

## Synthesis and Evaluation of Fenofibric Acid Ester Derivatives: Studies of Different Formulation with Their Bioavailability and Absorption Conditions

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A series of fenofibric acid ester pro-drugs (**JF-1-7**) were synthesized. The pharmacokinetic properties of these pro-drugs were examined after oral administration to rats at a dose of 20 mg kg<sup>-1</sup> to evaluate the relative bioavailability in rats. The bioavailability of the ester compounds, **JF-1**, **2**, **3**, **4**, **5**, **6**, and **7**, was significantly higher than that of fenofibrate. In particular, **JF-2** proved to be most promising. The oral administration (20 mg kg<sup>-1</sup>) of **JF-2** showed a relative bioavailability of approximately 272.8% compared to fenofibrate.

**Keywords:** pharmacokinetic properties, fenofibrate, fenofibric acid, bioavailability

### Introduction

Fenofibrate (Figure 1) is a pro-drug that is pharmacologically inactive and undergoes rapid hydrolysis at the ester bond to form the active metabolite fenofibric acid.<sup>1</sup> As a third-generation fenofibric acid derivative, fenofibrate is used mainly as a monotherapy to reduce elevated low-density lipoprotein cholesterol, total cholesterol, triglycerides, and apolipoprotein B levels; increase high-density lipoprotein cholesterol levels in patients with primary hyperlipidemia or mixed dyslipidemia; and reduce the triglyceride levels in patients with severe

hypertriglyceridemia. On the other hand, fenofibrate is a neutral, lipophilic compound that is practically insoluble in water, making it challenging to achieve consistent therapeutic levels.<sup>2,3</sup> One of the main disadvantages of this drug is the low consistently achieved therapeutic levels, because of its special chemical characteristics, such as its high lipophilicity, and low water-solubility.<sup>4,5</sup>

This study examined the bioavailability and absorption of various fenofibrate formulations.<sup>6-8</sup> Furthermore, a series of fenofibrates were prepared with different formulations to increase its overall solubility. Four known (**JF-1** to **4**) and three (**JF-5** to **7**) novel pro-drugs (Figure 2) were

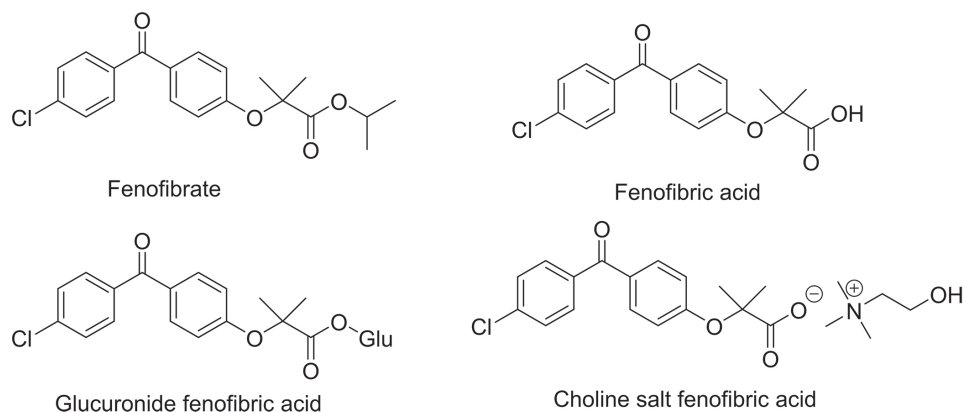


Figure 1. Fenofibric acid derivatives.

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synthesized using side chain halide intermediates. The main development of these derivatives is to change fenofibric acid to a fenofibric acid prodrug ester.<sup>9,10</sup> A series of fenofibrate derivatives were synthesized based on the screened pharmacokinetic properties of highly water-soluble lead compounds.<sup>11-14</sup>

## Experimental

### General

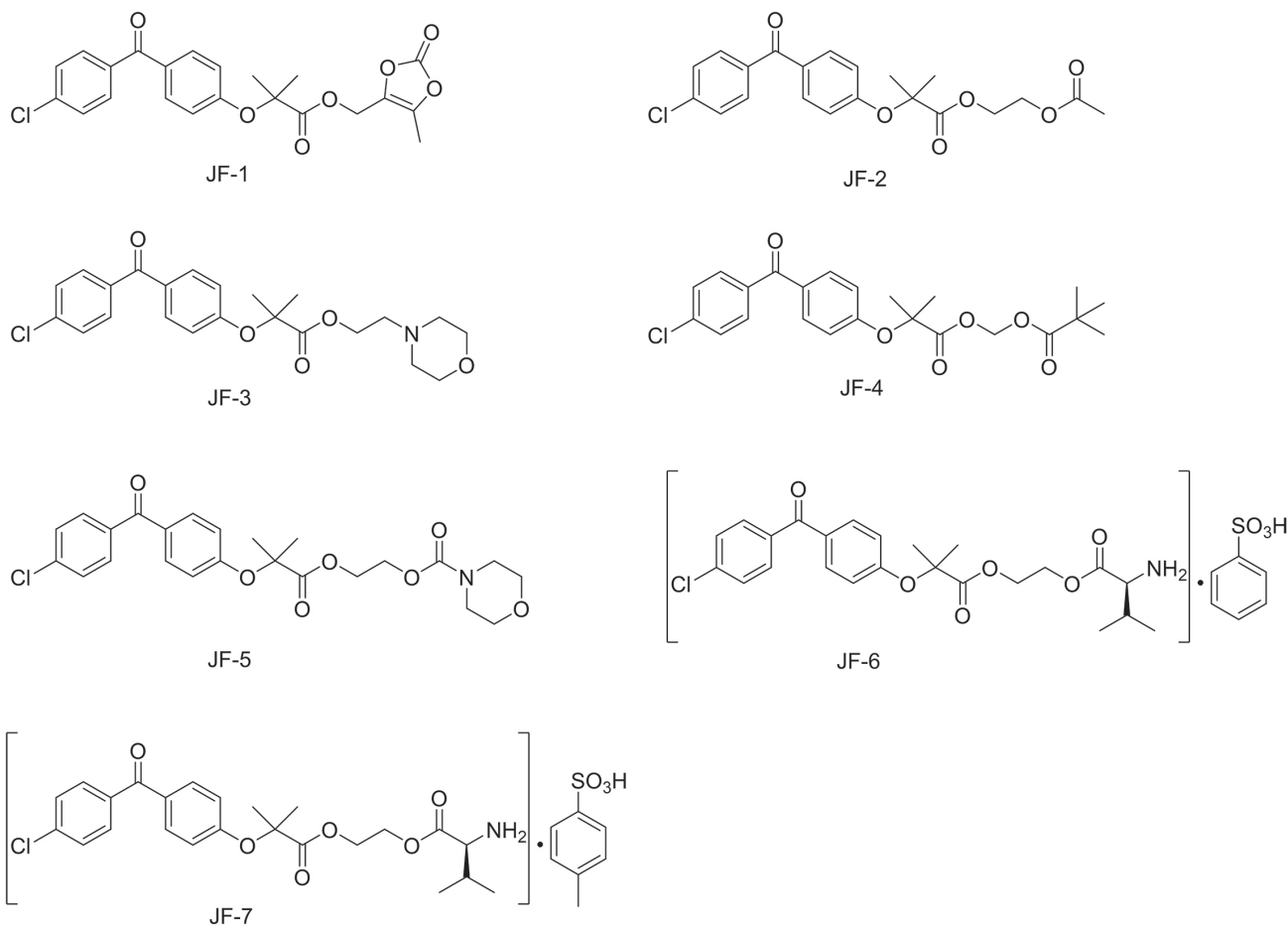
The <sup>1</sup>H nuclear magnetic resonance (NMR) spectra were taken at JEOL ECLITSE-300 Spectrometer (Japan). The chemical shifts are reported in parts *per million* (ppm) downfield relative to TMS (tetramethylsilane) as the internal standard (IS). The mass spectra (MS) were recorded on a Thermo Fisher (LCQ Fleet, Japan). The matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectra were recorded on a Voyager-DE STR (Japan). Silica gel (200-230 mesh) was used for open column chromatography. Thin layer chromatography (TLC) was performed on silica gel 60 F254 (Merck

DG&A, Germany). All solvents were freshly distilled from proper dehydrating agents under argon gas. All necessary chemicals were purchased from Sigma-Aldrich Corp. (USA) unless specified otherwise. **JF-2**, fenofibrate, and fenofibric acid were supplied by J2H Biotech (Ansan, South Korea). Sildenafil, an internal standard for high-performance liquid chromatography (HPLC) analysis, was purchased from Sigma-Aldrich Corp. (St. Louis, MO, USA). Acetonitrile and methanol were products from Burdick & Jackson (Muskegon, MI, USA). Polyethylene glycol 400 (PEG-400) was a product from Showa Chemical Corp. (Tokyo, Japan). All other chemical were of reagent or HPLC grade.

### Syntheses

#### Synthesis of (4-chlorophenyl)(4-hydroxyphenyl)methanone

AlCl<sub>3</sub> (4.0 g, 30 mmol) was added slowly to a stirred solution of anisole (2.16 g, 20 mmol) in dry toluene at 0 °C in an inert atmosphere. 4-Chlorobenzoyl chloride (3.5 g, 20 mmol) was added dropwise via a cannula. The reaction mixture was heated slowly under reflux for 1.5 h, and the



**Figure 2.** Series of fenofibric acid derivatives **JF-1-7**.

reaction was monitored by TLC. When the reaction was complete, it was cooled to room temperature, and then quenched slowly with 40 mL of distilled water. The crude product was washed with sufficient water and recrystallized with ethanol to give (4-chlorophenyl)(4-hydroxyphenyl) methane as a white solid (3.86 g, 83%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.75-6.89 (m, 8H), 5.66 (s, 1H).

#### Synthesis of fenofibric acid

NaOH (0.6 g, 15 mmol) was added to a stirred solution of (4-chlorophenyl) (4-hydroxyphenyl) methanone (3.49 g, 15 mmol) in dry 2-butanone (60 mL). The reaction mixture was heated under reflux for 1 h and isopropyl-(2-bromo-2-methyl)-propanonate (3.76 g) in dry 2-butanone (15 mL) was then added. The reaction mixture was heated under reflux for 8 h until the reaction was complete. Subsequently, 1 M NaOH 50 mL was added to the reaction, and the resulting mixture was heated under reflux for 4 h. The residue was partitioned between water with brine (20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (80 mL). The separated organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, concentrated, and recrystallized with acetone to give fenofibric acid as a white powder (4.3 g, 90%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 11.2 (s, 1H), 7.75-6.93 (m, 8H), 1.70 (m, 6H).

#### Synthesis of fenofibric acid derivative analogous

##### General procedure

A solution of 4-chloromethyl-5-1,3-dioxolen-2-one (2.94 g, 20 mmol) was added to fenofibric acid (3.18 g, 10 mmol) and K<sub>2</sub>CO<sub>3</sub> (2.76 g, 20 mmol) in *N,N*-dimethylacetamide (64 mL) at room temperature at such a rate that the reaction maintained an internal temperature of 60-65 °C overnight. The reaction mixture was cooled to 0 °C and water (100 mL) was added slowly. The resulting mixture was stirred at room temperature for 1.5 h, extracted with ethyl acetate (100 mL), and washed with brine (150 mL × 3). The solvent was distilled off under reduced pressure to obtain a residue. The residue was purified further by column chromatography to give the title compounds. The following compounds were synthesized according to this procedure.

#### Synthesis of (5-methyl-2-oxo-1,3-dioxol-4-yl)-methyl-2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanonate (**JF-1**)

This was obtained 4.0 g as a white solid. Yield: 93%; <sup>1</sup>H NMR (300 MHz, dimethyl sulfoxide (DMSO-*d*<sub>6</sub>)) δ 7.69-7.65 (m, 4H), 7.60-7.58 (d, 2H, *J* 6.3 Hz), 6.87-6.85 (d, 2H, *J* 6.6 Hz), 5.08 (s, 2H), 2.11 (s, 3H), 1.61 (s, 6H);

MS (MALDI-TOF) *m/z*, calcd. for C<sub>22</sub>H<sub>19</sub>ClO<sub>7</sub> [M - H]<sup>-</sup>: 430.1105, found: 430.1013.

#### Synthesis of 2-acetoxyethyl-2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanonate (**JF-2**)

This was obtained 3.4 g as a colorless oil liquid. Yield: 85%; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.70-7.68 (m, 4H), 7.60-7.58 (d, 2H, *J* 6.3 Hz), 6.90-6.88 (d, 2H, *J* 6.3 Hz), 4.43-4.32 (t, 2H, *J* 3.3 Hz), 4.18-4.15 (t, 2H, *J* 3.3 Hz), 1.88 (s, 3H), 1.60 (s, 6H); MS (MALDI-TOF) *m/z*, calcd. for C<sub>21</sub>H<sub>21</sub>ClO<sub>6</sub> [M - H]<sup>-</sup>: 404.0942, found: 404.0921.

#### Synthesis of 2-morpholinoethyl-2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanonate (**JF-3**)

This was obtained 3.5 g as a white solid. Yield: 81%; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.69-7.67 (m, 4H), 7.60-7.58 (d, 2H, *J* 6.3 Hz), 6.90-6.88 (d, 2H, *J* 6.3 Hz), 5.80 (s, 2H), 1.59 (s, 6H), 1.07 (s, 9H); MS (MALDI-TOF) *m/z*, calcd. for C<sub>23</sub>H<sub>26</sub>ClNO<sub>5</sub> [M - H]<sup>-</sup>: 431.139, found: 431.1136.

#### Synthesis of (2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoyloxy)methylpivalate (**JF-4**)

This was obtained 4.0 g as a white solid. Yield: 93%; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.69-7.67 (m, 4H), 7.60-7.58 (d, 2H, *J* 6.3 Hz), 6.90-6.88 (d, 2H, *J* 6.3 Hz), 5.80 (s, 2H), 1.59 (s, 6H), 1.07 (s, 9H); MS (MALDI-TOF) *m/z*, calcd. for C<sub>23</sub>H<sub>25</sub>ClO<sub>6</sub> [M - H]<sup>-</sup>: 432.0911, found: 432.0845.

#### Synthesis of (2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoyloxy)ethylmorpholine-4-carboxylate (**JF-5**)

This was obtained 4.1 g as a white solid. Yield: 86%; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.70-7.67 (m, 4H), 7.60-7.58 (d, *J* 6.3 Hz, 2H), 6.90-6.88 (d, 2H, *J* 6.6 Hz), 4.35-4.33 (t, 3H, *J* 3.3 Hz), 4.18-4.16 (t, 3H, *J* 3.3 Hz), 3.43 (br, 4H), 3.18 (br, 4H), 1.60 (s, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 206.1, 184.5, 183.6, 131.4, 131.2, 130.8, 130.7, 130.4, 128.5, 126.8, 123.0, 85.5, 85.0, 30.4, 29.9, 23.1, 22.0, 21.5; MS (MALDI-TOF) *m/z*, calcd. for C<sub>24</sub>H<sub>26</sub>ClNO<sub>7</sub> [M - H]<sup>-</sup>: 475.1279, found: 475.1283.

#### Synthesis of (2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoyloxy)ethyl-2-amino-3-methylbutanonate monobenzenesulfonate (**JF-6**)

This was obtained 5.1 g as a white solid. Yield: 82%; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 8.27 (s, 2H), 7.71-7.57 (m, 6H), 7.31-7.27 (m, 3H), 6.91-6.89 (d, 2H, *J* 6.3 Hz), 4.44-4.34 (m, 4H), 3.88-3.87 (d, 1H, *J* 3.0 Hz), 2.11 (m, 1H), 1.60 (s, 6H), 0.91-0.86 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 206.9, 184.5, 163.3, 147.1, 138.8, 130.7, 130.6, 130.3, 129.7, 128.7, 128.6, 124.1, 123.8, 85.8, 28.6,

23.0, 21.8, 21.7, 16.4, 16.2; MS (MALDI-TOF)  $m/z$ , calcd. for  $C_{30}H_{34}ClNO_9S [M - H]^-$ : 619.2147, found: 619.2136.

#### Synthesis of (2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoyloxy)ethyl-2-amino-3-methylbutanone mono-sylate (**JF-7**)

This was obtained 4.9 g as a white solid. Yield: 77%;  $^1H$  NMR (300 MHz,  $DMSO-d_6$ )  $\delta$  8.26 (s, 2H), 7.71-7.61 (m, 4H), 7.60-7.59 (d, 2H,  $J$  6.3 Hz), 7.47-7.45 (d, 2H,  $J$  6.3 Hz), 7.10-7.08 (d, 2H,  $J$  5.7 Hz), 6.91-6.89 (d, 2H,  $J$  6.3 Hz), 4.44-4.30 (m, 4H), 3.87-3.86 (d, 1H,  $J$  3.3 Hz), 2.26 (s, 3H), 2.11 (m, 1H), 1.60 (s, 6H), 0.91-0.86 (m, 6H);  $^{13}C$  NMR (75 MHz,  $DMSO-d_6$ )  $\delta$  206.5, 184.2, 165.7, 145.3, 138.4, 138.3, 132.6, 130.5, 130.3, 130.1, 129.9, 128.4, 124.9, 123.3, 122.2, 100.3, 87.5, 85.7, 30.6, 23.1, 22.0, 21.4; MS (MALDI-TOF)  $m/z$ , calcd. for  $C_{31}H_{36}ClNO_9S [M - H]^-$ : 633.1581, found: 633.1572.

#### Biology

##### Preparation of the calibration standards and quality control samples

A stock solution of fenofibric acid (1 mg  $mL^{-1}$ ) was prepared in methanol. The appropriate dilutions of the stock solution of fenofibric acid were then prepared with methanol (0.003, 0.005, 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, or 1 mg  $mL^{-1}$ ). Standard solutions of fenofibric acid in rat plasma were prepared by spiking with the appropriate volume (10 mg  $mL^{-1}$  of plasma) of the diluted stock solutions, giving final concentrations of 0.03, 0.05, 0.1, 0.2, 0.5, 1, 2, 5, or 10 mg  $mL^{-1}$  for plasma. The IS working solution was prepared by dissolving sildenafil in acetonitrile to give a final concentration of 10 mg  $mL^{-1}$ .

##### Preparation of plasma samples

A 50  $\mu L$  aliquot of the sample was deproteinized with 75  $\mu L$  of acetonitrile containing 1  $\mu g$   $mL^{-1}$  sildenafil (an

IS). After vortex-mixing and centrifugation at 3000 rpm for 10 min, the supernatant was transferred to a vial and a 20  $\mu L$  aliquot was injected directly into the HPLC column.<sup>15-25</sup>

#### HPLC analysis

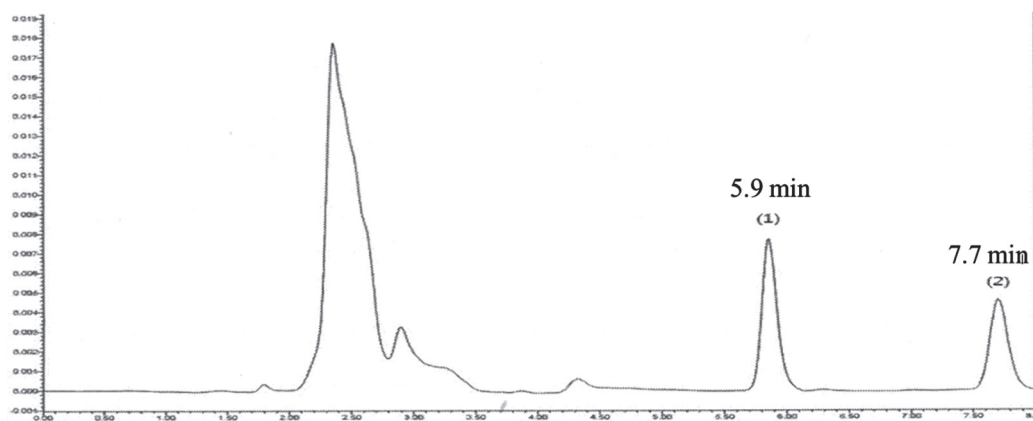
The HPLC system consisted of a Gilson-234 auto sampler (Gilson, Middleton, WI, USA), a Gilson 307 pump (Gilson), a capcell PACK (C18) column (250  $\times$  4.6 mm, i.d.: particle size, 5 mm, Shiseido, Tokyo, Japan), a model UV-118 UV/VIS detector (Gilson), and a model Gilson unipoint system software (Gilson). The mobile phase, 0.02 M ammonium acetate buffer:acetonitrile (35:36, v/v), was run at a flow rate of 1.0  $mL\ min^{-1}$ , and the column eluent was monitored using an ultraviolet detector at 280 nm at room temperature. The retention times of sildenafil (an internal standard) and fenofibric acid were approximately 5.9 and 7.7 min, respectively (Figure 3).<sup>26-32</sup>

#### Analytical method validation

The analytical method was validated with regard to its specificity, linearity, intra- and interday precision and accuracy, matrix effect, and stability according to the US Food and Drug Administration.<sup>33</sup>

#### Pharmacokinetic and statistical analyses

The total area under the plasma concentration-time curve to the last time (AUClast), maximum plasma concentration ( $C_{max}$ ), time to reach  $C_{max}$  ( $T_{max}$ ), and half-life ( $T_{1/2}$ ) were estimated using noncompartmental calculations carried out with WinNonlinTM 5.2.<sup>34</sup> All data are expressed as the mean  $\pm$  standard deviation (SD). The statistical significance of the differences between the 2 groups was analyzed using a Student's  $t$ -test carried out with SPSS.<sup>35</sup> A  $p$ -value  $< 0.05$  was considered significant.<sup>36-42</sup>



**Figure 3.** Representative HPLC chromatograms after deproteinization of drug-free rat plasma peaks: fenofibric acid (1) (5.9 min) and (2) (7.7 min).

## Animal experiments

The care and the use of experimental animals is in accordance to the Laboratory Animal Ethics Committee Sam Yang Company, South Korea (KR20170325142674).

Male Sprague-Daley rats, 6-8 week old and weighing 220-300 g, were purchased from Bio-Korea (Osan, South Korea). The rats were maintained in a clean room at between  $23 \pm 2$  °C with 12 h light (7:00 am-7:00 pm) and dark (7:00 pm-7:00 am) cycles, and a relative humidity of  $55 \pm 5\%$ . The rats were housed in metabolic cages (Tecniplast, Varese, Italy) under filtered pathogen-free air and with food (Sam Yang Company, PyeongTaek, South Korea) and water supplied *ad libitum*. The rats were fasted overnight before drug administration and for 4 h after dosing. **JF-2** was dissolved in PEG-400:distilled water 1:1 (v/v) to make a concentration of 5 mg mL<sup>-1</sup>. The rats were placed in a restrainer and administered a dose of 20 mg kg<sup>-1</sup> orally. Blood was collected in a heparinized tube at the pre-dose stage, and at 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 h after p.o. administration. Plasma was harvested after centrifugation at 3000 rpm and 4 °C for 10 min and stored frozen at -70 °C until it was analyzed.<sup>43-49</sup>

## Results and Discussion

### Chemistry

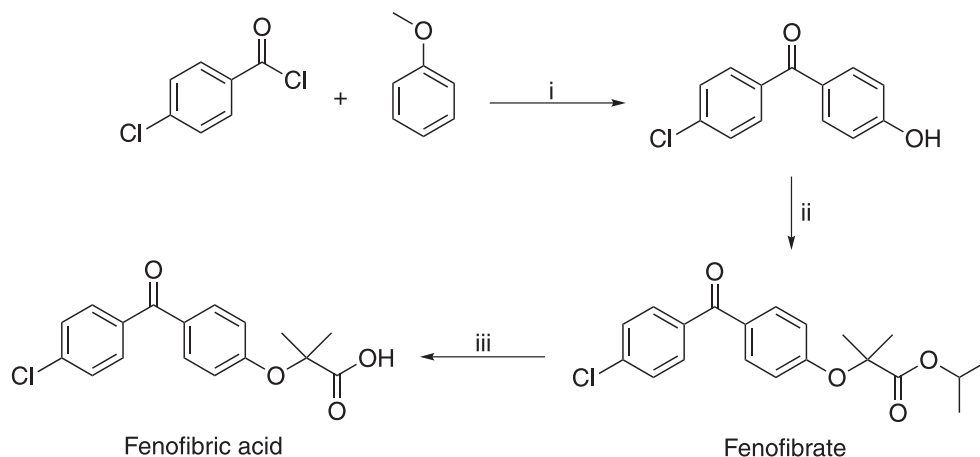
A general procedure for the preparation of the fenofibric acid pro-drug began from a serial reaction, such as Friedel-Crafts arylation, demethylation, deprotection, ester-hydrolysis under basic conditions.

A series of fenofibric acid esters, **JF-1-7**, were prepared using the optimized procedure from the starting material, 4-chlorobenzoylchloride and anisole, dissolved in dry dichloromethane using aluminum chloride as

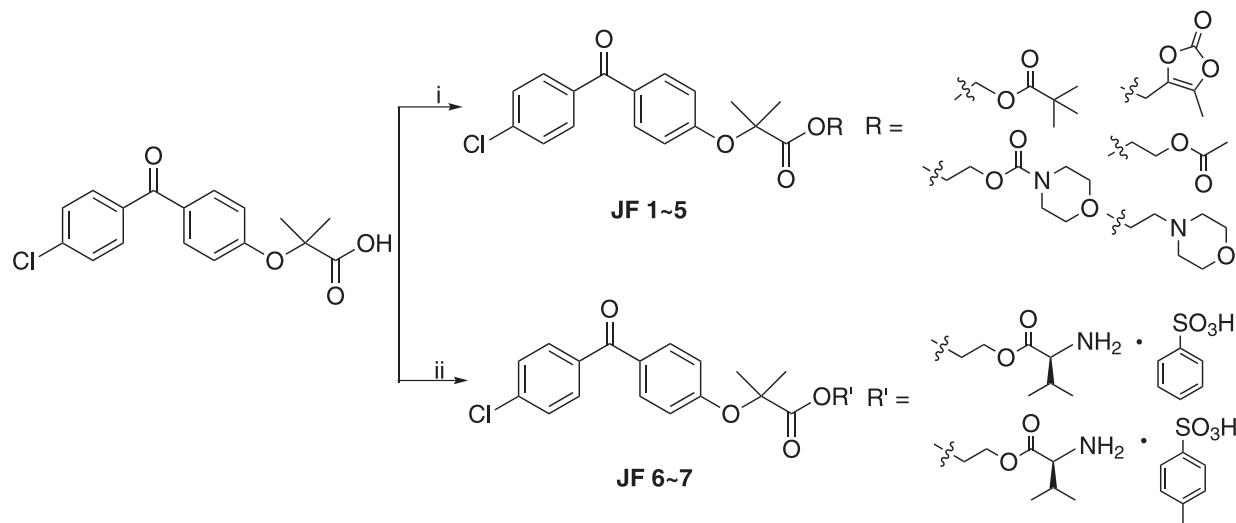
the Friedel-Craft reagent to afford (4-chlorophenyl)(4-hydroxyphenyl)methanone. The addition of isopropyl-2-bromo-2-methylpropanoate gave the fenofibrate, which was then treated with a 1 M NaOH solution to hydrolyze the ester to the acid form in the presence of the desired fenofibric acid compound (Scheme 1). Finally, fenofibric acid ester compounds were generated from fenofibric acid and side alkyl halide chain reagents was treated with potassium carbonate to produce the target compounds **JF-1-7** (Scheme 2).

Plasma samples were collected after the oral administration of **JF-2** and fenofibrate and the concentrations of fenofibric acid were determined using a validated HPLC method (Figure 4). The mean plasma concentration-time curves for fenofibric acid were measured after the oral administration of **JF-2** and fenofibrate to rats; the pharmacokinetic parameters are presented. After the oral administration of **JF-2**, the absorption of fenofibric acid from the rat portal vein was slow and the plasma concentrations of fenofibric acid decreased in a delay-released manners with a  $T_{max}$  and half-life of 6.0 and 7.9 h, respectively. The estimated total body clearance was 33.0 mL min<sup>-1</sup> kg<sup>-1</sup>, which was considerably smaller than the reported cardiac output of 295 mL min<sup>-1</sup> kg<sup>-1</sup> based on the blood data in rats.<sup>50</sup> This suggests that the first-pass effect of **JF-2** in the lung and heart could be almost negligible in rats.

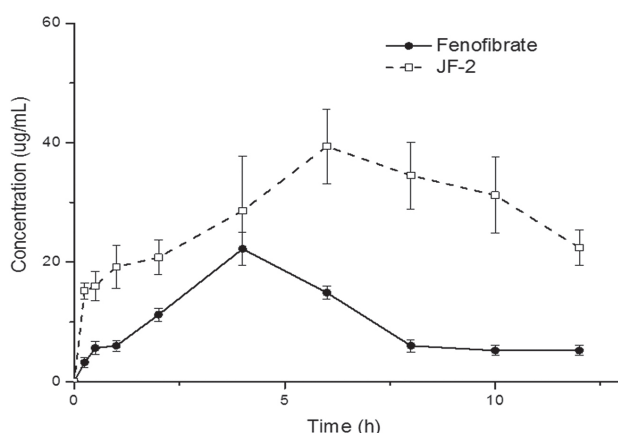
The maximum plasma concentrations of fenofibric acid were achieved 6.0 and 4.0 h after the oral administration of **JF-1-7** and fenofibrate, respectively (Table 1). The  $C_{max}$  values of **JF-2** and fenofibrate were  $39.19 \pm 6.65$  and  $22.78 \pm 3.68$  mg mL<sup>-1</sup>, and the AUClast values were  $343.13 \pm 61.79$  and  $125.80 \pm 22.42$  mg mL<sup>-1</sup> for **JF-2** and fenofibrate, respectively (Table 2). The  $C_{max}$  value of **JF-2** was 1.7 times higher than that of fenofibrate and the AUClast value of **JF-2** was 2.7 times higher than that of fenofibrate. **JF-2** appeared to have been well absorbed



**Scheme 1.** Reagents and conditions: (i) AlCl<sub>3</sub>, toluene, 0 °C; (ii) isopropyl 2-bromo-2-methylpropanoate, K<sub>2</sub>CO<sub>3</sub>, DMA; (iii) 1 M NaOH, 2-butanone, reflux.



**Scheme 2.** Reagents and conditions: (i)  $K_2CO_3$ , DMF, 65 °C; (ii) ethyl L-valinate, aryl sulfonic acid, THF.



**Figure 4.** Comparative pharmacokinetics of **JF-2** and fenofibrate after oral administration to rats.

**Table 1.** Comparison of JF series compounds and fenofibrate values

Compound	AUC <sub>0-12</sub> / (μg h mL <sup>-1</sup> )	C <sub>max</sub> / (μg mL <sup>-1</sup> )	BA / %
<b>JF-1</b>	61.28 ± 21.64	8.65 ± 3.24	48.7
<b>JF-2</b>	343.13 ± 61.79	39.19 ± 6.65	272.8
<b>JF-3</b>	157.03 ± 31.33	29.61 ± 5.78	124.8
<b>JF-4</b>	167.14 ± 28.39	19.05 ± 3.23	132.9
<b>JF-5</b>	157.58 ± 26.83	22.41 ± 4.44	125.3
<b>JF-6</b>	112.20 ± 21.13	15.57 ± 2.54	89.2
<b>JF-7</b>	156.09 ± 11.77	25.50 ± 1.80	124.1
Fenofibrate	125.80 ± 22.42	22.78 ± 3.68	–

AUC: area under the curve to the collected time point; C<sub>max</sub>: peak plasma concentration; BA: bioaggregate.

from the gastrointestinal tract compared to fenofibrate. The *p*-value of C<sub>max</sub> and AUC<sub>last</sub> between the 2 groups were 0.020 and 0.005, respectively. This suggests that **JF-2** was well absorbed from the gastrointestinal tract

**Table 2.** Pharmacokinetic parameters of fenofibric acid after a single oral administration of **JF-2** and fenofibrate at dose of 20 mg kg<sup>-1</sup> to male rats

Parameter	<b>JF-2</b> (n = 5)	Fenofibrate (n = 5)
AUC <sub>0-12</sub> / (g h mL <sup>-1</sup> )	343.13 ± 61.79	125.80 ± 22.42
C <sub>max</sub> / (g mL <sup>-1</sup> )	39.19 ± 6.65	22.78 ± 3.68
T <sub>max</sub> / h	6.00 ± 0.00	4.00 ± 0.00
T <sub>1/2</sub> / h	7.89 ± 1.49	3.46 ± 0.78

Data represent mean ± standard deviation (SD; n = 5). AUC: area under the curve to the collected time point; C<sub>max</sub>: peak plasma concentration; T<sub>max</sub>: time to reach the peak plasma concentration; T<sub>1/2</sub>: elimination half-life.

via peptide transporter 1. The considerable effect of **JF-2** on peptide transporter 1 is being tested based on homogenate studies.

## Conclusions

A series of fenofibric acid-substituted polar-function derivatives, such as dioxolone, alkyl acetate, alkyl none, morpholinyl carboxylate, ethyl L-valinate, and sulfonic acid salt, were synthesized. The coupling of the fenofibric acid with chain functional groups to produce the target compounds proceeded successfully, which can be further one-top substituted to produce the final compound in moderate yield. The effects of synthesized compounds on the biology assay in pharmacokinetics showed outstanding bioavailability. In particular, fenofibric acid and acetate-containing compound code **JF-2**, showed strong absorption and a high concentration. Overall, **JF-2** is a type of pro-drug with potential activity. **JF-2** is a special product that is closely related to human health. Further studies to find the optimal conditions for fenofibric acid are currently underway.

## Supplementary Information

Supplementary information (NMR spectrum) is available free of charge at <http://jbcs.sbq.org.br> as PDF file.

## Acknowledgments

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