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Synthesis and Biological Activity of Methanesulfonamide Pyrimidine- and *N*-Methanesulfonyl Pyrrole-Substituted 3,5-Dihydroxy-6-heptenoates, a Novel Series of HMG-CoA Reductase Inhibitors

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Abstract—A novel series of methanesulfonamide pyrimidine- and *N*-methanesulfonyl pyrrole-substituted 3,5-dihydroxy-6-heptenoates were synthesized and evaluated for their ability to inhibit the enzyme HMG-CoA reductase in vitro. Monocalcium bis(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl-*N*-methanesulfonylaminopyrimidin)-5-yl]-(3*R*,5*S*)-dihydroxy-(*E*)-6-heptenoate (**3a**, S-4522) was selected as a candidate for further evaluation. Compound **3a** was approximately four times more potent than lovastatin sodium salt (in inhibiting HMG-CoA reductase in vitro ($IC_{50}=11$ nM). Compound **3a** was shown to be the most potent cholesterol biosynthesis inhibitor in this series ($IC_{50}=1.12$ nM) in rat isolated hepatocytes; its inhibitory activity was approximately 100 times more potent than pravastatin.

Introduction

Hypercholesterolemia is now well recognized as a primary risk factor in coronary heart disease.[1,2] Clinical studies with lipid-lowering agents have established that decreasing elevated serum cholesterol levels reduces the incidence of cardiovascular mortality.[3,4]

Lovastatin (**1a**), pravastatin (**1b**) and fluvastatin (**2**) are potent hypocholesterolemic agents[5] which are widely used clinically. This class of compounds inhibits 3-hydroxy-3-methylglutaryl CoA reductase (HMG-CoA reductase), a major rate-limiting enzyme in cholesterol biosynthesis,[6] and has been shown to induce the expression of the low-density lipoprotein (LDL) receptor which mediates the clearance of LDL cholesterol from plasma.[7]

To obtain more potent reductase inhibitors, much effort has been expended on replacing the complex decalin portion of the mevinic acids (i.e. **1a** or **b**) with structurally simpler and achiral aromatic surrogates. In this connection, the pyrimidine- and pyrrole-substituted dihydroxy-6-heptenoates were reported to have strong activity for HMG-CoA reductase inhibition.[8]

As described above, inhibition of liver cholesterol synthesis causes increased hepatic LDL-receptor expression. From previous work on the relationship between tissue selectivity and lipophilicity, compounds with low calculated lipophilicity (CLOGP) values (<2.0) are known to show liver selectivity.[9] In order to reduce CLOGP values, the introduction of a chemically stable sulfonamide group ($\pi=-1.63$) as a hydrophilic moiety has been tried. Sulfonamide groups are particularly useful as spacers in connecting pharmacophores having a spatial arrangement of chemical groups that are recognized by a receptor. Furthermore, these groups seems stable in the metabolic sequence in vivo.

Herein, we report the synthesis and biological activity of methanesulfonamide pyrimidine- and *N*-methanesulfonyl pyrrole-substituted 3,5-dihydroxy-6-heptenoates as novel classes of highly active HMG-CoA reductase inhibitors. During this study, we found that the monocalcium bis(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl-*N*-methanesulfonylaminopyrimidin)-5-yl]-(3*R*,5*S*)-dihydroxy-(*E*)-6-heptenoate (**3a**, S-4522) possesses greater enzyme inhibitory activity than lovastatin (**1a**) and pravastatin (**1b**).

Chemistry

Synthesis of pyrimidine derivatives

The new substituted pyrimidine derivatives (**3a–g**) were synthesized in optically pure forms by the general method shown in Schemes 1 and 2, and are listed in Table 1. Knoevenagel reaction of *p*-fluorobenzaldehyde

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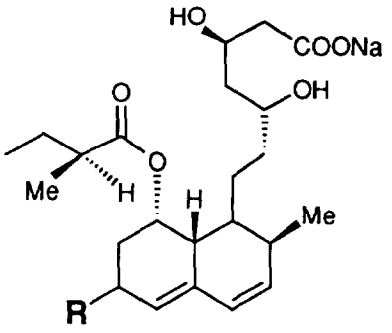
(**5**) with ethyl isobutyrylacetate (**6**) provided the unsaturated ketoester (**7**). Cyclocondensation of (**7**) with *S*-methylisothiourea hydrogen sulfate followed by dehydrogenation with DDQ afforded the pyrimidine ring. Pyrimidine sulfide (**8**) was oxidized by *m*-chloroperbenzoic acid (*m*-CPBA) to give sulfonylpyrimidine (**9**). This compound (**9**) was an important key intermediate for the synthesis of various sulfonamide derivatives. Methylamination of sulfone (**9**) with $MeNH_2$ in MeOH followed by treatment with methanesulfonyl chloride gave the *N*-methanesulfonylamino derivative of pyrimidine (**10**). Reduction of the ester of compound (**10**) with DIBAL-H followed by TPAP oxidation afforded the corresponding aldehyde (**11**). The heptenoate compound (**13**) was obtained by Wittig reaction with aldehyde **11** and the optically active ylide **12**.[10] The compound **13** was deprotected with HF in MeCN, and stereoselective chelation-controlled reduction with Et_2BOMe and $NaBH_4$ in THF:MeOH gave methyl (3*R*,5*S*,6*E*)-dihydroxyheptenoate (**14**). Hydrolysis of dihydroxyheptenoate (**14**) with aqueous NaOH afforded the sodium salt of heptenoate (**3a**-Na salt). Monocalcium bis(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl-*N*-methanesulfonylaminopyrimidin)-5-yl]-(3*R*,5*S*)-dihydroxy-(*E*)-6-heptenoate (**3a**, S-4522) was obtained as white powder from **3a**-Na salt on treatment with aqueous $CaCl_2$ (Scheme 1). The sodium salts of heptenoates **3b–g** were synthesized from **8**, **9** and **15** as shown in Scheme 2.

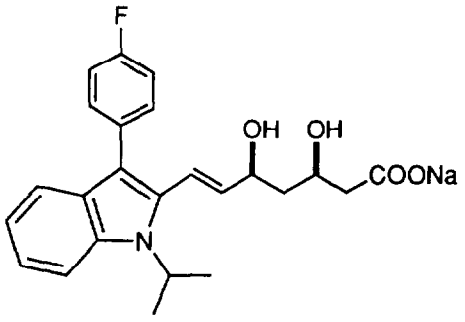
Synthesis of pyrrole derivatives

The methanesulfonyl pyrroles were synthesized in optically pure forms by the general method shown in Scheme 3 and are listed in Table 1.

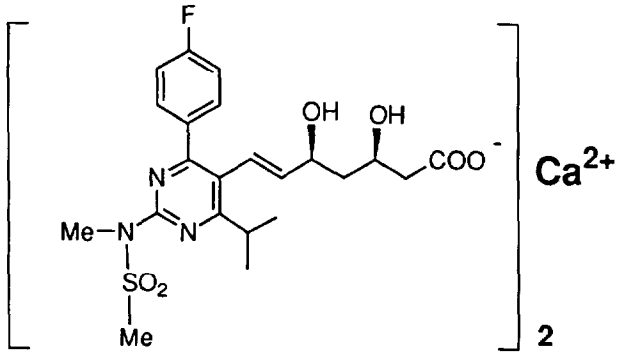
Cyclocondensation of ethyl isobutyrylacetate (**6**) with 2-amino-4′-fluoroacetophenone (**20**) in the presence of NaOAc in refluxing acetic acid gave 4-arylpyrrole-3-carboxylate ester (**21**). Pyrrole ethyl ester (**21**) was allowed to react with methanesulfonyl chloride to give the *N*-methanesulfonylpyrrole derivative (**22**). Reduction of the ester (**22**) with DIBAL-H followed by TPAP oxidation afforded the corresponding aldehyde (**23**). Compound **24** was obtained via Wittig reaction of the aldehyde (**23**) with optically active ylide (**12**). The



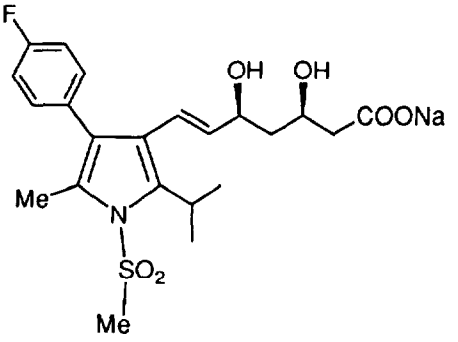
1a. R = α-Me (Lovastatin-Na)
1b. R = β-OH (Pravastatin-Na)



2. Fluvastatin

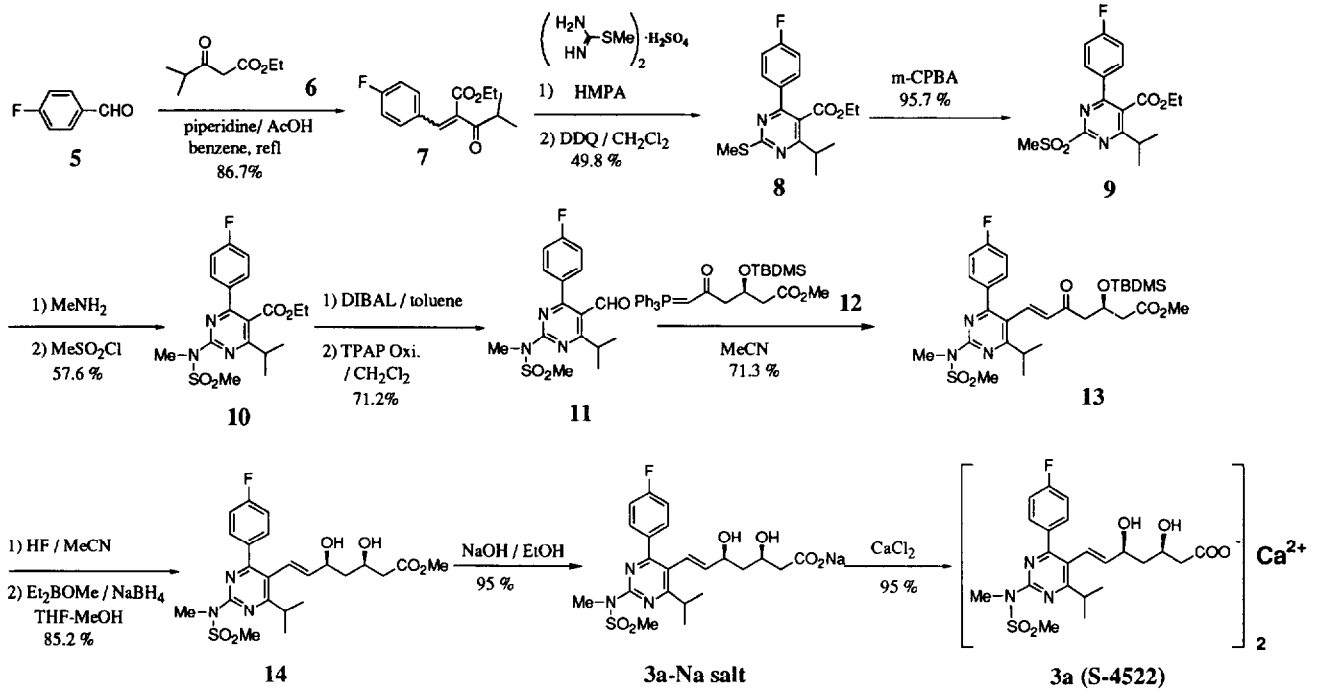


3a (S-4522)



4a

Figure 1.



Scheme 1.

compound (**24**) obtained was deprotected with HF in MeCN, and stereoselective chelation-controlled reduction with Et_2BOMe and $NaBH_4$ in THF:MeOH gave methyl (3*R*,5*S*,6*E*)-dihydroxyheptenoate (**26**). Hydrolysis of the dihydroxyheptenoate (**26**) with aqueous NaOH afforded the sodium salt of heptenoate (**4a**) (Scheme 3). The sodium salt of heptenoate (**4b**) was also synthesized in a similar manner.

Biological Results

The methanesulfonamide pyrimidine- and *N*-methanesulfonyl pyrrole-substituted 3,5-dihydroxy-6-heptenoates listed in Table 1 were evaluated for their ability to inhibit partially purified rat liver HMG-CoA reductase in vitro.[11]

The selected compound (**3a**, S-4522) was further evaluated for its ability to inhibit cholesterol biosynthesis in rat liver isolated hepatocytes, to increase m-RNA of LDL receptors and tissue (liver) selectivity, and to decrease plasma cholesterol levels in normolipemic male beagle dogs and cynomologus monkey in vivo. The results were compared with those obtained for **1a**, **b** and **2**.

Inhibition of rat liver HMG-CoA reductase was measured by an in vitro assay procedure based on the direct conversion of DL-3-hydroxy-3-methyl [3-^{14}C]-glutaryl-CoA to [^{14}C]mevalonolactone. The enzyme preparation and assay procedures used in this study were the same as those described in ref. 11. The data shown in Table 1 indicated that sulfonyl pyrrole derivatives were more potent than pravastatin (**1b**), fluvastatin (**2**) and lovastatin sodium salt (**1a**). The *N*-methanesulfonyl pyrimidine derivative (**3a**)[12] was the potent enzyme inhibitor and approximately 4.42 times more potent than lovastatin sodium salt (**1a**).

Compound **3a** was tested for its ability to inhibit cholesterol biosynthesis in rat liver isolated hepatocytes, based on its inhibition of the incorporation of sodium [^{14}C]acetate into cholesterol. Compound **3a** possessed an IC_{50} of 1.12 nM and was approximately 100-fold more potent than pravastatin sodium salt (**1b**) (IC_{50} 198 nM).[13]

Stronger inhibition of cholesterol biosynthesis in cells indicated greater increase of LDL receptors in human cells.[7] In cultured human hepatoma (HEP-G2) cells, **3a** caused approximately 10 times greater increase of m-RNA of LDL receptors than pravastatin (**1b**).[13] This result suggested **3a** to lead to a greater decrease in serum cholesterol than pravastatin (**1b**).

Inhibition of sterol synthesis in vivo was examined in different tissues of rat by measuring the incorporation of [^{14}C]acetate into digitonin-precipitable [^{14}C]sterols. Examination of the results of these studies have suggested that **3a** acted more potently in liver than peripheral tissue, which was expected from the lipophilicity value of **3a** (LOGP = 1.62).[13] The lipophilicity value less than 2 was suggested to be good for the liver selectivity.[9] The liver selective HMG-CoA reductase inhibitor indicates a potent cholesterol lowering and, moreover, reduced side effects in clinical use because the liver is a major site of cholesterol biosynthesis.

The activity of **3a** for decreasing plasma cholesterol levels in normolipemic male beagle dogs and cynomo-

logus monkey after administration po is more potent than pravastatin (**1b**). Compound **3a** reduced plasma cholesterol levels of beagle dogs by 26% and pravastatin (**1b**) by 18% at a repeated dose for 14 days of 3 mg/kg per day. Furthermore, **3a** reduced plasma cholesterol levels of cynomologus monkey by 22% at a dosage of 12.5 mg/kg and pravastatin (**1b**) reduced it by 19% at the dosage of 50 mg/kg.[13]

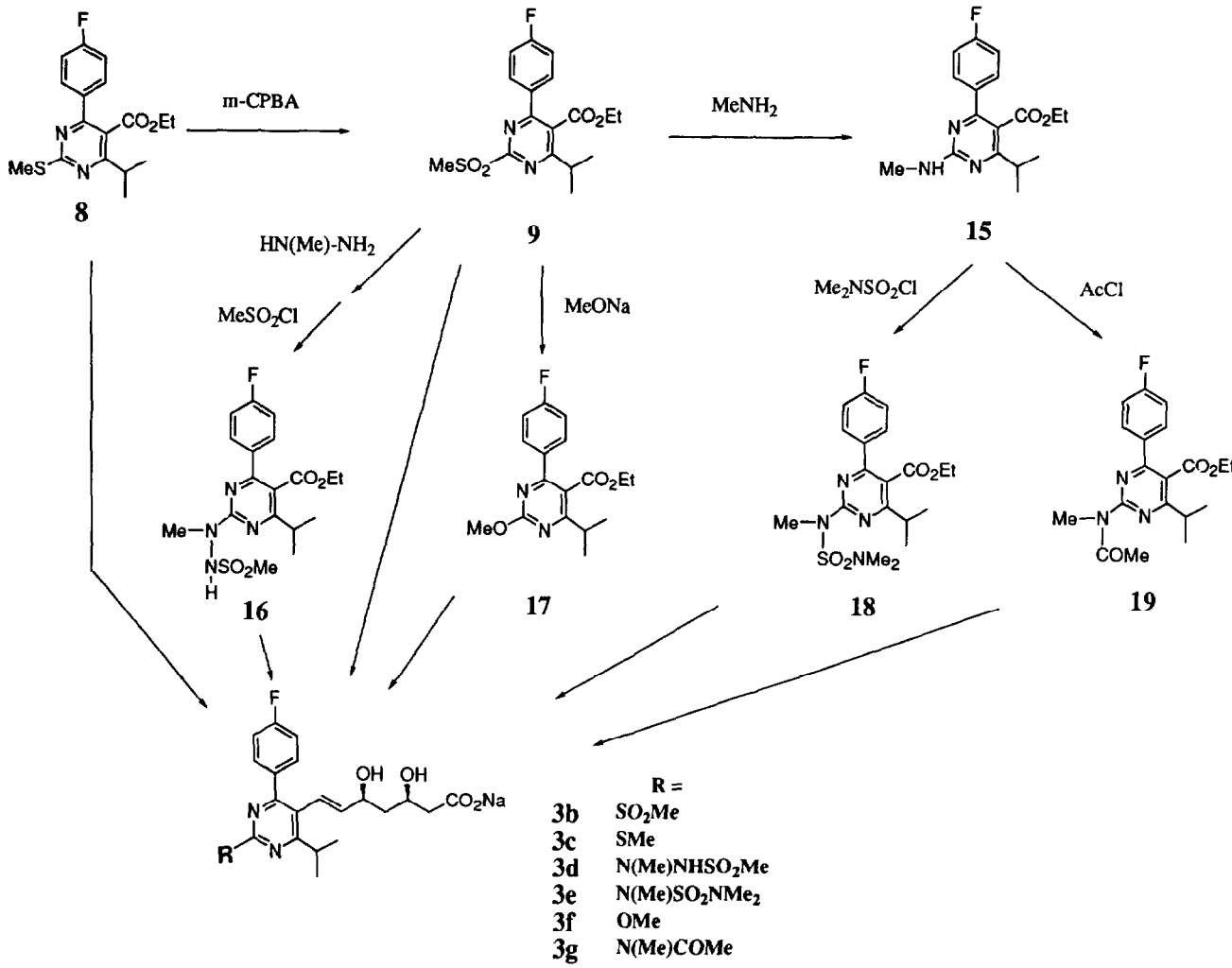
Conclusion

N-Methanesulfonyl pyrimidine- and pyrrole-substituted 3,5-dihydroxy-6-heptenoates were synthesized and found to exceed lovastatin sodium salt (**1a**), pravastatin (**1b**) and fluvastatin (**2**) in their ability to inhibit the enzyme HMG-CoA reductase in vitro and to decrease plasma cholesterol levels in vivo. Monocalcium bis(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl-*N*-methanesulfonylaminopyrimidin)-5-yl]-(3*R*,5*S*)-dihydroxy-(*E*)-6-heptenoate (**3a**, S-4522) was approximately four times more potent than lovastatin sodium salt (**1a**) in inhibiting HMG-CoA reductase in vitro and **3a** was the most potent cholesterol biosynthesis inhibitor in rat isolated hepatocytes, having been approximately 100 times more potent than pravastatin (**1b**). They are promising candidates for development of antiarteriosclerotic agents. The clinical trial of S-4522 (**3a**) is in progress.

Experimental Section

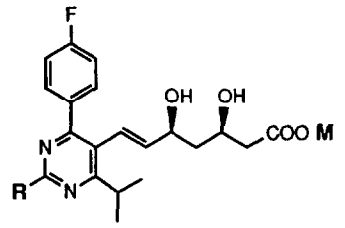
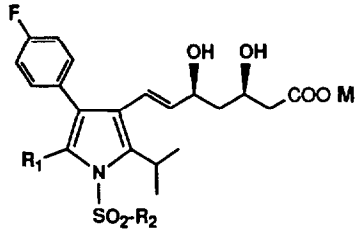
General

Reactions were carried out under a nitrogen atmosphere in anhydrous solvent (dried over molecular sieves type 4 Å). Organic extracts were dried over anhydrous $MgSO_4$. The solvent was removed at aspirator pressure using a rotary evaporator. TLC was performed with Merck precoated TLC plates silica gel 60 F_{254}, and the compounds were made visible using a fluorescent inspection lamp and iodine vapor. Gravity chromatography was done with Merck silica gel 60 (70–230 mesh). The melting points are uncorrected. ^1H and ^{13}C NMR spectra were determined as $CDCl_3$ solution at 200 and 50.3 MHz.



Scheme 2.

Table 1. Inhibition of HMG-CoA reductase in vitro[a]

	No.	R	M	Relative potency[b]
				
3a ~ g	**3a**	$N(Me)SO_2Me$	Ca	442
	3b	SO_2Me	Na	154
	3c	SMe	Na	385
	3d	$N(Me)NHSO_2Me$	Na	260
	3e	$N(Me)SO_2NMe_2$	Na	141
	3f	OMe	Na	279
	3g	N(Me)COMe	Na	179
				
4a ~ b	**4a**	$R_1=Me$ $R_2=Me$	Na	418
	4b	$R_1=H$ $R_2=Me$	Na	589
	1a	lovastatin-Na		100[c]
	1b	pravastatin		130
	2	fluvastatin		158

[a]Microsomal preparation of rat liver HMG-CoA reductase. See ref 11.
[b]Values represent the mean of at least two determinations performed with four doses with each concentration run in duplicate.
[c]For estimation of relative inhibitory potencies, lovastatin-Na was assigned as a value of 100. Lovastatin-Na averaged $IC_{50}=49$ nM and was used in every run as an internal standard.

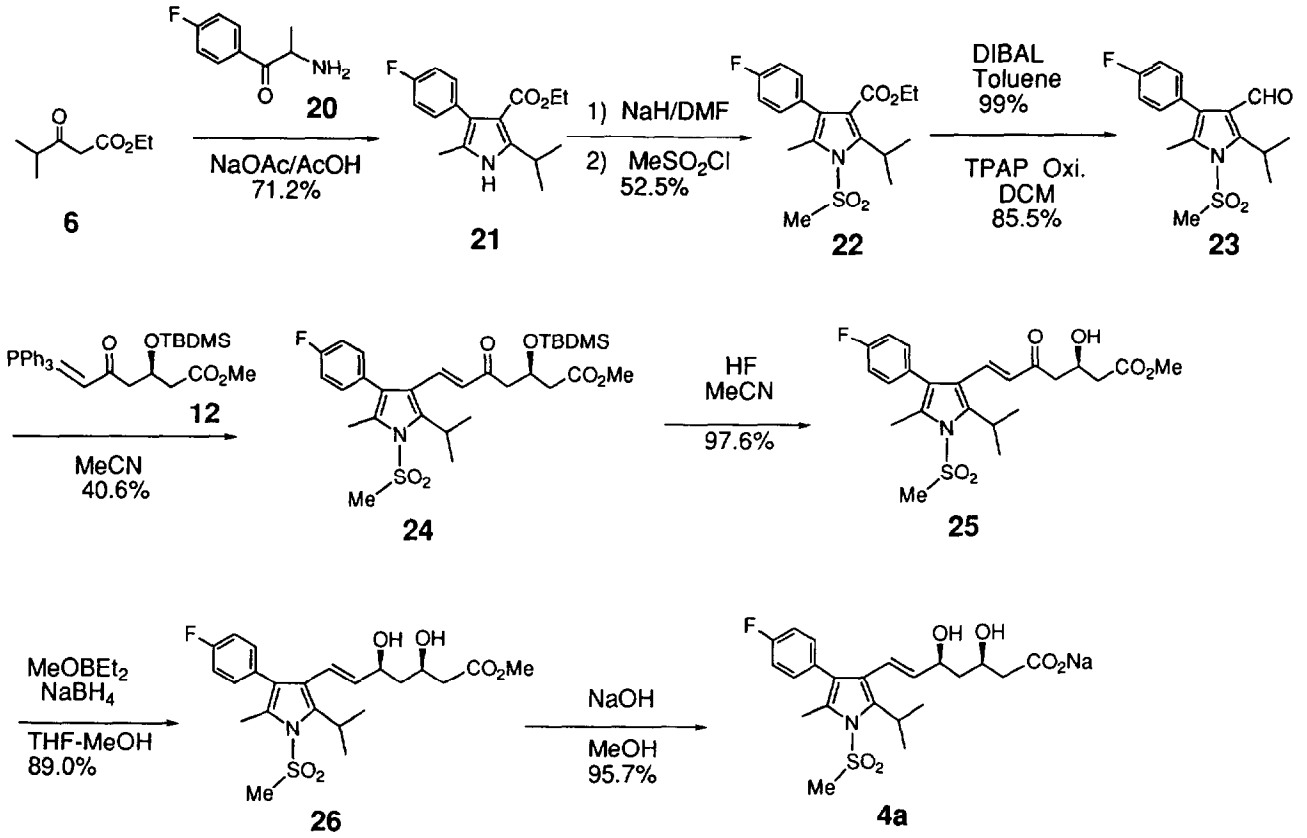
Evaluation of biological activity

The HMG-CoA reductase inhibitory effect was examined with preparation of rat liver microsomes from Sprague–Dawley rats, which had been allowed free access to ordinary diets containing 2% cholestyramine and water for 2 weeks. The microsomes were purified as described in ref 11.

Monocalcium bis(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl-*N*-methanesulfonyl aminopyrimidin)-5-yl]-(3*R*,5*S*) - dihydroxy - (*E*) - 6 - heptenoate (3a, S - 4522). The reaction of *p*-fluorobenzaldehyde (**5**) 81.81 g with ethyl isobutyrylacetate (**6**) gave 151.0 g (yield: 86.7%) of compound (**7**). The mixture of a solution of 44.68 g of compound **7** in 65 ml of HMPA and 28.24 g of *S*-methylisothiourea hydrogen sulfate was stirred at 100 °C for 22 h. The reaction mixture was extracted with Et_2O, and washed successively with satd sodium hydrogencarbonate and water. The organic layer was dried, and the solvent was distilled away. The obtained residue was mixed with 400 mL benzene and 21.64 g (0.095 mmol) DDQ. The mixture was stirred for 30 min. Then the mixture was subjected to silica gel column chromatography to give 24.31 g (yield: 49.8%) of compound **8**. NMR ($CDCl_3$): δ 1.10 (t, $J=7$ Hz, 3H); 1.31 (d, $J=7$ Hz, 6H); 2.61 (s, 3H); 3.18 (hept, $J=7$ Hz, 1H); 4.18 (q, $J=7$ Hz, 2H); 7.12 (m, 2H); 7.65 (m, 2H).

To a soln of 13.28 g (0.04 mmol) of compound **8** in $CHCl_3$ was added 17.98 g of *m*-chloroperbenzoic acid (*m*-CPBA), and the reaction mixture was stirred at room temperature. This was then washed successively with Na_2SO_4 and satd $NaHCO_3$. The soln was dried, and the solvent distilled away and washed with n-hexane to give 13.93 g (yield: 95.7%) of compound **9**. NMR ($CDCl_3$): δ 1.16 (t, $J=7$ Hz, 3H); 1.37 (d, $J=7$ Hz, 6H); 3.26 (hept, $J=7$ Hz, 1H); 3.42 (s, 3H); 4.28 (q, 2H); 7.18 (m, 2H); 7.76 (m, 2H); mp 123–125° C

To a soln of 52.7 g (144 mmol) of compound **9** in 500 mL absolute EtOH was gradually added a soln of 71.9 mL of 5 N methylamine in EtOH under ice-cooling. The reaction mixture was warmed to room temperature, stirred for 1 h and evapd under red. press. To the residue, water was added and the mixture was extracted with Et_2O, dried and evapd under red. press. to give 46.9 g. To a soln of 370 mg (1.213 mmol) of this compound in 5 mL of DMF was added 60 mg of 60% NaH under ice-cooling, and the reaction mixture was stirred for 30 min. Methanesulfonyl chloride, 208 mg, was then added, and the whole mixture was warmed to room temperature and stirred for 2 h. Ice-water was added to the mixture which was then extracted with Et_2O. The organic layer was washed with water and dried. The solvent was evapd under red. press., and the resulting residue was washed with EtOH:n-pentane to give 322 mg (yield: 57.6%) of compound **10**. NMR ($CDCl_3$): δ 1.10 (t, $J=7$ Hz, 3H); 1.32 (d, $J=7$ Hz, 6H); 3.24 (hept, $J=7$ Hz, 1H); 3.52 (s, 3H); 3.60 (s, 3H);



Scheme 3.

4.19 (q, $J=7$ Hz, 2H); 7.14 (m, 2H); 7.68 (m, 2H) ; mp 115–117 °C.

To a solution of 322 mg of compound **10** in 7 mL of anhydrous toluene was added dropwise 1.4 mL of DIBAL-H in 1.5 M toluene at −74 °C. The reaction mixture was stirred for 1 h and acetic acid added. The mixture was extracted with Et_2O, and the organic layer was washed with Na_2CO_3 bicarbonate and water, dried and evapd under red. press. to remove Et_2O. The obtained residue was subjected to silica gel column chromatography eluting with CH_2Cl_2:Et_2O (20:1) to give 277 mg of the alcohol derivative.

A suspension of 277 mg of the thus obtained alcohol derivative, 190 mg of 4-methylmorpholine-*N*-oxide, 6 mg of tetrapropyl-ammonium perruthenate (TPAP), 1.0 g of powder molecular sieve (MS) 4 Å, and 10 ml of CH_2Cl_2 was stirred for 2 h. The insoluble matter was filtered off and the solvent of two-thirds of the filtrate was distilled away under red. press. The resulting residue was subjected to silica gel column chromatography eluting with CH_2Cl_2 to give 196 mg (yield: 71.2%) of 4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl-*N*-methylsulfonylamino)-5-formyl-pyrimidine (**11**).

A soln of 190 mg of compound **11** and 450 mg of methyl (3*R*)-3-(tert-butyldimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidenehexanoate (**12**) in 5 mL of acetonitrile was refluxed under heating for 14 h and evapd under red. press. to remove acetonitrile. The resulting residue was subjected to silica gel column chromatography eluting with CH_2Cl_2 to give 233 mg (yield: 71.3%) of methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl-*N*-methylsulfonylamino)pyrimidin-5-yl]-(3*R*)-3-(tert-butyldimethylsilyloxy)-5-oxo-(*E*)-6-heptenoate (**13**).

To a soln of 16 g of compound **13** in 100 mL of acetonitrile was added dropwise a soln of 48% hydrogen fluoride in 400 mL of acetonitrile (1:19) under ice-cooling, and the mixture was warmed to room temperature and stirred for 1.5 h. The reaction mixture was neutralized with Na_2CO_3 and extracted with Et_2O. The organic layer was washed with sodium chloride, dried and evapd under red. press. to distill Et_2O to give 13 g of methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl-*N*-methanesulfonylamino)pyrimidin-5-yl]-(3*R*)-3-hydroxy-5-oxo-(*E*)-6-heptenoate.

To a soln of 13 g of this compound in 350 mL of anhydrous THF and 90 mL of methanol was added a soln of 29.7 mL of 1 M diethylmethoxyborane (Et_2BOMe):THF at −78 °C, and the mixture was stirred at the same temperature for 30 min. To the mixture was added 1.3 g of $NaBH_4$, and the mixture was stirred for 3 h. Acetic acid 16 mL was added, and the mixture was adjusted to pH 8 with satd Na_2CO_3 and extracted with Et_2O. The organic layer was washed with water, dried and Et_2O evaporated under red.

press. To the resulting residue was added MeOH, and the mixture evapd under red. press. The procedure was repeated three times. The resulting residue was subjected to silica gel column chromatography eluting with CH_2Cl_2 (3:1) to give 11.4 g (yield: 85.2%) of methyl 7-[4-(4-fluorophenyl)-6-iso-propyl-2-(*N*-methyl-*N*-methanesulfonylamino)pyrimidin-5-yl]-(3*R*,5*S*)-dihydroxy-(*E*)-6-heptenoate (**14**). NMR ($CDCl_3$): δ 1.27 (d, J=7 Hz, 6H); 1.53 (m, 2H); 2.47 (d, J=6 Hz, 2H); 3.36 (hept, J=7 Hz, 1H); 3.52 (s, 3H); 3.57 (s, 3H); 3.73 (s, 3H); 4.20 (m, 1H); 4.43 (m, 1H); 5.45 (dd, J=5, 16 Hz, 1H); 6.64 (dd, J=2, 16 Hz, 1H); 7.09 (m, 2H); 7.64 (m, 2H).

To a soln of 11.4 g of compound **14** in 160 mL of EtOH was added 223 mL of 0.1 N NaOH under ice-cooling. The reaction mixture was warmed to room temperature and stirred for 1 h. The solvent was distilled away under red. press., and Et_2O was added to the resulting residue, and the mixture was stirred to give 11.0 g (yield: 95.0%) of compound **3a**–Na salt). Anal. calcd for $C_{22}H_{27}N_3O_6SFNa \cdot 0.5H_2O$; C, 51.56; H, 5.51; N, 8.20; F, 3.71; Na, 4.49; H_2O, 1.76; found C, 51.81; H, 5.71; N, 8.04; Na, 4.60; H_2O, 1.61; MS *m/z* 1001 (MH^+); $[\alpha]_D$ +21.3±0.6 (*c*=1.009, 23.0 °C, H_2O); NMR (D_2O): δ 1.25 (dd, J=6.9 Hz, 6H); 1.40–1.73 (m, 2H); 2.22–2.35 (m, 2H); 3.42 (hept, J=6.9, 1H); 3.49 (s, 3H); 3.60 (s, 3H); 3.70 (m, 1H); 4.33 (m, 1H); 5.50 (dd, J=15.9 Hz, 6.6 Hz, 1H); 6.61 (d, J=15.9, 1H); 7.14 (t, J=8.7 Hz, 2H); 7.70 (t, J=4.8 Hz, 2H).

To a soln of 205 mg of compound **3a**-Na salt in 4 mL of H_2O was added 45 mg of $CaCl_2$ in 1 mL of H_2O. The resulting precipitate was removed by filtration, washed with H_2O, and dried under vacuum to give 162 mg (yield: 78.0%) of compound **3a** as a white powder. Anal. calcd for $C_{44}H_{54}N_6O_{12}S_2F_2Ca.H_2O$; C, 51.85; H, 5.54; N, 8.25; Ca, 3.93; H_2O, 1.77; found C, 51.77; H, 5.58; N, 8.52; Ca, 3.93; H_2O, 1.99; $[\alpha]_D$ +14.8±0.5 (*c* 1.012, 24.0 °C, 50% MeOH); NMR (DMSO-d_6): δ 1.26 (dd, J=6.8 Hz, 6H); 1.39–1.71 (m, 2H); 2.19–2.42 (m, 2H); 3.46 (hept, J=6.8 Hz, 1H); 3.50 (s, 3H); 3.52 (s, 3H); 4.02 (m, 1H); 4.34 (m, 1H); 5.53 (dd, J=16.0, 5.8 Hz, 1H); 6.61 (dd, J=16.0, 1.2 Hz, 1H); 7.14 (t, J=9 Hz, 2H); 7.70 (dd, J=10.2, 5.8 Hz, 2H).

Sodium(+)7-[4-(4-fluorophenyl)-2-isopropyl-5-methyl-1-methylsulfonylpyrrol-3-yl]-(3*R*),(5*S*)-dihydroxy-(*E*)-6-heptenoate (4a). A mixture of 6.33 g (40 mmol) ethyl isobutyrylacetate (**6**), 12.22 g (60 mmol) 2-amino-4′-fluoropropiophenone hydrochloride (**20**), 1 mL acetic acid, 5.58 g sodium acetate, and 0.7 mL water was refluxed for 4 h. After cooling, the reaction mixture was adjusted to pH 8 with satd $NaHCO_3$ and extracted with Et_2O. The extract was subjected to silica gel column chromatography eluting with CH_2Cl_2 to give compound **21**.

To a suspension of 948 mg (23.7 mmol) of 60% NaH in 50 mL of anhydrous DMF was added dropwise a soln of 5.93 g (21.5 mmol) of compound **21** in 60 mL of anhydrous DMF under nitrogen atmosphere, and the reaction mixture was stirred for 30 mins under ice-cooling. To the mixture was added dropwise a soln of 4.18 g (23.7 mmol) of benzenesulfonyl chloride in 10 mL of anhydrous DMF, and the mixture was stirred at room temperature for 2 h and treated with ice-water. The solution was extracted with Et_2O, and the organic layer was washed with water to give 9.65 g of oil. It was subjected to silica gel column chromatography eluting with n-hexane:CH_2Cl_2 (1:2) to give 8.65 g (yield: 96.6%) of compound **22**.

To a soln of 4.16 g (10 mmol) of compound **22** in 200 mL of anhydrous toluene was added dropwise 25 mL of 1 M DIBAL-H in toluene under a nitrogen atmosphere at −65 to −70 °C for 15 min, and the reaction mixture was stirred at the same temperature for 1 h. To the reaction mixture were added water and 10% HCl, and the mixture was warmed to room temperature and extracted with Et_2O. The insoluble material was filtered off on celite. The Et_2O layer was washed with water, dried and concd under red. press. to give 4.03 g of the hydroxymethyl compound. A mixture of 4.03 g (10.8 mmol) of *N*-methylmorpholine-*N*-oxide, 81 mg (0.23 mmol) of TPAP, and 20 g of powdered molecular sieves 4 Å in 150 mL of methylene chloride was stirred at room temperature for 2 h, and the insoluble material was filtered off on celite. The filtrate was concd to one-fifth of its original volume under reduced pressure. It was subjected to silica gel column chromatography eluting with methylene chloride to give 3.67 g (yield: 91.2%) of compound **23**.

Compound **23** 0.12 g (0.26 mmol) was allowed to react with (3*R*)-3-(tert-butyldimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidenehexanoate (**12**) in the same manner as described for the pyrimidine derivatives to give 0.1 g (yield: 84.7%) of compound **4a** as a powder. NMR ($CDCl_3$): δ 1.37 (d, J=7 Hz, 6H); 2.24 (s, 3H); 2.50 (d, J=6 Hz, 2H); 3.18 (s, 3H); 3.84 (m, 1H); 4.17 (m, 1H); 4.33 (m, 1H); 5.10 (dd, J=16, 6 Hz, 1H); 6.57 (dd, J=16 Hz, 1, 1H); 7.12 (m, 4H).

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12. (^{1}H NMR δ) **3b** (R=SO_2Me): yield 70.9% (D_2O) 1.27 (dd, *J*=7,2 Hz, 6H); 1.60 (m, 2H); 2.25 (d, *J*=6 Hz, d, 2H); 3.44 (s, 3H); 3.51 (hept, *J*=7 Hz, 1H); 3.70 (m, 1H); 4.33 (q, *J*=6 Hz, 1H); 5.65 (dd, *J*=5, 16 Hz, 1H); 6.71 (d, *J*=16 Hz, 1H); 7.23 (m, 2H); 7.60 (m, 2H), **3c** (R=SMe): yield 87.3% (D_2O) 1.20 (d, *J*=7 Hz, 6H); 1.47 (m, 1H); 1.61 (m, 1H); 2.26 (m, 2H); 2.54 (s, 3H); 3.36 (hept, *J*=7 Hz, 1H); 3.71 (m, 1H); 4.29 (m, 1H); 5.43 (dd, *J*=6 Hz, 16, 1H); 6.55 (d, *J*=16 Hz, 1H); 7.16 (m, 2H); 7.47(m, 2H), **3d** (R=N(Me)$NHSO_2Me$): yield: 74.7%(D_2O) 1.23 (d, *J*=7 Hz, 6H); 1.51 (m, 2H); 2.26 (d, *J*=6 Hz, 2H); 3.10 (s, 3H); 3.37 (hept, *J*=7 Hz, 1H); 3.44 (s, 3H); 3.70 (m, 1H); 4.29 (q, *J*=6 Hz, 1H); 5.39(dd, *J*=5, 16 Hz, 1H); 6.58 (d, *J*=16 Hz, 1H); 7.19 (m, 2H); 7.52 (m, 2H), **3e** (R=N(Me)SO_2NMe_2): yield: ($CDCl_3$, CD_3OD) 1.26 (d, *J*=6.6 Hz, 6H); 1.36–1.69 (m, 2H); 2.15–2.50 (m, 2H); 2.85 (s, 6H); 3 .41 (m, 2H); 3.64 (s, 3H); 4.04 (m, 1H); 4.37 (m, 1H); 5.48 (dd, *J*=5.6, 16 Hz, 1H); 6.54 (dd, *J*=1, 16 Hz, 1H); 7.05–7.66 (m, 4H), **3f** (R: OMe): yield 57.7% ($CDCl_3$, CD_3OD) 1.27 (d, *J*=6.6 Hz, 6H); 1.35–1.68 (m, 2H); 2.17–2.43 (m, 2H); 3.36 (m, 2H); 4.05 (s, 3H); 4.37 (m, 2H); 5.48 (dd, *J*=5.6, 16 Hz, 1H); 6.54 (dd, *J*=1.4, 16 Hz, 1H); 7.06–7.65 (m, 4H), **3g** (R: N(Me)COMe): yield 57.7% ($CDCl_3$) 1.27 (d, *J*=7 Hz, 6H); 1.57 (m, 2H); 2.17 (s, 3H); 2.27 (d, *J*=6 Hz, 2H); 3.72 (s, 3H); 3.50 (hept, *J*=7 Hz, 1H); 3.70 (m, 1H); 4.35 (q, *J*=6 Hz, 1H); 5.59 (dd, *J*=5, 16 Hz, 1H); 6.54 (d, *J*=16, 1H); 7.24 (m, 2H); 7.59 (m, 2H).

13. The result will be published separately.

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