Full Paper

In Vivo Antihyperlipidemic Activity of a New Series of *N*-(Benzoylphenyl) and *N*-(Acetylphenyl)-1-benzofuran-2-carboxamides in Rats

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A new series of *N*-(benzoylphenyl) and *N*-(acetylphenyl)-1-benzofuran-2-carboxamides (**3a**–**3d** and **4a′**–**4c′**) were synthesized. Compounds (**3a**, **3b**, and **4a′**–**4c′**) were tested *in vivo* using Triton-WR-1339-induced hyperlipidemic rats as an experimental model for their hypolipidemic activity. The tested animals were divided into eight groups: control, hyperlipidemic, **3a**, **3b**, **4a′**, **4b′**, **4c′**, and bezafibrate. At a dose of 15 mg/kg, the elevated plasma triglyceride (TG) levels were significantly reduced in compounds **3b** ($p < 0.0001$) and **4c′** ($p < 0.05$) after 12 and 24 h compared to the normal control group. Furthermore, high-density lipoprotein-cholesterol levels were remarkably increased in compounds **3b** ($p < 0.001$) and **4c′** ($p < 0.05$). Meanwhile, compound **4b′** slightly reduced the TG levels after 12 and 24 h. The present study demonstrated new properties of the novel series of benzofuran-2-carboxamides **3b** and **4c′** as potent lipid-lowering agents. It is, therefore, reasonable to assume that compounds **3b** and **4c′** may have a promising potential in the treatment of hyperlipidemia and coronary heart diseases.

Keywords: High-density lipoprotein-cholesterol / Hypolipidemic activity / *N*-(Benzoylphenyl) and *N*-(acetylphenyl)-1-benzofuran-2-carboxamides / Triglycerides / Triton-induced hyperlipidemia

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Introduction

Atherosclerosis, the underlying cause of heart attack, stroke, and peripheral vascular disease, is a main cause of morbidity and mortality worldwide [1–3]. One of the initial events in the development of atherosclerosis is the accumulation of cells containing excess lipids within the arterial wall [4, 5].

Hyperlipidemia is defined as an elevation of lipids in plasma. Several studies have showed that an intimate correlation exists between coronary heart diseases and hyperlipidemia; consequently a rational approach to the treatment and prevention of coronary heart diseases could be by decreasing any elevated levels of lipids in plasma [6, 7].

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Triglycerides (TG) are energy-rich compounds, primarily stored in liver and adipose tissue, and are mobilized in response to various metabolic signals. In plasma, TG, which are water insoluble, circulate as the neutral lipid core of lipoproteins, mainly chylomicrons, which carry dietary fat and are secreted by the small intestine, and very low-density lipoprotein-cholesterol (VLDL-C), which carries TG from the liver [8].

Fibrates and their derivatives are a group of drugs which have been widely used for a long time to treat hyperlipoproteinemia, among which is the well-known commercially available drug bezafibrate [9–11]. The major pharmacological mechanism of fibrates, including bezafibrate, is supposed to be an increased hydrolysis of TG by the induction of lipoprotein lipase and reduction of apolipoprotein C-III synthesis [12, 13].

Triton WR-1339 (a nonionic detergent resulting in milky serum that lasts up to 48 h) has been widely used to produce acute hyperlipidemia in animal models in order to screen

natural and chemical drugs [14]. The accumulation of plasma lipid by Triton WR-1339 appears to be due to the inhibition of lipoprotein lipase activity [15].

During the last decade, a lot of attention has been given to studies focused on the synthesis of benzofuran-containing agents and their pharmacological activities [16, 17]. From these studies, which include our previous published data, it was found that compounds containing the benzofuran ring have a promising potential effect as lipid-lowering agents [18–20].

For this purpose, this study has been conducted to evaluate the potential hypolipidemic effects of a new series of *N*-(benzoylphenyl) and *N*-(acetylphenyl)-1-benzofuran-2-carboxamides (**3a**, **3b**, and **4a′**–**4c′**).

Results

Induction of hyperlipidemia by Triton WR-1339

The plasma total cholesterol (TC), TG, high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) levels of all groups treated for 12 and 24 h are shown in Fig. 1. Triton WR-1339 caused a significant increase in plasma TC, TG, and LDL-C ($p < 0.0001$) levels in the hyperlipidemic control group (HG) at 12 and 24 h after Triton administration in comparison with the normal control group (NC). In fact, the increases of plasma TC concentration in the HG were 16 and 11.6% after 12 and 24 h as compared to the NC. TG and LDL-C levels in the HG were also elevated by 767 and 108% and 671 and 100% after 12 and 24 h, respectively.

Meanwhile a significant decrease ($p < 0.001$) in the HDL-C level occurred at 12 and 24 h after Triton injection compared to the NC.

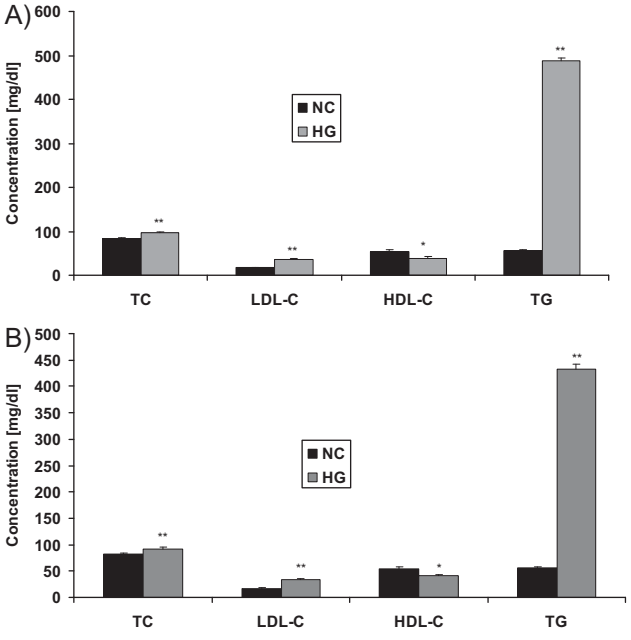


Figure 1. Effect of Triton WR-1339 on lipid profile after (A) 12 h and (B) 24 h. Values are means ± SD from eight animals in each group. NC, control group; HG, hyperlipidemic control group; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol. HG is compared to NC. $^{*}p < 0.001$ and $^{**}p < 0.0001$.

Effect of 3a, 3b, 4a′, 4b′, 4c′, and bezafibrate on rat plasma lipid profile

The plasma TC, TG, HDL-C, and LDL-C levels of BF-, **3a**-, **3b**-, **4a′**-, **4b′**-, and **4c′**-treated rats after 12 and 24 h are shown in Table 1. Importantly, the elevated plasma TG levels produced by Triton WR-1339 administration after 12 h were significantly suppressed by 73% ($p < 0.0001$) in BF, and by 61% ($p < 0.0001$), and 27% ($p < 0.05$) in **3b**- and **4c′**-treated rats, respectively, with respect to the hyperlipidemic control HG. TG levels were also significantly decreased by 68%, 65% ($p < 0.0001$), and 16% ($p < 0.05$) in BF-, **3b**- and **4c′**-treated rats after 24 h, respectively.

Meanwhile, compound **4b′** showed a slight decrease in TG levels by 12 and 8% after 12 and 24 h, respectively.

The HDL-C levels were significantly increased after 12 h of Triton administration, +31%, +28% ($p < 0.001$), and +21% ($p < 0.05$) in BF-, **3b**-, and **4c′**-treated rats, respectively, compared to HG-treated rats and were maintained until 24 h after Triton injection.

With the exception of compound **3b** none of the treated groups showed a significant reduction in plasma TC levels after 12 and 24 h of Triton administration. In fact, it was found that TC levels in compound **3b** were reduced by 19, 25% ($p < 0.001$) after 12 and 24 h, respectively, of Triton administration with respect to the hyperlipidemic control HG (Table 1).

After 12 and 24 h of treatment, LDL-C levels in **3b** were lowered by 34 and 35% ($p < 0.001$), respectively. Meanwhile, there were no significant changes in LDL-C levels in **4b′** and **4c′** after 12 and 24 h.

After 12 and 24 h of treatment, no significant differences in plasma TC, TG, HDL-C, and LDL-C levels in **3a** and **4a′** were observed compared to HG-treated rats (Table 1).

However, compounds **3c** and **3d** were not biologically tested because they are derivatives of compound **3a** which was revealed inactive.

Discussion

The results of the current study showed the potential hypolipidemic effects of compounds **3b** and **4c′** (Table 1) in Triton WR-1339-induced hyperlipidemic rats. Compounds **3b** and

Table 1. Effects of the novel **3a**, **3b**, **4a′**, **4b′**, **4c′**, and BF on plasma lipid levels in Triton WR-1339-induced hyperlipidemic rats after 12 and 24 h.

Lipid profile	TC (mg/dL)	TG [mg/dL]	HDL-C [mg/dL]	LDL-C [mg/dL]
12 h				
HG	95.6 ± 3.6	487.5 ± 7.7	39.0 ± 2.6	35.2 ± 1.9
3a	103.2 ± 5.2	468.0 ± 4.9	40.2 ± 3.1	37.5 ± 3.2
3b	77.2 ± 2.7[a]	188.3 ± 5.3[b]	50.1 ± 3.1[a]	19.3 ± 2.2[a]
4a′	100.1 ± 6.2	491.0 ± 8.8	38.6 ± 2.3	35.5 ± 2.0
4b′	94.3 ± 2.2	425.8 ± 7.9	42.5 ± 1.6	34.4 ± 3.3
4c′	83.5 ± 2.6	355.0 ± 6.8[c]	46.1 ± 1.3[c]	33.9 ± 2.2
BF	92.0 ± 3.1	129.7 ± 4.0[b]	51.2 ± 2.4[a]	31.1 ± 3.8
24 h				
HG	91.6 ± 3.2	433.5 ± 8.3	41.3 ± 1.9	33.8 ± 1.1
3a	93.2 ± 4.0	430.1 ± 3.2	41.9 ± 1.9	34.5 ± 2.1
3b	69.1 ± 1.6[a]	153.3 ± 3.0[b]	53.1 ± 2.1[a]	22.1 ± 1.9[a]
4a′	96.3 ± 5.1	436.6 ± 8.2	40.6 ± 1.5	33.4 ± 0.9
4b′	93.3 ± 1.7	396.0 ± 6.6	44.1 ± 0.9	33.4 ± 1.6
4c′	84.5 ± 2.2	366.0 ± 7.1[c]	48.1 ± 1.3[c]	29.9 ± 2.6
BF	94.4 ± 3.1	140.7 ± 3.0[b]	49.2 ± 3.1[a]	31.3 ± 3.8

Values are expressed as means ± SD from eight animals in each group. NC, normal control group; HG, hyperlipidemic + 4% DMSO control group; **3a**, **3a** + 4% DMSO; **3b**, **3b** + 4% DMSO; **4a′**, **4a′** + 4% DMSO; **4b′**, **4b′** + 4% DMSO; **4c′**, **4c′** + 4% DMSO; BF, bezafibrate + 4% DMSO; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.
3a, **3b**, **4a′**, **4b′**, **4c′**, and BF are compared with HG.
[a] $p < 0.001$.
[b] $p < 0.0001$.
[c] $p < 0.05$.

4c′ significantly reduced serum TG and increased serum HDL. Meanwhile, compound **3b′** slightly reduced TG and increased HDL.

In the literature, it has been reported that parenteral administration of Triton WR-1339 to adult rats could induce hyperlipidemia. In such models, the maximum plasma TC and TG levels were reached at 20 h followed by a decline to standard values [21, 22]. In the course of this study, the same model gave a similar pattern of lipid profile changes 12 and 24 h after Triton WR-1339 administration.

Plasma TG levels are controlled by a good balance between hepatic TG synthesis and secretion on one hand and plasma TG clearance on the other. Thus the observed reduction in plasma TG levels by compounds **3b**, **4b′**, and **4c′** could be consummate by reduced synthesis, reduced hepatic output, improved clearance, or a combination of these factors [23].

In addition, compounds **3b**, **4b′**, and **4c′** increased the HDL level, which is known for its preventive role against atherogenesis. HDL also promotes substantial cholesterol egress from the liver by facilitating the mobilization of TG and cholesterol from plasma to liver where it undergoes catabolism and then is eliminated in the form of bile acids [24, 25].

Promisingly, compound **3b** at a dose of 15 mg/kg body weight 12 and 24 h after Triton injection was more potent in reducing TG levels and in increasing HDL-C levels compared to bezafibrate at a dose of 100 mg/kg body weight, which in this study has been used as standard reference hypolipidemic drug.

In addition, it seems that the presence of a large lipophilic moiety is also important for the biological activity. So when benzophenone (**3b**) was replaced by a small lipophilic ring, in this case the actophenone (**3b′** and **3c′**), the activity was remarkably reduced.

In parallel, the current study shows that the compounds with a substitution in positions 3 and 4 were more active in comparison with position 2. This observation could be explained by the possible effect of the extended moiety of diphenylketone when substituted at positions 3 and 4 which encompass the best fit with the proposed three essential components of the proposed target which determine the activity that was proposed by our group previously [25]. On the contrary, the substitution at position 2 does not resemble the same fit with the proposed active component.

Overall, these preliminary observations lead us to conclude that the presence of a large lipopholic moiety, a carboxamide linker along with a heterocylic ring (able to form hydrogen bonds) are three important requirements to obtain hypolipidemic activity.

In summary, compounds **3b** and **4c′** were shown to improve lipid abnormalities such as hypertriglyceridemia

and hypercholesterolemia, and then elevated HDL levels in Triton induced rats, suggesting them as possible useful candidates in the treatment of patients with lipid abnormalities.

Experimental

Chemistry

Benzofuran-2-acyl chloride (**2**) was prepared in good yield by the reaction of benzofuran-2-carboxylic acid (**1**) with an excess amount of thionyl chloride under reflux (Scheme 1).

In spite of the weakness of 3-amino- and 4-aminobenzophenone derivatives as nucleophiles, their reaction with benzofuran-2-carboxylic acid (**2**) produced the target products by employment of an excess amount of triethylamine which converted compound (**2**) into more reactive species (**5**) (Scheme 2); in addition to its basic role as a soluble organic base.

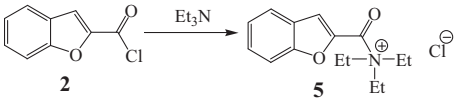
On the other hand, 2-aminobenzophenone derivatives failed to produce the corresponding compounds according to the former procedure, this may be attributed due to the intra hydrogen bonding in 2-aminobenzophenone derivatives. Instead a stronger base, sodium ethoxide, was used (Fig. 2).

All starting materials were purchased from Sigma–Aldrich (St. Louis, MO, USA) and used without further purification. Experiments were performed in purified solvents. Benzofuran-2-acyl chloride (**2**) was prepared according to the published procedure [19]. Melting points were determined using a Stuart Scientific electrothermal melting point apparatus and were uncorrected. Nuclear magnetic resonance (NMR), ^{1}H NMR, and ^{13}C spectra were acquired by a Bruker DRX 400 MHz instrument operating at 400.13 (^{1}H) and 100.61 MHz (^{13}C) relative to TMS as reference standard.

Infrared (IR) spectra were recorded on an Avatar Thermo Nicolet Impact 400 FT-IR spectrophotometer using the Smart Omni-Transmission software; all samples were prepared as potassium bromide (Acros, Belgium) discs. The EI-mass spectra were acquired on a Finnigan TQS 70, by 70 eV at 200°C. Elemental analyzer model is EA3000 A, Italy.

*General procedure for the synthesis of benzofuran carboxamide derivatives (**3a,c,d** and **4a′**)*

A solution of 4.4 mmol of benzofuran-2-acyl chloride (**2**) was added to a solution containing 4.4 mmol of a specified 2-aminobenzophenone (or 2-aminoacetophenone) and 0.6 g (8.8 mmol) of sodium ethoxide in dry *N*,*N*-dimethylformamide (DMF). The reaction mixture was refluxed for 36 h, and then cooled to room temperature. DMF was evaporated under reduced pressure and the residue was stirred for 10 min in $CHCl_3$ followed by purification using silica gel column chromatography (eluents: $CHCl_3$/MeOH) in a ratio of 993:7.



2 **5**

Scheme 2. Synthesis of the reactive species **5** *in situ*.

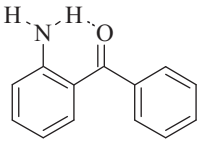


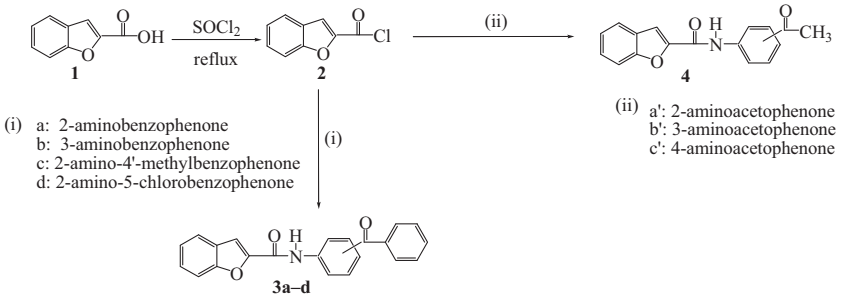
Figure 2. Intra hydrogen bonding in 2-aminobenzophenone.

*General procedure for the synthesis of benzofuran carboxamide derivatives (**3b** and **4b′**,**c′**)*

A solution of 4.4 mmol of benzofuran-2-acyl chloride (**2**) was added to a solution containing 4.4 mmol of 3-aminobenzophenone (or 3 (4)-aminoacetophenone) and 1.3 mL (8.8 mmol) of triethylamine (Et_3N) in dry *N*,*N*-DMF. The reaction mixture was refluxed for 24 h, and then cooled to room temperature. DMF and the excess Et_3N were evaporated under reduced pressure. The residue was extracted with dichloromethane and water; the organic layer was separated, then dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was recrystallized from dichloromethane/diethylether.

*N-(2-Benzoylphenyl)-1-benzofuran-2-carboxamide (**3a**)*

Yield, 39%; mp 168–170°C; ^{1}H-NMR ($CDCl_3$, 400.16 MHz) δ (ppm): 7.33–7.49 (m, 10H), 7.65 (d, 1H, J = 8.5 Hz), 7.70 (s, 1H), 7.73 (d, 1H, J = 8.1 Hz), 8.10 (d, 1H, J = 8 Hz), 8.91 (major), and 10.62 (s, 1H, NH, rotamors); ^{13}C-NMR ($CDCl_3$, 100.61 MHz) δ (ppm): 112.4, 114.9, 117.1, 124.9, 125.2, 126.7, 127.3, 128.2, 129.4, 130.3, 131.8, 132.5, 133.2, 134.7, 138.2, 139.1, 150.3, 159.2, 160.1, 199.2; IR (KBr) cm^{-1}: 1669, 1709 (CO), 3381 (NH); MS (EI/70 eV): m/z (%) = 118 (44) $[M-CONHPhCOPh]^+$, 146 (100) $[M-NHPhCOPh]^+$, 341 (25) $[M]^+$. Anal. Calcd. for $C_{22}H_{15}NO_3$: C, 77.41; H, 4.43; N, 4.10. Found: C, 77.01; H, 4.78; N, 3.84.



1 **2** **4** **3a–d**

Scheme 1. Reagents and conditions: (a) $SOCl_2$, THF, and reflux; (b) different aminobenzophenones, base, and DMF; (c) different aminoacetophenones, base, and DMF.

*N-(3-Benzoylphenyl)-1-benzofuran-2-carboxamide (**3b**)*

Yield, 81%; mp 119–121°C; ^{1}H-NMR ($CDCl_3$, 400.16 MHz) δ (ppm): 7.36–7.42 (m, 6H), 7.59 (d, 1H, J = 8.1 Hz), 7.63–7.69 (m, 2H), 7.71 (d, 1H, J = 8.4), 7.79 (s, 1H), 7.92 (d, 1H, J = 8.0 Hz), 8.02 (dd, 1H, J = 2.4, 8.1 Hz), 8.78 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 100.61 MHz) δ (ppm): 113.1, 114.8, 121.1, 121.7, 124.5, 125.1, 126.0, 126.8, 128.9, 130.5, 131.7, 132.4, 134.7, 136.0, 137.9, 143.3, 150.2, 158.3, 159.0, 197.1; IR (KBr) cm^{-1}: 1672, 1711 (CO), 3378 (NH); MS (EI/70 eV): m/z (%) = 118 (43) [M–CONHPhCOPh]$^+$, 146 (100) [M–NHPhCOPh]$^+$, 341 (19) [M]$^+$. Anal. Calcd. for $C_{22}H_{15}NO_3$: C, 77.41; H, 4.43; N, 4.10. Found: C, 77.10; H, 4.82; N, 3.72.

*N-[2-(4′-Methylbenzoyl)phenyl]-1-benzofuran-2-carboxamide (**3c**)*

Yield, 45%; mp 163–165°C; ^{1}H-NMR ($CDCl_3$, 400.16 MHz) δ (ppm): 7.23–7.51 (m, 9H), 7.64 (d, 1H, J = 8.5 Hz), 7.73 (s, 1H), 7.83 (d, 1H, J = 8.1 Hz), 8.15 (d, 1H, J = 8.0 Hz), 9.02 (major), and 10.53 (s, 1H, NH, rotamors); ^{13}C-NMR ($CDCl_3$, 100.61 MHz) δ (ppm): 23.1, 112.7, 114.5, 117.3, 124.7, 125.3, 126.1, 127.9, 128.1, 129.1, 129.7, 130.1, 133.0, 138.0, 138.3, 141.2, 150.6, 159.2, 160.2, 199.7; IR (KBr) cm^{-1}: 1673, 1713 (CO), 3383 (NH); MS (EI/70 eV): m/z (%) = 118 (39) [M–CONHPhCOPhCH$_3$]$^+$, 146 (100) [M–NHPhCOPhCH$_3$]$^+$, 355 (29) [M]$^+$. Anal. Calcd. for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82; N, 3.94. Found: C, 77.41; H, 5.08; N, 3.63.

*N-[2-(5-Chlorobenzoyl)phenyl]-1-benzofuran-2-carboxamide (**3d**)*

Yield, 37%; mp 194–196°C; ^{1}H-NMR ($CDCl_3$, 400.16 MHz) δ (ppm): 7.31–7.52 (m, 8H), 7.71–7.79 (m, 2H), 7.91 (s, 1H), 8.11 (d, 1H, J = 4.0 Hz), 8.92 (d, 1H, J = 8.1 Hz), 9.09 (major), and 10.58 (s, 1H, NH, rotamors); ^{13}C-NMR ($CDCl_3$, 100.61 MHz) δ (ppm): 112.1, 115.0, 119.1, 124.0, 124.9, 126.3, 128.1 130.2, 132.1, 132.7, 134.6, 135.2, 136.7, 139.0, 150.1, 159.0, 160.7, 203.2; IR (KBr) cm^{-1}: 1679, 1715 (CO), 3388 (NH); MS (EI/70 eV): m/z (%) = 118 (40) [M–CONHPhCOPhCl]$^+$, 146 (100) [M–NHPhCOPhCl]$^+$, 375, 377 (37, 11) [M]$^+$. Anal. Calcd. for $C_{22}H_{14}ClNO_3$: C, 70.31; H, 3.75; N, 3.73. Found: C, 70.11; H, 4.14; N, 3.46.

*N-(2-Acetylphenyl)-1-benzofuran-2-carboxamide (**4a′**)*

Yield, 44%; mp 204–206°C; ^{1}H-NMR ($CDCl_3$, 400.16 MHz) δ (ppm): 2. 51 (s, 3H, $COCH_3$), 7.31–7.40 (m, 5H), 7.68 (d, 1H, J = 8.4 Hz), 7.78 (d, 1H, J = 8.1 Hz), 7.85 (s, 1H), 8.10 (d, 1H, J = 8.0 Hz), 9.12 (major), and 10.54 (s, 1H, NH, rotamors); ^{13}C-NMR ($CDCl_3$, 100.61 MHz) δ (ppm): 27.1, 112.0, 113.8, 116.9, 124.5, 125.2, 127.1, 128.2, 129.9, 130.1, 136.1, 138.0, 140.1, 150.5, 159.0, 162.1, 204.2; IR (KBr) cm^{-1}: 1661, 1715 (CO), 3370 (NH); MS (EI/70 eV): m/z (%) = 118 (48) [M–CONHPhCOCH$_3$]$^+$, 146 (100) [M–NHPhCOCH$_3$]$^+$, 279 (29) [M]$^+$. Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.67; H, 4.98; N, 4.71.

*N-(3-Acetylphenyl)-1-benzofuran-2-carboxamide (**4b′**)*

Yield, 79%; mp 125–127°C; ^{1}H-NMR ($CDCl_3$, 400.16 MHz) δ (ppm): 2.61 (s, 3H, $COCH_3$), 7.30–7.39 (m, 3H), 7.60 (d, 1H, J = 8.1 Hz), 7.69 (d, 1H, J = 8.5 Hz), 7.75 (s, 1H), 7.90 (d, 1H, J = 8.1 Hz), 8.05 (dd, 1H, J = 2.4, 8.1 Hz), 8.31 (s, 1H), 8.45 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 100.61 MHz) δ (ppm): 26.2, 113.9, 114.9, 119.8, 120.3, 122.9, 123.5, 124.1, 129.9, 130.4, 138.2, 141.1, 142.1, 150.1, 158.0, 164.1, 202.1; IR (KBr) cm^{-1}: 1678, 1719 (CO), 3381 (NH); MS (EI/70 eV): m/z (%) = 118 (47) [M–CONHPhCOCH$_3$]$^+$, 146 (100) [M–NHPhCOCH$_3$]$^+$, 279 (21) [M]$^+$. Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.72; H, 4.91; N, 4.80.

*N-(4-Acetylphenyl)-1-benzofuran-2-carboxamide (**4c′**)*

Yield, 80%; mp 199–201°C; ^{1}H-NMR ($CDCl_3$, 400.16 MHz) δ (ppm): 2.61 (s, 3H, $COCH_3$), 7.21–7.28 (m, 2H), 7.31–7.45 (m, 3H), 7.70 (d, 1H, J = 8.5 Hz), 7.76 (s, 1H), 7.85–7.96 (m, 2H), 8.64 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 100.61 MHz) δ (ppm): 26.1, 113.1, 114.6, 118.2, 123.2, 123.9, 127.4, 129.1, 130.1, 134.8, 143.9, 148.1, 158.2, 166.1, 196.1; IR (KBr) cm^{-1}: 1679, 1715 (CO), 3372 (NH); MS (EI/70 eV): m/z (%) = 118 (46) [M–CONHPhCOCH$_3$]$^+$, 146 (100) [M–NHPhCOCH$_3$]$^+$, 279 (24) [M]$^+$. Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.83; H, 4.851; N, 4.91.

Pharmacological assay

Triton WR-1339 was obtained from Sigma–Aldrich. The rest of the chemicals (fine super grade) were purchased from Acros Organics (Amman, Jordan).

Animals and treatments

Sixty-four adult male Wistar rats of 2 months age, weighing around 180 g, bred in the animal care centre of the Faculty of Pharmacy, Al-Zaytoonah University, Amman, Jordan, were provided *ad libitum* access only to tap water throughout the experimental duration. Rats were maintained in a 12 h light–dark cycle under constant humidity and (22 ± 2°C). All experiments were performed in accordance with the Guidelines for Animal Welfare Committee of Al-Zaytoonah University.

Triton model of hyperlipidemia

Triton WR-1339 was dissolved in (DMSO) and administered intraperitoneally to the rats (250 mg/kg body weight) in order to induce hyperlipidemia.

Pharmacological experimental design

Overnight fasted rats were randomly divided into eight groups of eight animals each. The first group, serving as NC, received an intraperitoneal administration of normal saline; the second hyperlipidemic group (HG) received an intraperitoneal injection of Triton dissolved in 4% DMSO (in distilled water). In the third, fourth, fifth, sixth, and seventh groups, rats were intraperitoneally injected with Triton, followed by an intragastric administration (15 mg/kg body weight) of compounds **3a**, **3b**, **4a′**, **4b′**, and **4c′**, respectively, dissolved in 4% DMSO. The last group (BF) was also intraperitoneally injected with Triton and intragastrically treated with bezafibrate (100 mg/kg body weight) dissolved in 4% DMSO.

After 12 and 24 h of treatment, animals were anaesthetized with diethyl ether and blood was collected. The blood samples were immediately centrifuged (3000 rpm for 10 min) and the plasma was used for lipid analysis by an enzymatic method with an automated analyzer (Model Erba XL-300, Germany, Mannheim, Germany).

Statistical analysis

Results were expressed as mean ± SD. Data obtained were analyzed using Student's *t*-test, and the differences with $p < 0.05$ were considered statistically significant.

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References

[1] C. K. Glass, K. L. Witztum, *Cell* **2001**, *104*, 503–516.

[2] R. Ross, *New Engl. J. Med.* **1999**, *340*, 115–126.

[3] M. H. Frick, O. Elo, K. Haapa, O. P. Heinonen, P. Heinsalmi, P. Helo, J. K. Huttunen, P. Kaitaniemi, P. Koskinen, V. Manninen, H. Mäenpää, M. Mälkönen, M. Mänttäri, S. Norola, A. Pasternack, J. Pikkarainen, M. Romo, T. Sjöblom, E. A. Nikkilä, *New Engl. J. Med.* **1987**, *317*, 1237–1245.

[4] W. H. Frishman, *Am. J. Med.* **1998**, *104*, 18S–27S.

[5] J. L. Goldstein, W. R. Hazzard, H. G. Schrott, E. L. Bierman, A. G. Motulsky, *J. Clin. Invest.* **1973**, *52*, 1533–1543.

[6] P. Libby, U. Schoenbeck, F. Mach, A. P. Selwyn, P. Ganz, *Am. J. Med.* **1998**, *104*, 18S–27S.

[7] M. J. Martin, S. B. Hulley, W. S. Browner, L. H. Kuller, D. Wentworth, *Lancet* **1986**, *2*, 933–936.

[8] K. M. West, M. S. Ahuja, P. H. Bennet, *Diab. Care* **1983**, *6*, 361–369.

[9] K. Schoonjans, B. Staels, J. Auwerx, *J. Lipid Res.* **1996**, *37*, 907–925.

[10] H. N. Ginsberg, *Am. J. Cardiol.* **2001**, *87*, 1174–1180.

[11] T. Kuusi, C. Ehnholm, J. Viikari, R. Harkonen, E. Vartiainen, P. Puska, *J. Lipid Res.* **1989**, *30*, 1117–1126.

[12] J. R. Patsch, S. Prasad, A. M. Gotto, W. Patsch, *J. Clin. Invest.* **1987**, *80*, 341–347.

[13] P. E. Schurr, J. R. Schultz, T. M. Parkinson, *Lipids* **1972**, *7*, 69–74.

[14] H. Hayashi, S. Niinobe, Y. Matsumoto, T. Suga, *J. Biochem.* **1981**, *89*, 573–579.

[15] B. C. Ross, D. Middlemiss, D. Scopes, T. Jack, K. Cardwell, M. Dowle, D. Judd, S. Watson, U.S. 5498722. **1992**.

[16] G. Holzemann, K. Schiemann, H. Bottcher, T. Heinrich, C. Seyfried, J. Leibrock, C. Van Amsterdam, G. Bartoszyk, U.S. 7425574. **2008**.

[17] R. A. Parker, U.S. 4229467. **1980**.

[18] T. Sohda, H. Odaka, Y. Momose, U.S. 5723479. **1998**.

[19] G. Shattat, T. Al-Qirim, K. Sweidan, M. Shahwan, W. El-Huneidi, Y. Al-Hiari, *J. Enzyme Inhib. Med. Chem.* **2010**, *25* (*6*), 751–755.

[20] K. Yamamoto, R. Byrne, C. Edelstein, B. Shen, A. M. Scanu, *J. Lipid Res.* **1984**, *25*, 770–779.

[21] S. Otway, D. S. Robinson, *J. Physiol.* **1967**, *190*, 309–319.

[22] J. Skorve, A. Al-Shurbaji, D. Asiedu, I. Bjorkhem, L. Berglund, R. Bergel, *J. Lipid Res.* **1993**, *34*, 1177–1185.

[23] L. Anila, N. R. Vijayalakshmi, *J. Ethnopharmacol.* **2002**, *79*, 81–87.

[24] B. Staels, J. Dallongville, J. Auwerx, K. Schoonjans, E. Leitersdorf, J. C. Fruchart, *Circulation* **1998**, *98*, 2088–2093.

[25] G. Abu Sheikha, B. Hussin, Y. Al-Hiari, T. Al-Qirim, G. Shattat, *Z. Naturforsch. C* **2011**, *66c*, 93–103.

