–4.29 (m, 1H), 2.47–2.27 (m, 2H), 1.64–1.21 (m, 17H)
vii14	$C_{30}H_{32}F_4NO_4S$	+15.4, *c* 1, THF	70.8	126–8	9.07 (s, 1H), 8.07–8.02 (m, 1H), 7.24 (d, 1H, *J* = 16.0 Hz), 7.07–7.04 (m,2H), 6.93–6.88 (m, 2H), 6.30 (dd, 1H, *J* = 16.0, 5.6 Hz), 4.56–4.52 (m, 1H), 4.33–4.28 (m, 1H), 2.47–2.27 (m, 2H), 1.66–1.19 (m, 17H)
vii15	$C_{31}H_{35}F_3NO_5S$	+11.4, *c* 1, Acetone	21.8	132–4	9.11 (s, 1H), 8.06–8.00 (m, 1H), 7.27 (d, 1H, *J* = 16.0 Hz), 7.10 (t, 1H, *J* = 8.0 Hz), 6.71–6.58 (m,1H), 6.60–6.58 (m, 2H), 6.36 (dd, 1H, *J* = 16.4, 6.0 Hz), 4.58–4.54 (m, 1H), 3.70 (s, 3H), 4.34–4.28 (m, 1H), 2.48–2.28 (m, 2H), 1.66–1.23 (m, 17H)
vii16	$C_{33}H_{39}F_3NO_4S$	+7.5, *c* 0.32, Acetone	58.3	94–96	9.11 (s, 1H), 8.09–8.04 (m, 1H), 7.31 (dd, 1H, *J* = 16.4, 1.2 Hz), 7.08–6.98 (m,4H), 6.34 (dd, 1H, *J* = 16.0, 5.6 Hz), 4.58–4.54 (m, 1H), 4.33–4.30 (m, 1H), 2.84–2.81 (m,1H), 2.48–2.28 (m, 2H), 1.68–1.25 (m, 17H), 1.19 (d, 6H, *J* = 6.8 Hz)
vii17	$C_{36}H_{40}NO_4S_2$	+0.8, *c* 1, THF	26.2	109–10	9.05 (s, 1H), 8.32 (d, 1H, *J* = 9.2 Hz), 7.81 (d, 1H, *J* = 1.6 Hz), 7.54 (dd, 1H, *J* = 6.6, 1.6 Hz), 7.39–7.36 (m, 4H), 7.29–7.25 (m, 2H), 7.19–7.03 (m, 5H), 6.29 (dd, 1H, *J* = 16.2, 6.0 Hz), 4.55–4.51 (m, 1H), 4.32–4.29 (m, 1H), 2.47–2.28 (m, 2H), 1.62–1.24 (m, 17H)
vii18	$C_{36}H_{38}F_2NO_4S_2$	+6.4, *c* 0.7, Acetone	45.7	155–7	9.01 (s, 1H), 8.32 (d, 1H, *J* = 8.8 Hz), 7.70 (d, 1H, *J* = 1.6 Hz), 7.34 (dd, 1H, *J* = 10.0, 1.6 Hz), 7.24 (d, 1H, *J* = 16.4 Hz), 7.56–7.52 (m, 2H), 7.12–7.02 (m, 4H), 6.90–6.86 (m, 2H), 6.26 (dd, 1H, *J* = 16.4, 6.0 Hz), 4.55–4.51 (m, 1H), 4.32–4.29 (m, 1H), 2.48–2.28 (m, 2H), 1.65–1.23 (m, 17H)
vii19	$C_{38}H_{44}NO_6S_2$	−3.6, *c* 1, CH_2Cl_2	52.8	oil	9.05 (s, 1H), 8.30 (d, 1H, *J* = 8.8 Hz), 7.84 (d, 1H, *J* = 1.2 Hz), 7.46 (dd, 1H, *J* = 9.0, 2.0 Hz), 7.30–7.24 (m, 2H), 7.11–7.05 (m, 3H), 6.91–6.88 (m, 1H), 6.66–6.59 (m, 3H), 6.30 (dd, 1H, *J* = 16.0, 5.6 Hz), 4.56–4.52 (m, 1H), 4.32–4.29 (m, 1H), 3.77 (s, 3H), 3.67 (s, 3H) 2.47–2.27 (m, 2H), 1.64–1.25 (m, 17H)
vii20	$C_{42}H_{52}NO_4S_2$	−10.2, *c* 0.84, CH_2Cl_2	21.7	107–8	9.05 (s, 1H), 8.36 (d, 1H, *J* = 8.8 Hz), 7.77 (d, 1H, *J* = 1.6 Hz), 7.38 (dd, 1H, *J* = 9.0, 1.6 Hz), 7.51–7.49 (m, 2H), 7.30–7.28 (m,3H), 7.07–7.00 (m, 4H), 6.30 (dd, 1H, *J* = 16.2, 5.6 Hz), 4.58–4.54 (m, 1H), 4.35–4.32 (m, 1H), 2.98–2.95 (m,1H), 2.85–2.82 (m, 1H), 2.49–2.30 (m, 2H), 1.67–1.35 (m, 17H), 1.31 (d, 6H, *J* = 6.8 Hz), 1.21 (d, 6H, *J* = 7.2 Hz),
vii21	$C_{36}H_{39}FNO_4S_2$	+1.2, *c* 1, Acetone	67.4	oil	8.97 (s, 1H), 8.05 (d, 1H, *J* = 10.8 Hz), 7.60 (d, 1H, *J* = 7.2 Hz), 7.23 (dd, 1H, *J* = 16.4, 1.2 Hz), 7.58–7.55 (m, 2H), 7.44–7.40 (m, 3H), 7.21–7.11 (m, 3H), 7.05–7.03 (m, 2H), 6.29 (dd, 1H, *J* = 16.4, 6.0 Hz), 4.55–4.50 (m, 1H), 4.31–4.28 (m, 1H), 2.47–2.26 (m, 2H), 1.62–1.20 (m, 17H)
vii22	$C_{36}H_{37}F_3NO_4S_2$	+5.3, *c* 0.88, Acetone	35.6	106–8	8.94 (s, 1H), 8.05 (d, 1H, *J* = 11.2 Hz), 7.59–7.50 (m, 3H), 7.25–7.04 (m, 5H), 6.93–6.88 (m, 2H), 6.27 (dd, 1H, *J* = 16.4, 5.6 Hz), 4.55–4.51 (m, 1H), 4.32–4.29 (m, 1H), 2.48–2.28 (m, 2H), 1.65–1.25 (m, 17H)

Table 6 (*continued*)

Compound	Formula	$[a]_D^{25}$	Yield (%)	Mp (°C)	^{1}H NMR δ ppm in $CDCl_3$
vii23	$C_{38}H_{43}FNO_6S_2$	−2.4, *c* 1, Acetone	59.3	123–5	8.98 (s, 1H), 8.04 (d, 1H, *J* = 11.2 Hz), 7.65 (d, 1H, *J* = 7.6 Hz), 7.35–7.30 (m, 1H), 7.27–7.23 (m, 1H), 7.14–7.07 (m, 3H), 6.96–6.93 (m, 1H), 6.68–6.59 (m, 3H), 6.30 (dd,1H, *J* = 16.0, 5.6 Hz), 4.56–4.52 (m, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 4.32–4.29 (m, 1H), 2.47–2.27 (m, 2H), 1.63–1.20 (m, 17H)
vii24	$C_{42}H_{51}FNO_4S_2$	−6.1, *c* 1, CH_2Cl_2	45.4	94–5	8.95 (s, 1H), 8.05 (d, 1H, *J* = 11.6 Hz), 7.53–7.49 (m, 3H), 7.30–7.25 (m, 3H), 7.05–6.96 (m, 4H), 6.33 (dd, 1H, *J* = 16.0, 5.6 Hz), 4.55–4.51 (m, 1H), 4.31–4.27 (m, 1H), 2.96–2.93 (m, 1H), 2.82–2.79 (m, 1H), 2.46–2.26 (m, 2H), 1.64–1.41 (m, 17H), 1.28 (d, 6H, *J* = 6.8 Hz), 1.17 (d, 6H, *J* = 7.2 Hz)
vii25	$C_{36}H_{38}F_2NO_4S_2$	−1.8, *c* 1, CH_2Cl_2	20.5	178–80	9.09 (s, 1H), 7.97 (dd, 1H, *J* = 10.0, 1.2 Hz), 7.39–7.37 (m, 3H), 7.29–7.15 (m, 6H), 7.07–7.05 (m, 2H), 6.36 (dd, 1H, *J* = 16.4, 5.6 Hz), 4.56–4.53 (m, 1H), 4.31–4.29 (m, 1H), 2.47–2.27 (m, 2H), 1.62–1.23 (m, 17H)
vii26	$C_{36}H_{36}F_4NO_4S_2$	+7.6, *c* 1, CH_2Cl_2	47.5	167–70	9.03 (s, 1H), 7.96 (dd, 1H, *J* = 10.4, 2.0 Hz), 7.25 (dd, 1H, *J* = 16.4, 1.2 Hz), 7.47–7.43 (m, 2H), 7.09–7.06 (m, 2H), 6.99–6.89 (m, 4H), 6.34 (dd, 1H, *J* = 16.0, 5.6 Hz), 4.57–4.53 (m, 1H), 4.33–4.30 (m, 1H), 2.49–2.28 (m, 2H), 1.67–1.23 (m, 17H)
vii27	$C_{38}H_{42}F_2NO_6S_2$	+9.7, *c* 0.78, Acetone	52.9	119–21	9.10 (s, 1H), 7.95 (dd, 1H, *J* = 10.4, 2.0 Hz), 7.27 (d, 1H, *J* = 16.0 Hz), 7.17–7.09 (m, 2H), 6.93–6.89 (m, 2H), 6.76–6.60 (m, 4H), 6.38 (dd, 1H, *J* = 16.4, 5.6 Hz), 4.58–4.54 (m, 1H), 4.32–4.29 (m, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 2.47–2.28 (m, 2H), 1.65–1.22 (m, 17H)
vii28	$C_{42}H_{50}F_2NO_4S_2$	+10.4, *c* 1,THF	42.6	107–8	9.08 (s, 1H), 7.98 (dd, 1H, *J* = 10.0, 1.2 Hz), 7.36–7.29 (m, 3H), 7.13–6.99 (m, 6H), 6.36 (dd, 1H, *J* = 16.0, 5.6 Hz), 4.58–4.54 (m, 1H), 4.34–4.30 (m, 1H), 2.87–2.81 (m, 2H),2.48–2.28 (m, 2H), 1.68–1.25 (m, 17H), 1.22–1.19 (m, 12H)
vii29	$C_{42}H_{44}NO_4S_3$	−10.2, *c* 1.0, CH_2Cl_2	80.4	138–40	8.95 (s, 1H), 8.13 (s, 1H), 7.57 (s, 1H), 7.54–7.52 (m, 2H), 7.43–7.39 (m, 3H), 7.32–7.24 (m, 6H), 7.14–7.09 (m, 3H), 6.86–6.84 (m, 2H), 6.27 (dd, 1H, *J* = 16.0, 5.6 Hz), 4.55–4.50 (m, 1H), 4.31–4.28 (m, 1H), 2.46–2.26 (m, 2H), 1.64–1.25 (m, 17H)
vii30	$C_{42}H_{41}F_3NO_4S_3$	+4.2, *c* 1, Acetone	29.4	158–60	8.95 (s, 1H), 7.98 (s, 1H), 7.50 (s, 1H), 7.56–7.51 (m, 2H), 7.36–7.32 (m, 2H), 7.28–7.23 (m, 3H), 7.15–7.11 (m, 2H), 7.04–7.00 (m, 2H), 6.86–6.84 (m, 2H), 6.29 (dd, 1H, *J* = 16.0, 5.6 Hz), 4.57–4.53 (m, 1H), 4.33–4.30 (m, 1H), 2.48–2.28 (m, 2H), 1.69–1.28 (m, 17H)
vii31	$C_{45}H_{50}NO_7S_3$	−7.6, *c* 1.04, CH_2Cl_2	58.6	oil	8.96 (s, 1H), 8.18 (s, 1H), 7.63 (s, 1H), 7.33–6.82 (m, 10H), 6.63–6.60 (m, 1H), 6.44–6.40 (m, 2H), 6.28 (dd, 1H, *J* = 16.4, 6.0 Hz), 4.55–4.51 (m, 1H), 4.31–4.28 (m, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H), 2.46–2.27 (m, 2H), 1.64–1.22 (m, 17H)
vii32	$C_{51}H_{62}NO_4S_3$	−8.3, *c* 0.86, CH_2Cl_2	36.6	110–1	8.91 (s, 1H), 8.04 (s, 1H), 7.53 (s, 1H), 7.49 (d, 2H, *J* = 8.0 Hz), 7.32–7.25 (m, 5H), 7.19 (d, 2H, *J* = 8.4 Hz), 6.99 (d, 2H, *J* = 8.8 Hz), 6.76 (d, 2H, *J* = 8.0 Hz), 6.25 (dd, 1H, *J* = 16.0, 5.6 Hz), 4.56–4.52 (m, 1H), 4.32–4.29 (m, 1H), 2.98–2.91 (m, 2H), 2.82–2.46 (m, 1H), 2.46–2.27 (m, 2H), 1.66–1.34 (m, 17H), 1.31–1.19 (m, 18H),
vii33	$C_{34}H_{26}FNO_3S_3$	−0.8, *c* 1, CH_2Cl_2	59.2	159–61	9.13 (s, 1H), 8.19 (d, 1H, *J* = 10.8 Hz), 7.27–7.06 (m, 16H), 6.33 (dd, 1H, *J* = 16.0, 5.6 Hz), 4.54–4.50 (m, 1H), 4.32–4.28 (m, 1H), 2.47–2.27 (m, 2H), 1.61–1.18 (m, 17H)
vii34	$C_{42}H_{40}F_4NO_4S_3$	+9.2, *c* 1, Acetone	60.2	194–6	9.10 (s, 1H), 8.17 (d, 1H, *J* = 10.4 Hz), 7.27–7.19 (m, 5H), 7.10–7.05 (m, 2H), 6.94–6.86 (m, 6H), 6.31 (dd, 1H, *J* = 16.0, 5.2 Hz), 4.54–4.53 (m, 1H), 4.33–4.29 (m, 1H), 2.48–2.28 (m, 2H), 1.65–1.19 (m, 17H)
vii35	$C_{45}H_{49}FNO_7S_3$	+10.0, *c* 1, Acetone	80.0	oil	9.13 (s, 1H), 8.18 (d, 1H, *J* = 10.4 Hz), 7.25 (dd, 1H, *J* = 16.4, 1.2 Hz), 7.13–7.03 (m, 3H), 6.80–6.58 (m, 9H), 6.44 (dd, 1H, *J* = 16.4, 6.0 Hz), 4.56–4.52 (m, 1H), 4.31–4.28 (m, 1H), 3.70–3.67 (m, 9H), 2.47–2.27 (m, 2H), 1.64–1.20 (m, 17H)

(*continued on next page*)

Table 6 (*continued*)

Compound	Formula	$[a]_D^{25}$	Yield (%)	Mp (°C)	^{1}H NMR δ ppm in $CDCl_3$
vii36	$C_{51}H_{61}FNO_4S_3$	+2.9, *c* 1, Acetone	57.3	111–2	9.13 (s, 1H), 8.17 (d, 1H, *J* = 10.4 Hz), 7.28 (d, 1H, *J* = 16.0 Hz), 7.13 (t, 4H, *J* = 8.4), 7.07–6.99 (m, 8H), 6.32 (dd, 1H, *J* = 16.4, 6.0 Hz), 4.56–4.51 (m, 1H), 4.32–4.29 (m, 1H), 2.86–2.79 (m, 3H), 2.47–2.27 (m, 2H), 1.65–1.22 (m, 17H), 1.20–1.18 (m, 18H)
vii37	$C_{48}H_{48}NO_4S_4$	+2.7, *c* 1, THF	38.1	160–2	9.00 (s, 1H), 7.87 (s, 1H), 7.42–7.02 (m, 19H), 6.74–6.72 (m, 2H), 6.28 (dd, 1H, *J* = 16.4, 6.0 Hz), 4.54–4.49 (m, 1H), 4.30–4.287 (m, 1H), 2.46–2.26 (m, 2H), 1.63–1.22 (m, 17H)
vii38	$C_{48}H_{44}F_4NO_4S_4$	+8.4, *c* 1, Acetone	35.5	169–71	8.99 (s, 1H), 7.71 (s, 1H), 7.40–7.37 (m, 2H), 7.25–7.03 (m, 6H), 6.93–6.79 (m, 7H), 6.73–6.69 (m, 2H), 6.30 (dd, 1H, *J* = 16.4, 6.0 Hz), 4.56–4.52 (m, 1H), 4.31–4.28 (m, 1H), 2.47–2.27 (m, 2H), 1.67–1.24 (m, 17H)
vii39	$C_{52}H_{56}NO_8S_4$	+10.4, *c* 1, Acetone	76.7	oil	8.94 (s, 1H), 8.03 (s, 1H), 7.39–7.29 (m, 3H), 7.17–6.96 (m, 6H), 6.75–6.55 (m, 8H), 6.32 (dd, 1H, *J* = 16.4, 5.6 Hz), 4.65–4.61 (m, 1H), 4.36–4.33 (m, 1H), 3.80–3.63 (m, 9H), 2.07 (s, 3H), 2.50–2.31 (m, 2H), 1.77–1.23 (m, 17H)
vii40	$C_{60}H_{72}NO_4S_4$	+6.9, *c* 1, Acetone	70.9	144–6	8.99 (s, 1H), 7.84 (s, 1H), 7.32–7.21 (m, 6H), 7.14–7.11 (m, 2H), 7.05–6.94 (m, 7H), 6.67–6.65 (m, 2H), 6.28 (dd, 1H, *J* = 16.0, 6.0 Hz), 4.54–4.52 (m, 1H), 4.31–4.28 (m, 1H), 2.97–2.94 (m, 1H), 2.85–2.76 (m, 3H), 2.47–2.27 (m, 2H), 1.65–1.34 (m, 17H), 1.30–1.14 (m, 24H)

[a] The definition of R, R_1, R_2, and R_3 is the same as Table 1.

and the organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated. The resulting oil was purified by silica gel chromatography (petroleum ether–EtOAc, 2:1) to provide the title compound (0.30 g, 81.4%) as white solid. mp: 177–178 °C. ^{1}H NMR δ ppm in $CDCl_3$:9.08 (s, 1H), 8.08–8.03 (m, 1H), 7.35 (dd, 1H, *J* = 16.4, 1.6 Hz), 7.23–7.14 (m, 3H), 7.04–7.02 (m, 2H), 6.36 (dd, 1H, *J* = 16.0, 5.6 Hz), 5.37–5.32 (m, 1H), 4.37–4.35 (m, 1H), 2.76–2.62 (m, 2H), 2.05–1.77 (m, 2H).

All other 3,5-dihydroxy-3,5-*O*-isopropylidene-6-heptenoates were converted to the corresponding pyran-2-ones in the similar manner. The spectra data of **A1**–**A40** are shown in Table 2.

6.13. Isolation of HMG CoA reductase

Male Holtzman–Sprague–Dawley rats were acclimated to an alternate 12-h light–dark cycle for a period of 2–3 weeks. The animals, weighing 200–250 g, were fed ordinary diets containing 2% cholestyramine and water for 4 days prior to sacrifice at the mid-dark period, which is the diurnal high point of enzyme activity.[10]

The microsomal fraction enriched in solubilized HMG CoA reductase was prepared by slow freezing (−80 °C) and thawing according to the method of Heller and Shrewsbury.[12] The Bradford Method (Coomassie brilliant blue) was used for enzyme quantitation.

6.14. HMG CoA reductase inhibition assay in vitro

The HMG CoA reductase inhibitory activity was assayed spectrophotometrically, following the method of Kleinsek et al.,[9] 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 μg/140 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 N 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.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2007.08.044.

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