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Synthesis and Biological Evaluation of Orally Active Hypolipidemic Agents

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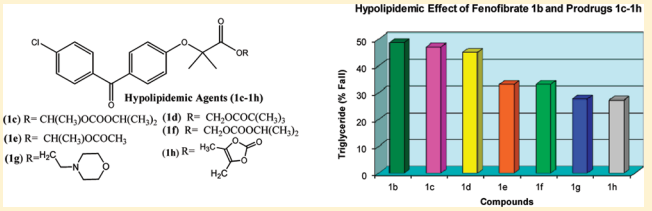
Supporting Information

ABSTRACT:



A series of novel fenofibric acid ester prodrugs **1c**−**1h** were synthesized and evaluated with the aim of obtaining potent hypolipidemic agents. Prodrugs **1c** and **1d** exhibited potent hypochlolesterolemic activity, lowering the mice plasma triglyceride level up to 47% in Swiss albino mice after oral administration of 50 mg/kg/day for 8 days. Fenofibric acid ester prodrugs **1c**−**1h** were found lipophilic like fenofibrate (**1b**), indicated by partition coefficients measured in octanol−buffer system at pH 7.4. On the basis of in vivo studies, prodrugs **1c** and **1d** emerged as potent hypolipidemic agents.

INTRODUCTION

Fenofibrate (**1b**, Figure 1) is a third-generation, well-known lipid regulating agent which has been on the market for a long time. It corresponds to the nomenclature of 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl propionate. After its absorption, which is known to take place in the duodenum and other parts of the gastrointestinal tract, it is metabolized in the body to the active metabolite fenofibric acid (**1a**).[1−7] Fenofibrate is >90% bound and has an elimination half-life of approximately 20 h, allowing once-daily administration. Fenofibrate requires special pharmaceutical formulations in order to ensure good bioavailability, especially after oral administration. Accordingly, fenofibrate has been prepared in several different formulations. The bioavailability of the micronized form is around 30% greater than that of the unmodified drug.[1−3] More recently, the dissolution of micronized fenofibrate was further enhanced by the development of a modified release tablet formulation (bioavaibility was increased by a further 25%). This new tablet formulation will replace the micronized fenofibrate capsule.[4−6]

The most common adverse events observed after fenofibrate administration affected the gastrointestinal system, the skin, and appendages. Abnormal liver function tests and increase creatine kinase activity are frequently reported.[1,2,8−10] In general, it is reported that fibrates can reduce the level of triglycerides by 30−50% and increases HDL cholesterol level by 5−6%. The magnitude of their effect is directly related to the severity of lipoprotein abnormalities at baseline.[11−13]

The mechanism of the action of fenofibrate on lipoprotein metabolism appears to involve the activation of specific nuclear receptor called peroxisome proliferator-activated receptors α (PPARα),[14] which are expressed in the liver. Activation of PPARα modulates the expression of several genes involved in lipoprotein metabolism. The activity of lipoprotein lipase is increased and results in an increase in the clearance of circulating triglyceride rich lipoproteins.[15] It is established that the apolipoprotein C-III (apoC-III) inhibits lipoprotein lipase.[16] The biosynthesis of apoC-III is decreased by fibrates.[15] Hence low apoC-III levels will further enhance the clearance of triglyceride rich lipoproteins. In addition to the antihyperlipidemic effects, fenofibrate has anti-inflammatory action, as evidenced by a reduction in acute phase reactants such as C-reactive protein as well as a number of cytokines, IL-6, TNF-α, and interferon-γ. This pleiotropic effect of the fenofibrate contributes in their coronary risk-reducing ability.[17−19] Moreover, several studies indicate that fibrates decrease the level of factors promoting coagulation and increase fibrinolysis. The dual hypolipidemic/antiplatelet effect of fibrates renders them interesting candidates for reducing the risk of atherosclerosis and its thrombotic complications,[20] which are the major causes of coronary artery diseases.[21,22] α-Asorane bioisosteric analogues of fibrates such as clofibrate, bezafibrate, and fenofibrate have significant hypocholesterolaemic activity.[23−25] These interesting findings motivates us to prepare new fenofibric acid ester prodrugs **1c**−**1h** that might hold promising hypolipidemic activity.

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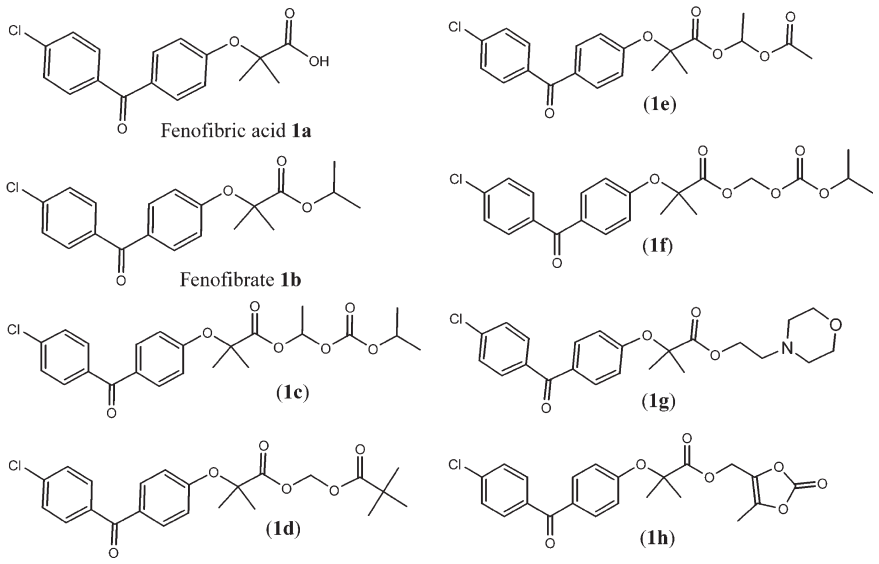

Figure 1. Chemical structures of fenofibric acid (**1a**), fenofibrate (**1b**), and prodrugs **1c**−**1h**.

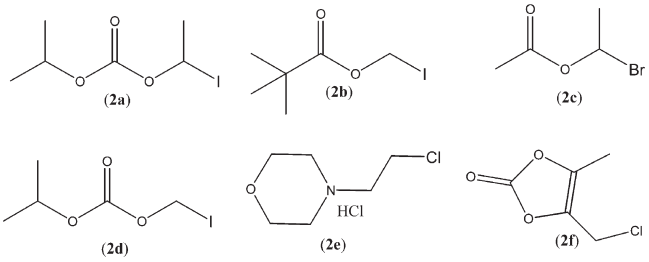

Figure 2. Chemical structures of iodoethylisopropyl carbonate (**2a**), iodomethyl pivalate (**2b**), 1-acetoxyethyl bromide (**2c**), iodomethylisopropyl carbonate (**2d**), 4-(2-chloroethyl) morpholine hydrochloride (**2e**), and 4-chloromethyl-5-methyl-1,3-dioxol-2-one (**2f**).

All prodrugs were evaluated for their hypolipidemic activity in male Swiss albino mice (SAM), without micronization of compounds. These prodrugs showed moderate to very good efficacy in lowering triglycerides (TG) and total cholesterol (TC). This study investigated the hypolipidemic activity, particle size distribution, powder X-ray diffraction, and partition coefficient (log *P*) of prodrugs **1c**−**1h**.

CHEMISTRY

A series of prodrugs **1c**−**1h** were readily prepared by condensation of fenofibric acid (**1a**) with appropriate promoiety **2a**−**2f** (Figure 2), in the presence of 1,1,3,3,-tetramethyl guanidine (TMG) or sodium carbonate or potassium carbonate in polar aprotic solvent like dimethylacetamide (DMAc) or dimethylformamide (DMF), to give the corresponding fenofibric acid ester prodrugs in good yield in good yields (85%, 85%, 85%, 82%, 69%, 83%), as depicted in Scheme 1. The structures of all prodrug compounds were established by ^{1}H NMR, ^{13}C NMR, mass spectrometry, and elemental analysis, and their purity in excess of 99.0% was confirmed by HPLC analysis.

1-Iodooethylisopropyl carbonate (**2a**) was prepared in 90% yield by treatment of 1-chloroethylisopropyl carbonate with sodium iodide and 18-crown-6 in toluene at 100 °C for 7 h. Iodomethyl pivalate (**2b**) and iodomethylisopropyl carbonate (**2d**) were synthesized as per the procedure given in our earlier published articles.[26,27] 1-Acetoxyethyl bromide (**2c**) was synthesized in 84% yield by treatment of vinyl acetate with hydrobromic acid (g) at 32−38 °C. The preparation of promoieties **2a** and **2b** was performed as depicted in Scheme 2. Commercially available 4-(2-chloroethyl) morpholine hydrochloride (**2e**), and 4-chloromethyl-5-methyl-1, 3-dioxol- 2-one (**2f**) were used in the preparation of prodrugs **1g** and **1h** (Scheme 1). The structures of promoieties were established by IR, ^{1}H NMR, and purity in excess of 97% (except **2a**) was confirmed by GC.

RESULTS AND DISCUSSION

Pharmacological Evaluation. Fenofibrate (**1b**) is usually orally administered with maximum dose 120 mg per day for patients suffering from hypertriglyceridemia. It is poorly and variably absorbed when taken with food, and about 60% of the dose of the conventional form is effectively absorbed and found in the blood as fenofibric acid. Bioavailability of **1b** is very low when administered without micronization.[1−3] With the aim of improving hypolipidemic activity series of fenofibric acid ester, prodrugs **1c**−**1h** were synthesized from the fenofibric acid (**1a**) and evaluated for lipid lowering potential in male Swiss albino mice (SAM), a moderate hypertriglyceridemic animal model.[25,26] The mice were treated with **1c**−**1h** and **1b** by oral gavage at a dose of 50 mg/kg body weight for 8 days. The in vivo profile of **1c**−**1h** was compared with a reference drug **1b** for hypolipidemic activity. The daily oral administration of **1c**−**1h** lowered significantly the plasma triglyceride level (TG) (Table 1 and Figure 3). Experimental values of triglyceride reduction of **1b** are in line with those reported earlier.[29−31] Prodrugs **1c** and **1d** showed equipotent triglyceride lowering activity as **1b** and were more potent than the rest of the prodrugs **1e**−**1h**. Total cholesterol did not show significant changes in the fenofibrate as well as prodrugs treated animals, and former values are in line with the literature.[26−28] Interestingly, prodrugs **1c**, **1d**, **1f**, and **1h** appear to be marginally more potent in total cholesterol lowering activity than **1b** (Table 1 and Figure 4).

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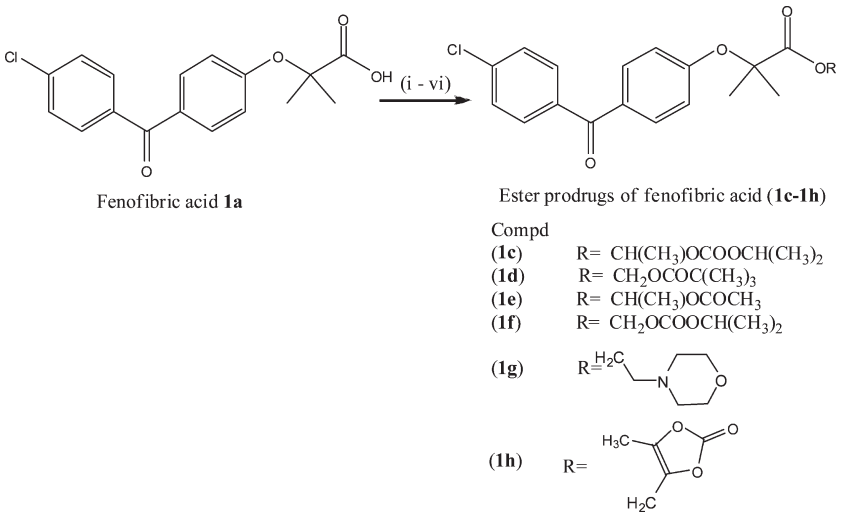
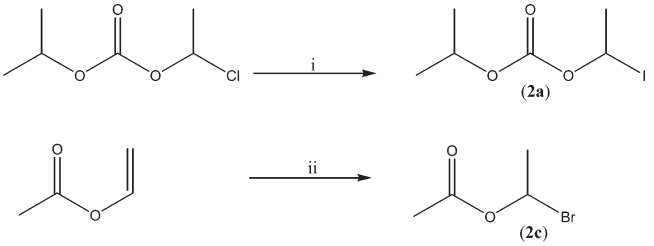
Scheme 1. Synthesis of Ester Prodrugs of Fenofibric Acid 1c−1h[a]



[a] Reagents and conditions: (i) $ICH(CH_3)OCOOCH(CH_3)_2$, DMAc, TMG, −5 °C, 45 min; (ii) $ICH_2OCO(CH_3)_3$, DMAc, TMG, −5 °C, 15 min; (iii) $BrCH(CH_3)OCOCH_3$, K_2CO_3, DMAc, 30 °C, 30 min; (iv) $ICH_2OCOO(CH_3)_2$, DMAc, TMG, O °C, 30 min; (v) promoiety **2e**, K_2CO_3, DMF, 60 °C, 5 h; (vi) promoiety **2f**, Na_2CO_3, DMAc, 30 °C, 17 h.

Scheme 2. Synthesis of Promoieties 2a, 2c[a]



[a] Reagents and conditions: (i) NaI, 18-crown-6, toluene, 100 °C, 7 h; (ii) HBr (g) 32−38 °C.

Particle Size Distribution. Bioavailability of an active pharmaceutical ingredient (API) administered orally depends upon its particle size. Fenofibrate (**1b**) is currently micronized before formulation to get sufficient bioavailability (30−50%).[1−3] The pharmacological profiles of prodrugs **1c**−**1h** indicate that **1c** and **1d** showed equipotent hyperlipidemic activity as reference drug fenofibrate (**1a**) even though these prodrug compounds have higher particle size distribution (Table 2). Hence it may be concluded that prodrugs **1c** and **1d** may not require a special kind of pharmacological formulation like micronization/or spray drying to improve its efficacy.

Partition Coefficient. To examine the fundamental process of the transfer of drug to the biological membrane, the partition coefficient of prodrugs **1c**−**1h** and the reference drug fenofibrate (**1b**) was determined by HPLC method in octanol−buffer system at 25 °C. Partition coefficient of **1b** was in line with the value reported in the literature.[32] Partition coefficient values are summarized in Table 3. Prodrugs **1c**−**1h** were found lipophilic as identical to fenofibrate (**1b**), and the compound **1g** was less lipophilic than **1b**. Ionization of prodrugs was not observed during determination of partition coefficient.

Aqueous Solubility. Aqueous solubility is an important physicochemical parameter of an active pharmaceutical ingredient (API), and its knowledge has fundamental importance in a wide range of applications and research areas. The orally administered drug should be stable at various pH environments encountered in the gastrointestinal tract to deliver the intact prodrug to the systemic circulation. Six fenofibric acid ester pro drugs evaluated for aqueous solubility at pH 1−9. Prodrugs **1c**−**1h** and the reference drug fenofibrate (**1b**) were stable and practically insoluble at 1−9. The fenofibrate solubility result was in line with the reported earlier.[32] Limit of detection (LOD) and limit of qualification (LOQ) of **1b** and **1c**−**1h** were estimated by HPLC at a wavelength of 254 nm. Aqueous solubility of prodrugs was less, which is related to the higher lipophilicity. The experimental results are depicted in Table 5. Increased molecular size by introducing a bulky group through ester linkage can lead to poor solubility of ester prodrugs. Aqueous solubility of ester prodrug **1g** was comparatively more, which could be related to the lower lipophilicity relative to other prodrugs in this series (Table 4).

Solid State Morphology. The existence of multiple crystal forms with differences in the solid state properties can translate

Table 1. Hypolipidemic Effect of Prodrugs 1c−1h and Fenofibrate (1b) on Triglyceride (TG) and Total Cholesterol (TC) Level in Swiss Albino Mice (SAM)[a]

	dose		TG		TC	
compd	mg/kg	μmol/kg	(mg/dL)	% fall	(mg/dL)	% fall
control			129.7 ± 7.6		126.8 ± 3.5	
1b	50	138.5	66.6 ± 1.9	48.6	122.60 ± 2.7	5.5
1c	50	111.5	68.7 ± 2.5	47.0	119.70 ± 1.9	7.7
1d	50	115.7	71.3 ± 5.0	45.0	118.00 ± 3.3	9.0
1e	50	123.7	86.7 ± 8.4	33.1	134.30 ± 4.8	−3.5[b]
1f	50	115.1	86.7 ± 5.5	33.1	120.30 ± 7.2	7.2
1g	50	116.0	93.9 ± 9.7	27.6	126.63 ± 4.6	2.4
1h	50	116.2	94.4 ± 5.0	27.2	115.20 ± 4.1	11.2

[a] Each value represents the mean ± SE (n = 10). The percentage of TG and TC lowering action are shown relative to normal control. [b] Negative value increase in the level of measured parameter % fall and % rise are calculated for groups in relation to the control group.

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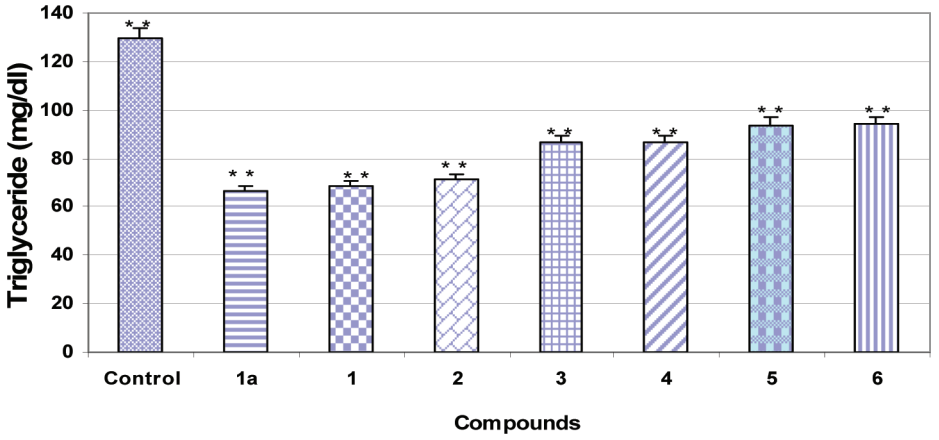

Figure 3. Plasma triglyceride levels in Swiss albino mice treated via oral gavage for 8 days with fenofibrate (**1b**) and prodrugs **1c**−**1h**. Bar represents mean ± SE (n = 10 mice per group; ** $p < 0.05$ relative to vehicle control).

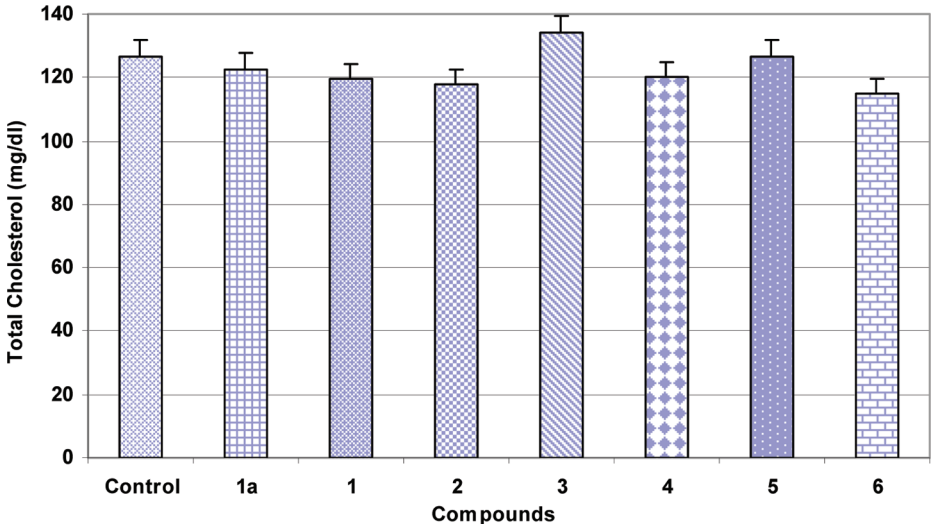

Figure 4. Decrease in plasma total cholesterol level in Swiss albino mice treated via oral gavage for 8 days with fenofibrate (**1b**) and prodrugs **1c**−**1h**. Bars represent percent total cholesterol change from vehicle control and represents the mean ± SE (n = 10 mice per group).

Table 2. Particle Size Distribution of Fenofibrate (1b) and Prodrugs 1c−1h

	particle size distribution (in μm)				
compd	<10%	<50%	<75%	<90%	<100%
1b	0.5	7.8	9.0	18.4	49.3
1c	1.0	20.6	67.1	302.8	645.3
1d	0.4	3.4	10.6	33.9	91.4
1e	0.3	4.4	21.5	45.0	427.6
1f	2.0	292.8	473	645	878.7
1g	0.8	6.8	9.4	31.16	60.5
1h	2.0	28.8	37.1	84.1	200.0

Table 3. Partition Coefficient of Fenofibrate (1b) and Prodrugs 1c−1h in Aqueous Solution

	partition coefficient (log P)[a]
compound	0.2 M phosphate buffer pH 7.4
1b	4.78
1b[b]	5.24
1c	5.43
1d	4.70
1e	4.65
1f	4.91
1g	3.50
1h	4.35

[a] Results are expressed as the mean of three tests (n = 3). [b] Partition coefficient reported in the literature.[32]

into significant effects on the chemical stability, bioavailability,[33] and processability,[34] including powder flowability[35,36] and compressability[37] of active pharmaceutical ingredient (API). Typically, the thermodynamically stable crystalline form is preferred because the risk of solid-state transformations (i.e., solid-state phase transitions) during process and storage is minimized. Hence it is necessary to know the solid state morphology of prodrug

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Table 4. Aqueous Solubility, Limit of Detection, and Limit of Qualification of Fenofibrate (1b) and Prodrugs 1c−1h in Buffer Solutions at 40 °C for 4 h

			aqueous solubility (μg/mL)[a]				
compd	LOD[b] (μg/mL)	LOQ[b] (μg/mL)	pH 1.0	pH 3.0	pH 5.2	pH 7.4	pH 9.0
1b	0.036	0.108	0.003	0.005	0.075	0.13	0.24
1c	0.032	0.097	ND	ND	0.001	0.001	0.022
1d	0.011	0.033	ND	ND	0.001	0.002	0.001
1e	0.013	0.039	ND	ND	0.003	0.002	0.003
1f	0.027	0.081	ND	0.002	0.002	0.002	0.006
1g	0.028	0.084	0.005	0.015	38.0	1.92	4.80
1h	0.0094	0.0284	0.23	0.002	0.003	0.002	0.004

[a] Buffer solutions are prepared as per USP 32. [b] Experimentally determined. Results are reported as mean (n = 3). LOD, limit of detection; LOQ, limit of qualification; ND, not detected in HPLC analysis.

Table 5. Gradient Elution Program

time (min)	mobile phase A	mobile phase B
0−2	90	10
2−3	30	70
3−12	30	70
12−15	90	10
15−20	90	10

compounds. PXRD pattern of prodrugs **1c**−**1h** appeared highly crystalline when screened in a Bruker AXS D8 Advance diffractometer (Figures 5, 6, 7, 8, 9, and 10). All prodrugs exhibit sharp 2θ peaks corresponds to well define crystal lattices. The prodrug **1c** possesses sharp peaks at 2θ equal to 4.51°, 9.08°, 9.42°, 10.83°, 12.51°, 13.69°, 14.00°, 14.72°, 15.88°, 16.20°, 17.39°, 17.61°, 18.31°, 19.00°, 19.82°, 20.20°, 20.76°, 21.03°, 21.42°, 21.89°, 22.39°, 22.96°, 23.67°, 24.41°, 25.42°, 25.76°. The prodrug **1d** possesses sharp peaks at 2θ equal to 5.33°, 8.38°, 9.56°, 10.62°, 11.24°, 15.48°, 15.94°, 16.50°, 16.76°, 17.05°, 17.57°, 17.78°, 18.30°, 18.53°, 19.08°, 20.04°, 20.73°, 21.28°, 21.75°, 22.54°, 23.35°, 24.52°, 25.34°, 25.69°, 26.63°, 26.93°, 27.85°. The prodrug **1e** possesses sharp peaks at 2θ equal to 5.53°, 9.88°, 12.78°, 13.80°, 14.11°, 16.72°, 17.66°, 19.43°, 19.96°, 20.46°, 21.67°, 22.42°, 23.98°, 24.86°, 25.75°, 27.30°, 28.86°, 29.72°, 30.32°, 32.94°. The prodrug **1f** possesses sharp peaks at 2θ equal to 8.69°, 17.46°, 26.32°, 35.36°, 40.02°. The prodrug **1g** possesses sharp peaks at 2θ equal to 7.35°, 13.39°, 14.75°, 16.45°, 18.46°, 19.54°, 19.91°, 20.46°, 22.62°, 23.51°, 27.95°, 29.76°, 30.27°. The prodrug **1h** possesses sharp peaks at 2θ equal to 5.73°, 7.61°, 9.36°, 11.47°, 13.54°, 14.03°, 15.29°, 16.35°, 16.52°, 16.71°, 18.61°, 18.79°, 19.16°, 19.49°, 22.65°, 23.04°, 23.53°, 24.61°, 24.87°, 25.37°, 26.14°, 27.29°, 29.71°. Further, the stability of the crystalline forms were confirmed by the absence of any noticeable change in XRD pattern on exposing to 50 °C and 85% RH for two days. These prodrugs **1c**−**1h** exhibit sharp single peak in DSC, which further confirms the stable nature of the crystalline forms.

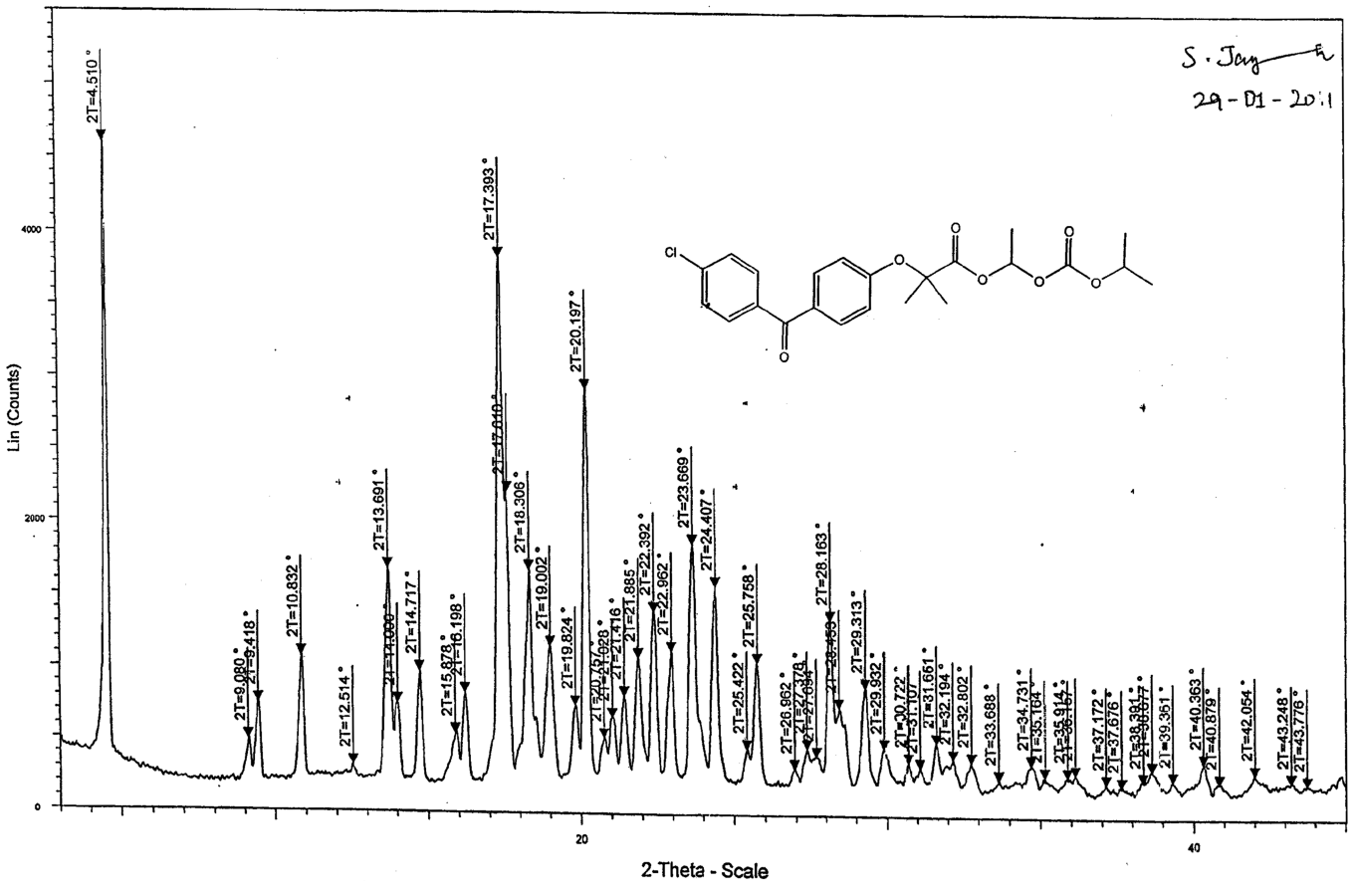

Figure 5. PXRD diffractogram for prodrug **1c**.

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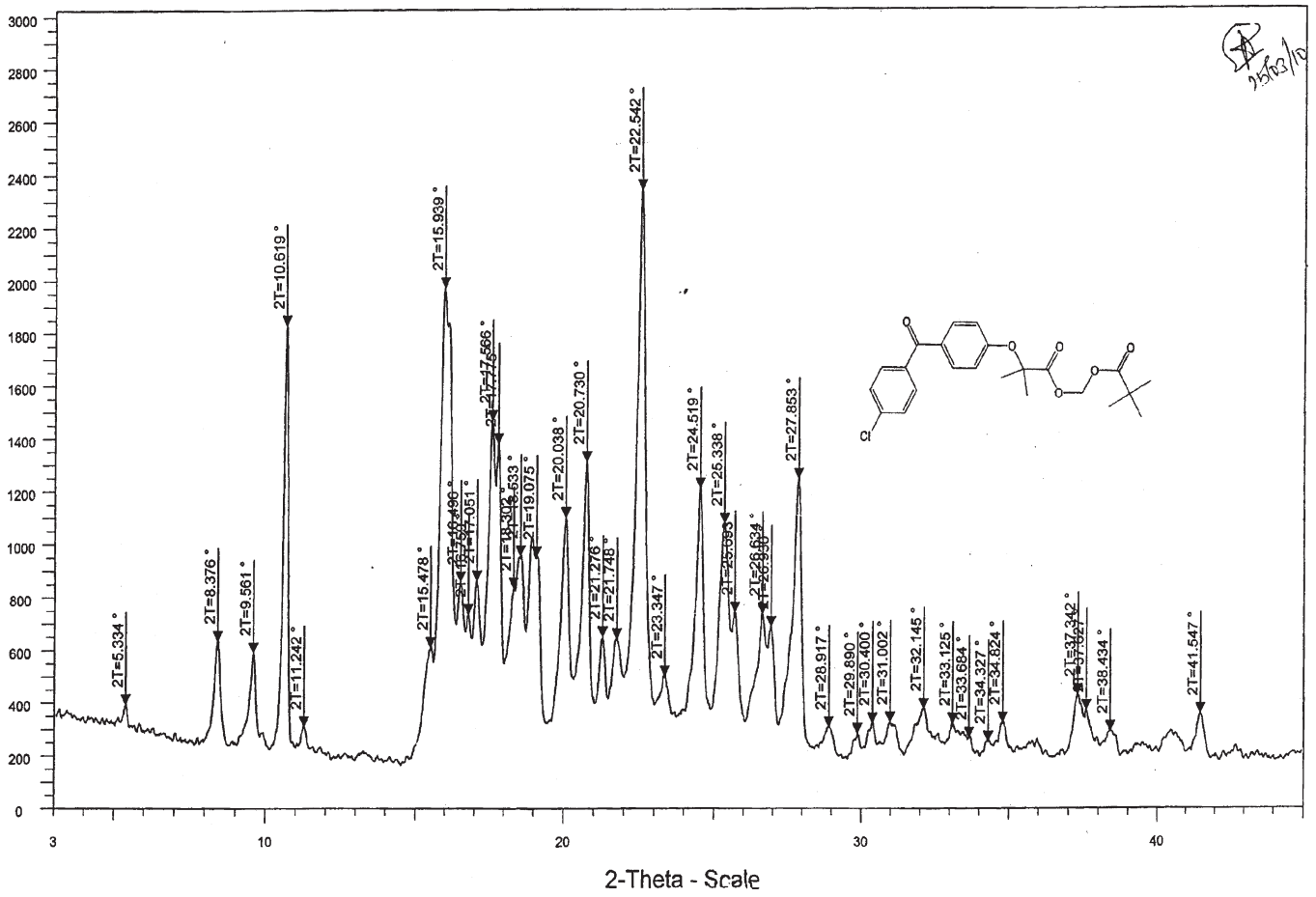

Figure 6. PXRD diffractogram for prodrug **1d**.

CONCLUSION

Novel fenofibric acid ester prodrugs **1c**−**1h** were synthesized and evaluated for their hypolipidemic activity by known experimental techniques[28,29] in male Swiss albino mice in comparison with reference drug fenofibrate (**1b**). Prodrugs **1c** and **1d** demonstrated significant efficacy in lowering triglyceride (47% and 45%). Thus, on the basis of preliminary in vivo studies, prodrugs **1c** and **1d** emerged as potent hypolipidemic drugs and which may mitigate the bioavailability issue leading to an accelerated drug release without special kind of pharmaceutical formulation/or micronization. These preliminary results suggest that this class of compounds are potent hypolipidemic agents. Further investigation including a dose response will be studied to determine the mode of action of these agents on lipid metabolism.

EXPERIMENTAL SECTION

Materials and Methods. Melting points were determined on an MR VIS (Lab India) melting point apparatus and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Advance spectrophotometer using $CDCl_3$ solvent. The chemical shifts are reported in ppm downfield from zero, and coupling constants are reported in hertz (Hz). IR spectra were acquired by using a FTIR Perkin-Elmer model RXI and FTIR spectrophotometer Nicolet 380 (Thermo Nicolet); software was Omnic. Mass spectra were recorded on a PE-SCIEX API-3000 LCMS/MS (Applied Biosystem) spectrophotometer. HPLC analysis was performed by using a Waters Alliance system, pump model 2695 with UV detector model 2487 and Shimadzu LC 2010 CHT with UV detector. Particle size distribution analysis was performed on Malvern particle size analyzer model Master Sizer S. All prodrug compounds were analyzed by HPLC, and their purity was confirmed to be excess of 99.0%. GC analysis was performed on Perkin-Elmer model Clarus-500 instrument, and purity of promoieties **2b**−**2d** was confirmed to be in excess of 97%. The promoiety **2a** was obtained with purity 92.9% (after deleting toluene solvent peak. Toluene response was found to be 7 times more than that of **2a** in GC analysis). Promoiety **2a** is unstable and hence it was used in the next stage without further purification. UV spectra were recorded by using a Shimadzu UV-2401 PC spectrophotometer. Powder XRD of prodrugs was performed on Bruker AXS D8 Advance diffractometer. Particle size distribution analysis was performed on Malvern Master Sizer S. In vivo study was performed on Clinical Chemistry analyzer (Erba XL 300) by using an ERBA diagnostics kit. The in vivo study was carried out by using protocol approved by the Institutional Animal Ethics Committee (IAEC) and compiled with National Institute of Health (NIH) guidelines on handling of experimental animals. An inbreed colony (at Orchid Research Laboratory, India) of male Swiss albino mice (SAM) were used for the study. Commercially available promoieties **2e** and **2f** were gifted by M/s Matrix Laboratories, India. Finofibric acid and Fenofibrate (EP) samples were gifted by D. K. Pharmachem Pvt. Ltd., India.

*1-Iodoethylisopropyl Carbonate (**2a**).* A solution of 1-chloroethylisopropyl-carbonate (10 g, 0.06 mol) in toluene (600 mL) was allowed to react with anhydrous sodium iodide (11.2 g, 0.0747 mol) in the presence of catalyst 18-crown-6 (0.5 g) at 100 °C for 5 h under nitrogen atmosphere. Then, the reaction mixture was cooled to 2 °C and washed with 2.5% sodium thiosulfate (35 mL) and brine (135 mL). The organic

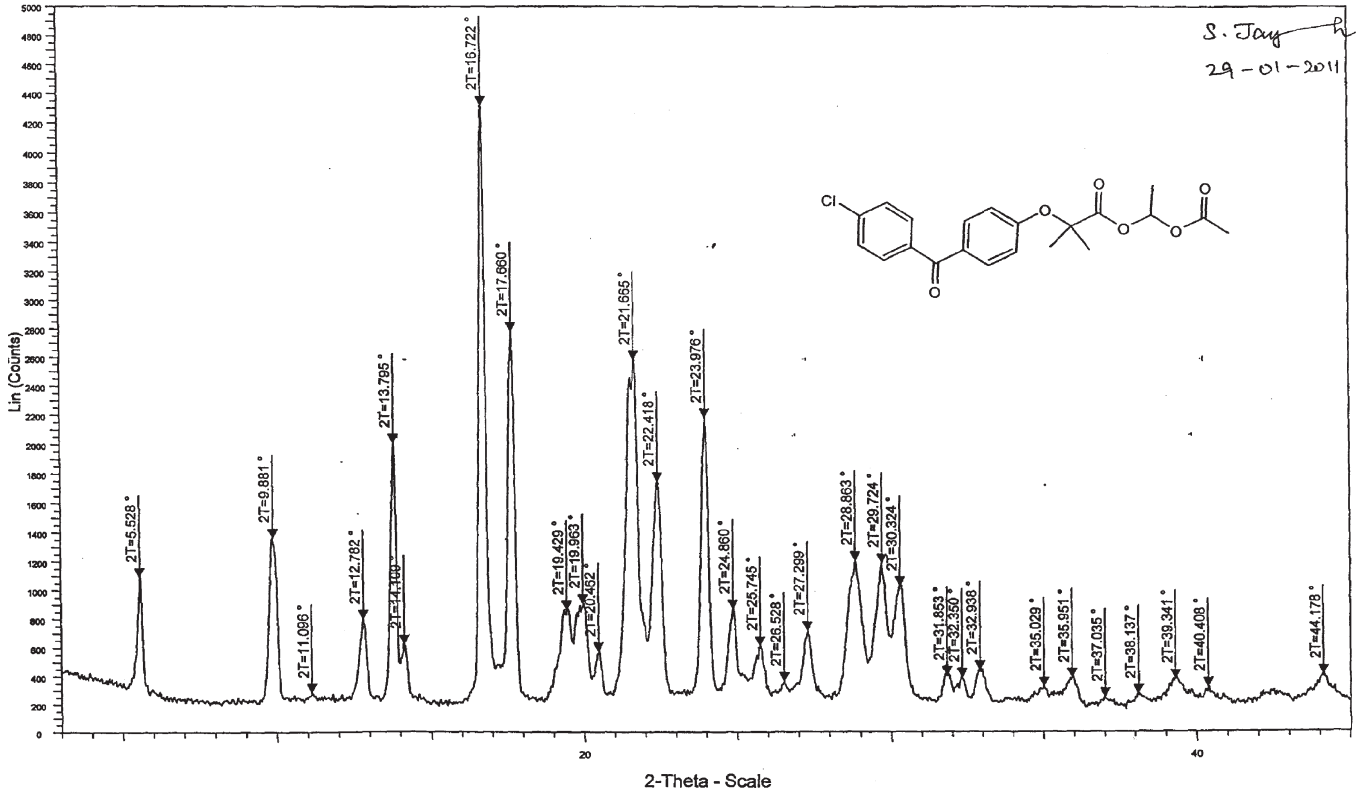

Figure 7. PXRD diffractogram for prodrug **1e**.

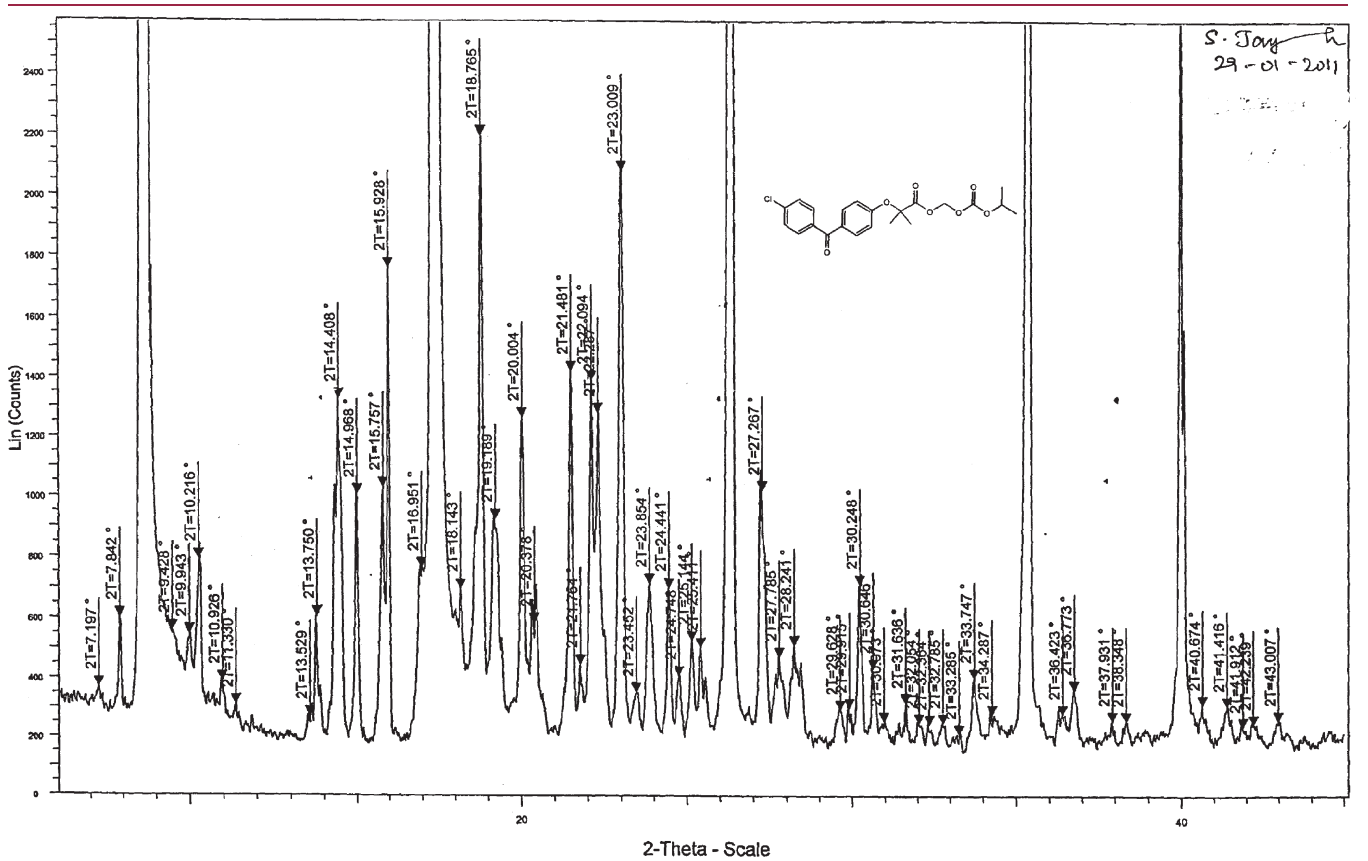

Figure 8. PXRD diffractogram for prodrug **1f**.

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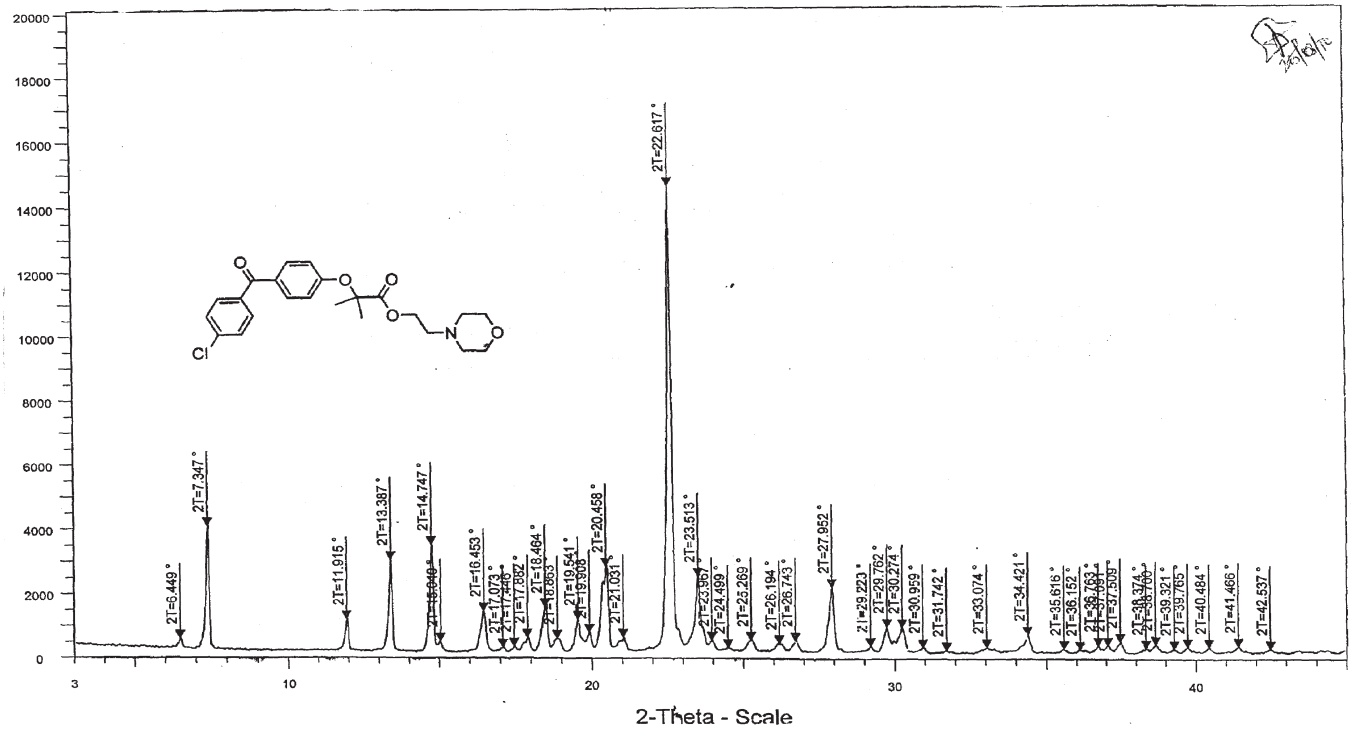

Figure 9. PXRD diffractogram for prodrug **1g**.

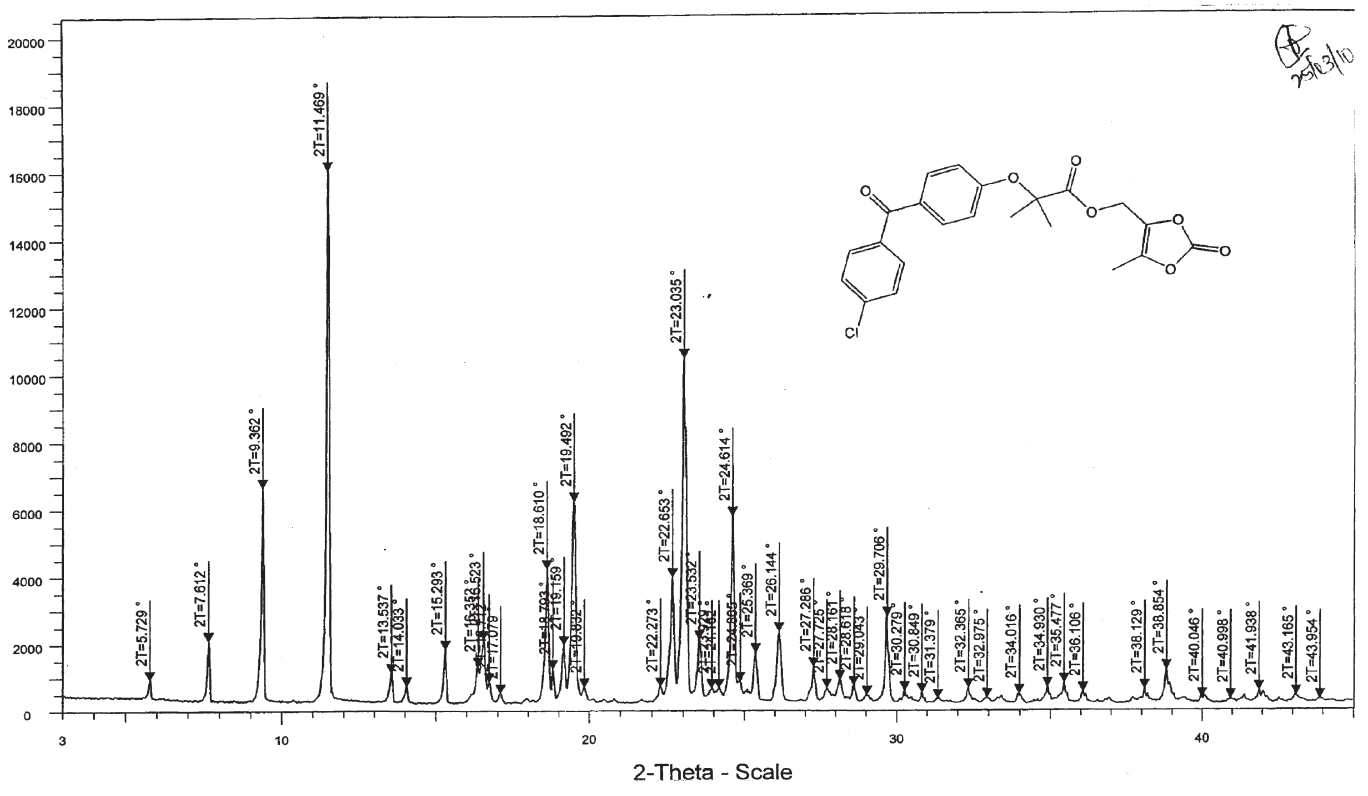

Figure 10. PXRD diffractogram for prodrug **1h**.

layer was evaporated under vacuum to afford promoiety **2a** as pale-yellow oil, which was used as such after purity correction in the synthesis of prodrug (14 g, 90%). Purity by GC 92.9%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.33 (d, 6H, J = 6.12 Hz, $-OCH(CH_3)_2$), 1.83 (d, 3H, J = 5.88 Hz, $-CH(CH_3)$, 4.9 (sept, 1H, J = 6.12 Hz, $-OCH(CH_3)_2$), 6.4 (q, 1H, J = 5.88 Hz, $-OCHCH_3$). IR (Nujol) cm^{-1} 1759 (C═O), 1080 (C−O).

*1-Acetoxyethyl Bromide (**2c**).* Hydrogen bromide gas (47 g, 0.58 mol) was purged under continuous cooling at 32−38 °C to vinyl

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acetate (50 g, 0.58 mol). The reaction mixture was stirred for 60 min at 35 ± 1 °C. The reaction progress was monitored by GC. After completion of reaction, the reaction mixture subjected for distillation to afford promoiety **2c** as colorless fuming liquid (81.2 g, 84%). Purity by GC 97.28%. ^{1}H NMR (DMSO, 400 MHz): δ 1.51 (d, 3H, J = 5.30 Hz, −CHCH_3), 2.1 (s, 3H, −COCH_3), 6.4 (q, 1H, J = 5.30 Hz, −OC*H*Br-(CH_3). IR (Nujol) cm^{-1} 1762 (C═O), 1084 (C−O).

*2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropionic Acid 1-Isopropoxy Carbonyloxyethyl Ester (**1c**).* Compound **1a** (2 g, 6.27 mmol) was dissolved in DMAc (10 mL) at 25 °C. The reaction mixture was cooled to −5 °C. TMG (0.77 g, 6.649 mmol) was added once, and the mixture was stirred for 20 min at −5 ± 2 °C. Then, 1-iodoethylisopropyl carbonate (1.62 g, 6.28 mmol) was added at −5 °C. The reaction mixture was stirred for 45 min at −5 °C under N_2 atmosphere. Reaction completion was monitored by HPLC. The reaction mixture was transferred to a mixture of ethyl acetate (25 mL), water (80 mL), and sodium thiosulfate (0.5 g) under vigorous stirring. The organic phase was separated, washed with brine (220 mL), decolorized with activated carbon (0.4 g), and filtered. After evaporation of solvent in vacuo, the desired product **1c** was obtained as an oil which solidified upon cooling to a pale-yellow crystalline solid (2.4 g, 85%), mp 83.9 °C. Chromatographic purity (HPLC) 99.42%; MS (+ESI) m/z = 449 (M + H)$^+$. IR (KBr) cm^{-1} 1756 (*C*═*O*), 1654 (*C*═*O*), 1259.1 (C−O−C str). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.15 (d, 6H, J = 6.2 Hz, −CH(CH_3)$_2$), 1.41 (d, 3H, J = 5.4 Hz, −OCH(O)CH_3), 1.6 (s, 6H, −OC(CH_3)$_2$CO), 4.74 (sept, 1H, J = 6.2 Hz, −OC*H*(CH$_3$)$_2$], 6.73 (q, 1H, J = 5.4 Hz, −OC*H*(O)CH$_3$), 6.81 (d, 2H, J = 8.8 Hz, Ar-*H*), 7.37 (d, 2H, J = 8.4 Hz, Ar-*H*), 7.63 (d, 2H, J = 8.4 Hz, Ar-*H*), 7.65 (d, 2H, J = 8.8 Hz, Ar-*H*). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 18.23, 20.54(2C), 23.84, 24.53, 71.93, 78.0, 90.98, 116.51(2C), 129.4 (2C), 130.81, 130.94 (2C), 131.08 (2C), 135.34, 137.35, 151.44, 158.29, 170.71, 193.15. Anal. Calcd for $C_{23}H_{25}ClO_7$: C, 61.54; H, 5.61. Found: C, 61.45; H, 5.58.

*2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic Acid Pivoloxymethyl Ester (**1d**).* Compound **1a** (2.0 g, 6.279 mmol) was dissolved in DMAc (10 mL) at 25 °C. The reaction mixture was cooled to −5 °C under N_2 atmosphere. TMG (0.78 g, 6.64 mmol) was added, and the mixture was stirred at for 20 min at −5 °C. Then, promoiety **b** (1.62 g, 6.694 mmol) was added once at −5 °C. The reaction mixture was stirred vigorously at −5 °C for 15 min. Reaction progress was monitored by HPLC. The reaction mixture was transferred to a mixture of ethyl acetate (30 mL), water (80 mL), and sodium thiosulfate (0.6 g) under vigorous stirring at 25 °C. The organic phase was separated, washed with brine (220 mL), decolorized with activated carbon (0.4 g), and filtered. The solvent was evaporated completely under vacuum to get solid residue. Water (50 mL) was added, stirred for 20 min at 10 °C, filtered, washed with water (50 mL), and dried under vacuo at 45 °C for 4 h to afford **1d** as white crystalline solid (2.3 g, 85%), mp 80.3 °C. Chromatographic purity (HPLC) 99.65%; MS (+ESI) m/z = 433 (M + H)$^+$. UV max (ethanol) 284.4 nm (36 mM^{-1} cm^{-1}). IR (KBr) cm^{-1} 1747 (*C*═*O*), 1648 (*C*═*O*). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.17 (s, 9H, −C(CH_3)$_3$), 1.67 (s, 6H, −C(CH_3)$_2$), 5.84 (s, 2H, −OCH_2O), 6.86 −7.74 (m, 8H, Ar-*H*). ^{13}C NMR (CDCl$_3$, 100 MHz) δ 25.39 (2C), 26.87 (3C), 38.98, 79.22, 80.17, 117.71 (2C), 128.7 (2C), 130.80, 131.32 (2C), 132.1 (2C), 136.43, 138.58, 159.40, 172.65, 176.87, 194.29. Anal. Calcd for $C_{23}H_{25}ClO_6$: C, 63.81; H, 5.82. Found: C, 63.75; H, 5.72.

*2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropionic acid 1-acetoxyethyl ester (**1e**).* Compound **1a** (2 g, 6.279 mmol) was dissolved in DMAc (10 mL) at room temperature. Potassium carbonate (0.46 g, 3.32 mmol) was added, and the mixture was stirred for 90 min at 32 °C under N_2 atmosphere and cooled to −5 °C. Then, 1-acetoxyethyl bromide (1.3 g, 7.789 mmol) was added at −5 °C. The reaction temperature was increased to 30 °C in 30 min and stirred for 30 min. Reaction completion was monitored by HPLC. After completion of reaction, the reaction mixture was transferred to a mixture of ethyl acetate (30 mL), water (80 mL), and sodium thiosulfate (0.5 g). The pH of reaction mixture was adjusted to 10.5 by addition of sodium carbonate, and the organic phase was separated, washed with brine (400 mL), treated with activated carbon (0.5 g), and filtered. After evaporation of solvent in vacuo, the desired product **2e** was obtained as oil which solidified upon cooling to a white solid (2.2 g, 69%). Chromatographic purity (HPLC) 99.66%; mp 102 °C; MS (+ESI) m/z = 405.1 (M + H)$^+$. IR (KBr) 1689 (C═O), 1652 (C═O), 762 (C−Cl str). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.44 (d, 3H, J = 5.4 Hz, −OCH(O)CH_3), 1.67 (s, 6H, ArOC(CH_3)$_2$), 2.03 (s, 3H, −OCOCH_3), 6.92 (q, 1H, J = 5.4 Hz, −OC*H*(O)CH$_3$), 6.89 (d, 2H, J = 8.8 Hz, Ar-*H*), 6.7.4 (d, 2H, J = 8.4 Hz, Ar-*H*), 7.7 (d, 2H, J = 8.4 Hz, Ar-*H*), 7.75 (d, 2H, J = 8.8 Hz, Ar-*H*). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 18.1, 19.69, 23.92, 24.47, 78.0, 88.2, 116 (2C), 127.5 (2C), 129.5, 130.16 (2C), 130.93 (2C), 135.3, 137.4, 158.3, 167.8, 170.7, 193.2. Anal. Calcd for $C_{21}H_{21}ClO_6$: C, 62.30; H, 5.23. Found: C, 62.20; H, 5.12.

*2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropionic Acid Isopropoxycarbonyl Oxymethyl Ester (**1f**).* Compound **1a** (2 g, 6.279 mmol) was dissolved in DMAc (10 mL) at room temperature. TMG (0.763 g, 6.588 mmol) was added at 0 °C, and the reaction mixture was stirred for 20 min under N_2 atmosphere at −2 ± 1 °C. To that, iodomethylisopropyl carbonate (1.53 g, 6.27 mmol) was added at 0 °C, and the mixture was stirred at 0 °C for 30 min. The reaction progress was monitored by HPLC. The reaction mixture was added under stirring to a mixture of ethyl acetate (25 mL), water (80 mL), and sodium thiosulfate (0.5 g), and the mixture was stirred for 10 min at pH 10.5 and 25 °C. The organic layer was separated, washed with brine solution (120 mL), filtered, and solvent was evaporated completely in vacuo to get viscous oil product, which upon cooling afforded **1f** as white crystalline solid (2.3 g, 83%). Chromatographic purity (HPLC) 99.60%; mp 76.5 °C; MS (+ESI) m/z = 435.1 (M + H)$^+$. IR (KBr) 1745 (C═O), 1654 (C═O). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.24 (d, 6H, J = 6.2 Hz, −OCH(CH_3)$_2$), 1.69 (s, 6H, −ArOC(CH_3)$_2$), 4.8 (sept, 1H, J = 6.2 Hz, −OC*H*(CH$_3$)$_2$), 5.83 (s, 2H, −OCH_2O), 6.87−7.74 (m, 8H, Ar-*H*). ^{13}C NMR (CDCl$_3$): δ 21.7 (2C), 25.37 (2C), 74.47, 79.25, 82.55, 117.7 (2C), 128.71 (2C), 130.8, 131.33 (2C), 132.17 (2C), 126.47, 138.57, 153.19, 159.38, 172.58, 194.29. Anal. Calcd for $C_{22}H_{23}ClO_7$: C, 60.76; H, 5.33. Found: C, 60.55; H, 5.25.

*2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic Acid 2-Morpholin-4-yl Ethyl Ester (**1g**).* 4-(2-Chloroethyl)morpholine hydrochloride (1.787 g, 9.6 mmol), potassium carbonate (1.511 g, 1.09 mmol), and compound **1a** (3 g, 9.4 mmol) were added in DMF (18 mL), and the reaction mixture was stirred at 60 °C for 5 h under N_2 atmosphere. Reaction progress was monitored by HPLC. The reaction mixture was transferred to a mixture of ethyl acetate (45 mL) and water (120 mL) under vigorous stirring and stirred for 10 min at pH 10.5 and 25 °C. The organic phase was separated, washed with brine solution (180 mL), decolorized with activated carbon (0.25 g), filtered, and the solvent was removed in vacuo. Water (50 mL) was added and the slurry stirred for 30 min at 25 °C, filtered, and washed with water (50 mL), and dried under vacuum at 45 °C to afford **1g** as white crystalline powder (2.5 g, 70%). Chromatographic purity (HPLC) 99.58%; mp 89.5 °C; MS (+ESI) m/z = 432.1 (M + H)$^+$; UV max (ethanol) 286.6 nm (21 mM^{-1} cm^{-1}). IR (KBr) 1732 (C═O), 1648 (C═O), 760 (C−Cl str). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.68 (s, 6H, −C(CH_3)$_2$), 2.42 (t, 4H, J = 4.32 Hz, −N(CH_2)$_2$), 2.58 (t, 2H, J = 5.72 Hz, −OCH$_2$CH_2N), 3.62 (t, 4H, J = 4.32 Hz, −O(CH_2)$_2$), 4.31 (t, 2H, J = 5.72 Hz, −OCH_2CH$_2$N), 6.88−7.74 (m, 8H, Ar-*H*). ^{13}C NMR (CDCl$_3$): δ 25.65 (2C), 53.84 (2C), 57.06, 62.74, 67.09 (2C), 79.53, 117.55 (2C), 128.75 (2C), 130.6, 131.34 (2C), 132.17 (2C), 136.52, 138.6, 159.78, 173.76, 194.34. Anal. Calcd for $C_{23}H_{26}ClNO_5$: C, 63.96; H, 6.07; N, 3.24. Found: C, 63.78; H, 5.99; N, 3.21.

*2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic Acid, 5-Methyl-2-oxo-[1,3]dioxol-4-yl-methyl Ester (**1h**).* Compound **1a** (3 g, 9.4 mmol) was dissolved in DMAc (12 mL) at 30 °C. Sodium carbonate

(0.75 g, 7 mmol) and 4-chloromethyl-5-methyl-1,3-dioxol-2-one (1.58 g, 10.6 mmol) were added at 30 °C, the mixture was heated to 30 °C, and the mixture was stirred for 17 h under N_2 atmosphere. Reaction completion was monitored by HPLC. Then the reaction mixture was transferred to a mixture of ethyl acetate (41 mL), water (120 mL), and sodium thiosulfate (0.6 g) under vigorous stirring. The organic phase was separated, washed with brine (180 mL), decolorized with activated carbon (0.25 g), and filtered. The solvent was evaporated completely in vacuo, and methanol (15 mL) was added and then stirred for 20 min at 0 °C, filtered, and dried under vacuum to afford desired product **1h** as a white crystalline powder (3.5 g, 83%); mp 91.6 °C; chromatographic purity (HPLC) 99.11%; MS (+ESI) m/z = 431 (M + H) $^+$; UV max (ethanol) 284.2 nm (22 mM^{-1} cm^{-1}). IR (KBr) cm^{-1} 1821.6 (C═O), 1740 (C═O), 1656 (C═O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.67 (s, 6H, ArOC(CH_3)$_2$), 2.14 (s, 3H, ═C-CH_3), 4.93 (s, 2H, −OCH_2C), 6.82−7.74 (m, 8H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ 9.5, 25.22 (2C), 54.83, 79.44, 117.35 (2C), 128.73 (2C), 130.92, 131.34 (2C), 132.11 (2C), 132.98, 136.35, 138.56, 140.66, 151.9, 159.38, 173.46, 194.26. Anal. Calcd for $C_{22}H_{19}ClO_7$: C, 61.33; H, 4.45. Found: C, 61.19; H, 4.38.

GC Analysis. *Analysis Method for Promoieties **2a**.* The following equipment and parameters were used: instrument, Perkin-Elmer; model Clarus 500; column DB-1, 30 m × 0.53 mm, 1.5 μm, oven temperature 75 °C; ramp rate 10 °C/min up to 200 °C; final oven temperature 200 °C for 10 min; injection temperature, 150 °C; detector temperature 250 °C; flow (carrier) 5.0 mL/min; injection volume 0.2 μL. Split, 20:1.

*Analysis method for promoiety **2c**.* The following equipment and parameters were used: Instrument, Perkin-Elmer head space GC, model Clarus 500; column, DB-5, 30 m length × 0.53 mm internal diameter, 5.0 μm film thickness; reagents, *n*-tetradecane (AR grade, purity >99.0%); carrier gas (nitrogen flow), 3.5 ± 0.3 mL/min; detector, FID; initial oven temperature, 50 °C; initial time, 6.0 min; rate '1', 15 °C/min; final oven temperature, 110 °C; final time '1', 6 min; rate '2', 15 °C/min; final oven temperature '2', 250 °C; final oven temperature '2', 10 min; injector temperature, 125 °C; detector temperature, 270 °C; split ratio, 1:10; run time, 36 min.

Preparation of Sample. A solution of 1-acetoxyethyl bromide (**2c**) in *n*-tetradecane in an approximate ratio 1:1 by volume in a clean and dry glass vial was prepared.

Procedure. Inject First, 0.4 μL each of *n*-tetradecane and sample solution was injected with a suitable syringe into the chromatograph, and then the percentage area of 1-acetoxyethyl bromide after the inhibiting peak of *n*-tetradecane was noted. Approximate retention time (RT) of 1-1-acetoxyethyl bromide and *n*-tetradecane was 12 and 24 min, respectively.

HPLC Analysis. *Testing Procedure for In-Process Analysis, Aqueous Solubility, Chromatograpghic Purity, Partition Coefficient Analysis, and Limit of Detection.* A reverse phase HPLC method was used. Instruments used: HPLC, Waters Alliance, pump model 2695, UV detector model 2487, and Shimadzu LC 2010 CHT with UV detector. Mobile phase A was prepared by mixing glacial acetic acid (2.0 mL) in Milli Q water 1000 mL), filtered through 0.45 μm filter, and degassed by sonication (pH of this solution is around 3.0). Mobile phase B involved filtered and degassed methanol (HPLC grade). Chromatographic parameters were as follows: column, YMC-Pack C-8, 100 mm length, 4.6 mm internal diameter, 3 μm particle size; flow rate, 0.8 mL/min; wavelength, 254 nm; injection volume, 20 μL; run time, 30 min. The gradient elution program is depicted in Table 5.

Hypolipidemic Activity. Hypolipidemic activity of the test compounds **1c**−**1h** and reference drug fenofibrate (**1b**) were evaluated in male Swiss albino mice (SAM) model reported previously.[27]

Materials. Carboxy methyl cellulose (CMC) was purchased from Aldrich Chemicals (St. Louis, USA); Tween 80 was purchased from Sigma Aldrich Chemicals and the Triglyceride kit from ERBA Diagnostics.

Animals. Male Swiss albino mice (SAM) of 22−35 g body weight were obtained from the in-house animal facility of Orchid Research Laboratories, India. Animal were kept for one week at a controlled temperature 22−24 °C under 12 h light and 12 h dark cycle for accommodation with free access to standard laboratory chow and water ad libitum. All experiments were carried out by using protocol approved by the Institutional Animals Ethics Committee (IAEC) and compiled with National Institutes of Health (NIH) guidelines on handling of experimental animals.

Formulation. All the compounds were suspended in vehicle (Tween 80 5 μL/mL in 0.5% CMC, 10 mL/kg).

Statistical Analysis. Mean values of treated groups were compared to those of the vehicle treated group. Statistical significance was determined by one-way analysis of variance (ANOVA), followed by Dunnett's test. Results were expressed as mean ± SE from 8 to 10 animals in each group. A P value <0.05 was considered significant.

Method. Male Swiss albino mice (SAM) were grouped into 8 groups (n = 8−10).

Group 1: Normal control untreated SAM received 0.5% CMC (control vehicle).
Group 2: Administered fenofibrate (**1b**) orally and considered as reference drug.
Group 3: Administered test compound **1c** orally.
Group 4: Administered test compound **1d** orally.
Group 5: Administered test compound **1e** orally.
Group 6: Administered test compound **1f** orally.
Group 7: Administered test compound **1g** orally.
Group 8: Administered test compound **1h** orally.

Animals were treated orally with reference compound **1b** and test compounds **1c**−**1h** at a dose of 50 mg/kg body weight for 8 days. After 8 days of treatment, animals were fasted for 12 h. On the ninth day after giving respective treatment, blood samples were collected one hour postadministration of test compounds **1c**−**1h** as well as **1b**. Blood was collected under mild ether anesthesia. Plasma was separated by centrifugation at 4000 rpm for 10 min for measurement of triglyceride (TC) and total cholesterol (TC) level by spectrophotometrically using a commercially available ERBA kit. The results obtained were expressed as mean ± SE. Statistical analysis was done by one-way analysis of variance (ANOVA), followed by Dunnett's test, and P < 0.05 was considered as statistically significant.

Aqueous Solubility. The solubility of fenofibric acid ester prodrugs **1c**−**1h** was determined at 40 °C in 0.1 M boric acid buffer at pH 9, 0.2 M phosphate buffer at pH 7.4, 0.1 M phosphate buffer at pH 5.2, 0.1 M citric acid buffer at pH 3.0, and 0.2 M hydrochloric acid buffer at pH 1.0. Test compound (5 mg each) in buffer solution (10 mL) was incubated at 40 °C for 4 h at 400 rpm on mechanical shaker. The solution was filtered through 0.20 μm membrane filter, and the filtrate was analyzed quantitatively by HPLC at wavelength 254 nm for its solubility.

Determination of Partition Coefficient. The partition coefficients of fenofibrate (**1b**) and prodrugs **1c**−**1h** were determined in octanol−buffer system by HPLC method at 25 °C. The aqueous phase was 0.2 M phosphate buffer of pH 7.4. Before use, the 1-octanol and buffer solution were mutually saturated for 24 h by shaking at 400 rpm on mechanical shaker at 25 °C. A known concentration of compounds in 1-octanol (5 mL) and buffer solution (5 mL) was shaken on mechanical shaker for 60 min at 400 rpm at 25 °C and centrifuged at 3500 rpm for 5 min. The concentration of the test compound (solute) in both phases was analyzed quantitatively by HPLC at 254 nm. Each experiment was repeated in triplicate, and mean value was considered for log P estimation. The partition coefficient (log P) was calculated by following equation.

$$\log P_{oct/wat} = \log\left(\frac{[\text{solute}]_{\text{octanol}}}{[\text{solute}]^{\text{un-ionized}}_{\text{water}}}\right)$$

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Particle Size Distribution. Instrument: Malvern particle size analyzer, model Master Sizer S.

Analytical Condition. RPM in dispersion unit, 2000; sample time, 20 s (10000 sweeps); % obscuration, 25 ± 2.5. Sample measurement stability duration, 7 min; presentation, 3 OHD; dispersant, purified water pH 7.0−7.5 (pH adjusted with dilute ammonia solution).

Sample Preparation. Test sample (∼100 mg) was taken in 100 mL size beaker, and dispersant (10 drops) was added followed by addition of Tween-80 (2 drops). Thick paste was obtained. About 50 mL of dispersant was added to get homogeneous suspension and then sonicated for 3−4 min.

Procedure. Dispersion unit and flow cell was cleaned with *n*-hexane, and then about 100 mL of dispersion medium was poured into the dispersion unit. RPM was set (2000). After stabilization, instrument was aligned. Further sample was added gradually until ∼25% obscuration was attained. After 7 min of stabilization, particle size distribution was measured.

■ ASSOCIATED CONTENT

Supporting Information. Chromatographic purity (GC) and ^{1}H NMR data for promoieties; chromatographic purity (HPLC), ^{1}H NMR, ^{13}C NMR, IR, and mass and particle size distribution data for prodrugs. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

HPLC, high performance liquid chromatography; GC, gas chromatograph; API, active pharmaceutical ingredient; DMAc, dimethyl aceatamide; DMF, dimethyl formamide; Ar, aryl; PPAR-α, peroxisome proliferator activated receptor alpha; SE, standard error; TC, total cholesterol; TG, triglyceride; HDL, high density cholesterol; LDL, low density cholesterol; SAM, Swiss albino mice; RT, retention time; BDL, below detection limit; LOD, limit of detection; LOQ, limit of qualification

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