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Original Research Article

Synthesis and *in vivo* anti-hyperlipidemic activity of novel n-benzoylphenyl-2-furamide derivatives in Wistar rats

Suhair Hikmat[1], Tariq Al-qirim[1]*, Dania Alkabbani[1], Ghassan Shattat[2], Ghassan Abu Sheikha[1], Dima Sabbah[1], Reema Abu khalaf[1] and Yusuf Al-hiari[3]

[1]Faculty of Pharmacy, Al-Zaytoonah University of Jordan, Amman, Jordan, [2]College of Science and Health Professions, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia, [3]Faculty of Pharmacy, University of Jordan, Amman, Jordan

For correspondence: **Email: tariq.qirim@zuj.edu.jo; **Tel:** 009624291511; **Fax:** 00962 6 4291432*

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Abstract

Purpose: *To synthesize and evaluate the anti-hyperlipidemic activity of a novel series of N-(benzoylphenyl)-2-furamides (**3a**, **3b**, **4a**, **4b** and **4c**).*
Methods: *Compounds (**3a**, **3b**, **4a**, **4b** and **4c**) were successfully synthesized by reacting activated furan-2-carbonyl-chloride derivatives with aminobenzophenones at 60 °C for 36 h. Hyperlipidemia was induced in overnight fasted rats by intraperitoneal administration of Triton WR-1339 (300 mg/kg). to overnight fasted rats. The rats were divided into six groups: control, hyperlipidemic, hyperlipidemic plus compounds **3b**, **4b**, **4c**, and hyperlipidemic plus bezafibrate-treated. Eighteen hours later, blood samples were collected and plasma lipid profile determined using enzymatic methods.*
Results: *At a dose of 15 mg/kg body weight, the elevated plasma triglyceride (TG) levels, total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) levels were significantly reduced by compounds **4b** ($p < 0.001$) and **4c** ($p < 0.0001$) 18 h later, compared to the hyperlipidemic group. Furthermore, compounds **4b** and **4c** significantly increased high density lipoprotein cholesterol (HDL-C) levels by 29 and 34 %, respectively.*
Conclusion: *The findings indicate the high potency of N-(benzolphenyl)-2-furamides (**4b** and **4c**) as lipid-lowering agents. Thus, these compounds **4b** and **4c** may used as lead compounds for the development of new derivatives and agents for targeting dyslipidemia and cardiovascular diseases.*

Keywords: *Triton WR-1339-induced hyperlipidemic rats, N-(benzoylphenyl)-2-furamides, Lipid-lowering activity, Cardiovascular disease, Synthesis*

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INTRODUCTION

Cardiovascular diseases have become a major health problem in developing countries. Hyperlipidemia is defined as high levels of lipids (fat, cholesterol and triglycerides) circulating in the bloodstream [1,2]. Epidemiological studies demonstrate that hyperlipidemia is the most prevalent indicator of susceptibility to atherosclerosis and heart diseases [3-5]. Thus, decreasing plasma lipid levels play a major role in the treatment and prevention of coronary heart diseases [6]. For this reason, many studies have been conducted to evaluate the potential lipid-lowering activity of synthetic and naturally compounds.

Triton WR-1339, a non-ionic detergent (oxyethylated tertiary octylphenol formaldehyde polymer) has been widely used in *in vivo* studies to produce acute hyperlipidemia in animal models in order to study the lipid-lowering effect

of natural or chemical drugs [7]. Triton WR-1339 has been found to prevent the catabolism of triglycerol-rich lipoprotein by lipoprotein lipase [8,9].

There are many classes of lipid-lowering agents in existence. Fibrates and their derivatives including bezafibrate are class of drugs widely used to treat hypertriglyceridemia [10]. Bezafibrate significantly reduces serum triglyceride and free fatty acid levels [11]. The major mechanism of fibrates is by the induction of lipoprotein lipase and efficient reduction of apolipoprotein C-III-containing particles, which are markers for increased risk of atherosclerosis [12-14].

In the last decade, many studies have shown that furan derivatives have promising potentials as lipid-lowering agents [15-17]. Therefore, the present study focuses on the synthesis and pharmacological evaluation of a novel series of *N*-(benzoylphenyl)-2-furamides as models for their lipid-lowering activity (Figure 1).

EXPERIMENTAL

Materials and methods

All chemicals, reagents and solvents were of analytical grade and used directly without further purification. Chemicals and solvents were purchased from the corresponding companies (Sigma-Aldrich; St. Louis, MO, USA and Acros; Belgium).

Melting points (MP) were recorded using Gallenkamp melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded using Shimadzu IR Affinity-1 spectrophotometer. All samples were prepared as potassium bromide (Acros, Belgium) discs. ^{1}H and ^{13}C NMR spectra were recorded using Bruker 300 MHz (Avance III, Switzerland Department of chemistry, the University of Jordan). Chemical Shifts are given in δ units using TMS as an internal reference. Chemical shifts are given in δ (ppm) using TMS as internal reference; deuterated solvents were used and stated with each compound. Thin Layer Chromatography (TLC) was performed on 20 x 20 cm aluminum plates pre-coated with fluorescent silica gel GF254 (Fluka, Germany) and visualized by UV light (at 254 and/or 360 nm).

Synthesis of the targeted compounds

5-(3-Hydroxyphenyl) furan-2-carboxylic acid **(2)**: methyl-5-(3-hydroxyphenyl) furan-2-carboxylate **(1)** (1 g, 4.58 mmol) was treated with 10 mL of 10 % sodium hydroxide solution (6N) at 90 °C for 24 h. Then, the solution was neutralized with 10 % hydrochloric acid (2N), under ice conditions. The crude solid was filtered to afford methyl-5-(3-hydroxyphenyl) furan-2-carboxylic acid **(2)** as a white powder.

5-(3-Hydroxyphenyl) furan-2-carbonyl chloride **(3):** 5-(3-hydroxyphenyl) furan-2-carboxylic acid **(2)** (0.75 g, 3.675 mmol) was treated with oxalyl chloride (0.63 mL, 7.2 mmol). Thereafter, the solution was refluxed for 48 h and then evaporated under reduce pressure. The crude product was then co-evaporated twice with (10 mL) benzene to give 5-(3-hydroxyphenyl) furan-2-carbonyl chloride **(3)** as pale yellow solid.

N-(4-Benzoylphenyl)-5-(3-hydroxyphenyl)-2-furamide **(3a)**: 5-(3-hydroxyphenyl) furan-2-carbonyl chloride **(3)** (0.5 g, 2.10 mmol) was dissolved in 10 mL dichloromethane (DCM). Then 100 mg of 4-(dimethylamino) pyridine (DMAP) was added. The mixture was stirred at room temperature for 15 min. Then 0.82 g, 4.20 mmol of 4-aminobenzophenon and 10 mL N, N dimethylformamide (DMF) were added to the reaction mixture.

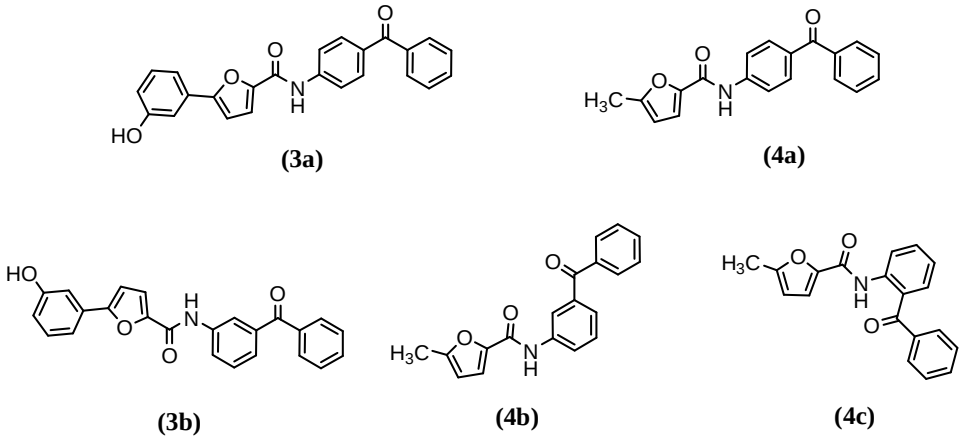


Figure 1: Chemical structures of novel *N*-(benzoylphenyl)-2-furamides (3a, 3b, 4a, 4b and 4c)

The reaction mixture was heated at 60 °C for 36 h. Solvents were evaporated and the residue was purified by column chromatography using chloroform (100 %) as eluent to afford the targeted compound **(3a)** as a fine yellow solid.

N-(3-Benzoylphenyl)-5-(3-hydroxyphenyl)-2-furamide **(3b)**: 5-(3-hydroxyphenyl) furan-2-carbonyl chloride **(3)** (0.5 g, 2.10 mmol) was dissolved in 10 mL of dichloromethane. Then, 100 mg of 4-(dimethylamino) pyridine was added. The mixture was stirred at room temperature for 15 min. Then (0.829 g, 4.206 mmol) of 3-aminobenzophenon and 10 mL of N, N dimethylformamide were added to the reaction mixture. The reaction mixture was heated at 60 °C for 36 h. Solvents were evaporated and the residue was purified by column chromatography using chloroform (100 %) as eluent to afford the targeted compound **(3b)** as a fine yellow solid.

N-(4-Benzoylphenyl)-5-methyl-2-furamide **(4a)**: 5-methylfuran-2-carbonyl chloride **(4)** (0.5 g, 3.45 mmol) was dissolved in (10 ml) of dichloromethane. Then, 100 mg of 4-(dimethylamino) pyridine was added. The mixture was stirred at room temperature for 15 min. Then, (1.36 g, 6.91 mmol) of 4-aminobenzophenon was added to the reaction mixture. The reaction mixture was heated at 60 °C for 24 h. DCM was evaporated and the residue was purified by column chromatography using chloroform/methanol (80:20) as eluent to afford the targeted compound **(4a)** as a white powder.

N-(3-Benzoylphenyl)-5-methyl-2-furamide **(4b)**: 5-methylfuran-2-carbonyl chloride **(4)** (1g, 6.91 mmol) was dissolved in (10 mL) of dichloromethane. Then, 100 mg of 4-(dimethylamino) pyridine was added. The mixture was stirred at room temperature for 15 min. Then (2.72 g, 13.83 mmol) of 3-aminobenzophenon was added to the reaction mixture. The reaction mixture was heated at 60 °C for 24 h. DCM was evaporated and the residue was purified by column chromatography using chloroform/methanol (80:20) as eluent to afford the targeted compound **(4b)** as a white powder.

N-(2-Benzoylphenyl)-5-methyl-2-furamide **(4c)**: 5-methylfuran-2-carbonyl chloride **(4)** (0.8 g, 5.53 mmol) was dissolved in (10 mL) of dichloromethane. Then, 100 mg of 4-(dimethylamino) pyridine was added. The mixture was stirred at room temperature for 15 min. Then (2.18 g, 11.06 mmol) of 2-aminobenzophenon was added to the reaction mixture. The reaction mixture was heated at 60 °C for 24 h. DCM was evaporated and the residue was purified by column chromatography using chloroform/methanol (80:20) as eluent to afford the targeted compound **(4c)** as a white powder.

Animals and treatments

Male Wistar rats weighing 180 g were obtained from the animal house of the Faculty of Pharmacy, Al-Zaytoonah University of Jordan. The animals were provided *ad libitum* access only to tap water throughout the experimental duration and maintained in a 12 h light-dark cycle under standard laboratory conditions (22 ± 2 °C).

Principles of laboratory animal care as described in the European Community guidelines were followed [18]. All experiments were approved by the Animal Welfare Committee of the University (approval ref no. 6ZAWC/2016).

Triton model of hyperlipidemia

Acute hyperlipidemia was developed in animals by intraperitoneal administration of Triton WR-1339 (Tyloxapol, Sigma-Aldrich) to the rats at a dose of (300 mg/kg body weight) [19].

Determination of anti-hyperlipidemic activity

After injection of Triton, the overnight fasted rats were randomly divided into six groups of eight animals each. Normal control group (NCG) received an intraperitoneal administration of normal saline; hyperlipidemic control group (HCG) received an intraperitoneal injection of Triton WR-1339 dissolved in distilled water. In the third, fourth and fifth groups, hyperlipidemic rats were given intragastrically (15 mg/kg body weight) of compounds **3b**, **4b** and **4c** respectively.

In the last group the hyperlipidemic rats were given intragastrically (100 mg/kg body weight) of bezafibrate (BF) [20,21]. At 18 h following triton administration animals were anaesthetized and blood samples were collected from the renal artery. The blood samples were immediately centrifuged (3000 rpm for 10 min) and the serum was used for lipid profile analysis by an enzymatic method with an automated analyzer (Model Erba XL-300, Mannheim, Germany).

Statistical analysis

All anti-hyperlipidemic activity data are presented as mean ± SEM (n = 8). The data were analyzed using Student's t-test, and $p < 0.05$ was

considered statistically significant (SPSS version 2015, IBM SPSS Statistics).

RESULTS

Chemistry

According to the proposed aims, a series of *N*-(benzoylphenyl)-5-(3-hydroxyl phenyl)-2-furamide (**3a** and **3b**) were synthesized starting from methyl-5-(3-hydroxyphenyl)furan-2-carboxylate **(1)** as shown in Scheme 1. Two different aminobenzophenone substitutions were used, 4-aminobenzophenone for compound *N*-(4-benzoylphenyl)-5-(3-hydroxyphenyl)-2-furamide **(3a)**, and 3-aminobenzophenone for *N*-(3-benzoylphenyl)-5-(3-hydroxyphenyl)-2-furamide **(3b)**.

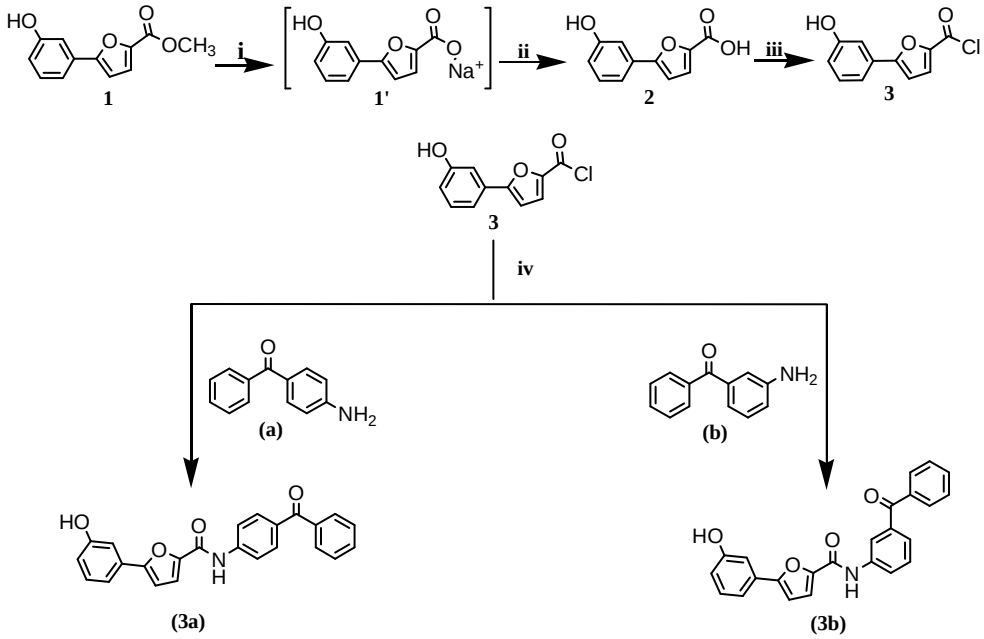
At the same time, a series of *N*-(benzoylphenyl)-5-methyl-2-furamide (**4a**, **4b** and **4c**) were synthesized starting from 5-methylfuran-2-carbonylchloride **(4)** as shown in (Scheme 2). Three different aminobenzophenone substitutions were used, 4-aminobenzophenone for compound *N*-(4-benzoylphenyl)-5-methyl-2-furamide **(4a)**, 3-aminobenzophenone for *N*-(3-benzoylphenyl)-5-methyl-2-furamide **(4b)**, and 2-aminobenzophenone for *N*-(2-benzoylphenyl)-5-methyl-2-furamide **(4c)**.

N-(4-Benzoylphenyl)-5-(3-hydroxyphenyl)-2-furamide (3a)

Yield 34 %; m.p.: 198-200 °C; R_f: 0.33 ($CHCl_3$)/MeOH, 98:2); IR (KBr) cm^{-1}: 3263 (N-H), 3055 (O-H), 1689 (CO, ketone), 1651 (CO, amide), 1597, 1527, 1411, 1311, 1280, 1180, 925, 848, 786, 702, 594, 509, 424, 385 cm^{-1}. 1H-NMR (500 Hz, d6-DMSO) δ (ppm): 10.52 (br, s, 1H, CONH), 8.38 (s, 1H, OH), 7.96 (s, 1H, Ar-H), 7.71 (d, J = 1.35 Hz, 1H, furan-H), 7.66 (m, 6H, Ar-H), 7.55 (m,3H, Ar-H), 7.38 (d, J = 8.45 Hz, 1H, furan-H), 7.25 (m, 1H, Ar-H), 6.6 (m, 2H, Ar-H); 13C-NMR (d6-DMSO): δ = 195.3 (1C), 160.7 (1C), 142.7 (1C), 137.9 (2C), 132.8 (2C), 132.3 (1C), 132.2 (1C), 132.7 (2C), 129.8 (2C), 128.9 (4C), 128.4 (1C), 127.6(1C), 127.0 (1C), 119.0 (2C), 116.8 (1C), 116.6 (1C) ppm.

N-(3-Benzoylphenyl)-5-(3-hydroxyphenyl)-2-furamide (3b)

Yield: 32 %; m.p.: 200-202 °C; R_f: 0.30 ($CHCl_3$/MeOH, 98:2); IR (KBr) cm^{-1}: 3549 (N-H), 3278 (O-H), 1680 (CO, ketone), 1658 (CO, amide), 1589, 1543, 1481, 1435, 1404, 1311, 1280, 1165, 1126, 979, 902, 864, 786, 717, 648, 594. 1H-NMR (300 Hz, $CDCl_3$) δ(ppm): 8.85 (br, s , 1H, CONH), 8.74 (s, 1H, OH), 8,48 (s, 1H, Ar-H), 8.34 (d, J = 3.0 Hz, 1H, furan-H), 7.96 (d, J = 9.0 Hz, 1H, furan-H), 7.87 (s,1H, Ar-H), 7.76 (m, 3H, Ar-H), 7.67 (m, 2H, Ar-H), 7.51 (m, 6H, Ar-H); 13C-NMR ($CDCl_3$) δ (ppm): 196.6 (1C), 162.6 (1C), 159.7 (1C), 139.1 (1C), 138.3 (1C), 137.5 (1C), 137.4 (1C), 137.1 (1C), 137.0 (1C), 133.0 (1C), 132.8 (1C), 130.1 (2C), 129.7 (1C), 129.1 (1C), 128.5 (1C), 128.4(2C), 126.8 (1C), 126.4 (1C), 124.0 (1C), 122.4 (1C), 121.1 (1C), 119.6 (1C).



Scheme 1: Synthesis of *N*-(benzoylphenyl)-5-(3-hydroxylphenyl)-2-furamide (3a, 3b). Reagents and conditions: (i): NaOH 10 % solution (6N)/reflux, 24 h; (ii): HCl (0 °C); (iii):$C_2O_2Cl_2$, DCM/reflux (50 °C), 48 h; (iv): DMAP, DMF, (60°C), 36 h

N-(4-Benzoylphenyl)-5-methyl-2-furamide (4a)

Yield: 45 %; m.p.: 106-108 °C; R_f: 0.5 ($CHCl_3$/MeOH, 98:2); IR (KBr) cm^{-1}: 3533 (N-H), 3008 (CH_3), 1666.52 (CO, ketone), 1666.50 (CO, amide), 1589, 1519, 1404, 1319, 1280, 1249, 1211, 1134, 1018, 925, 848, 794, 748, 702, 624, 509. 1H-NMR (500 Hz, $CDCl_3$) δ(ppm):8.20 (br, s, 1H, CONH), 7.88 (d, J = 8.65 Hz, 2H, Ar-H), 7.81 (m, 4H, Ar-H), 7.60 (t, J = 7.4 Hz, 1H, Ar-H), 7.54 (t, J = 8 Hz, 2H, Ar-H), 7.20 (d, J = 3.35 Hz,1H, furan-H), 6.21 (d, J = 2.65 Hz,1H, furan-H), 2.43 ppm (s, 3H, CH_3); 13C-NMR($CDCl_3$) δ(ppm): 195.6 (1C), 156.2 (1C), 155.4 (1C), 145.8(1C), 141.6 (1C), 137.9 (1C), 133.0 (1C), 132.2 (1C), 131.6 (2C), 129.8 (2C), 128.3 (2C), 118.8(2C), 117.4 (1C), 109.3 (1C), 13.9 (1C).

N-(3-Benzoylphenyl)-5-methyl-2-furamide (4b)

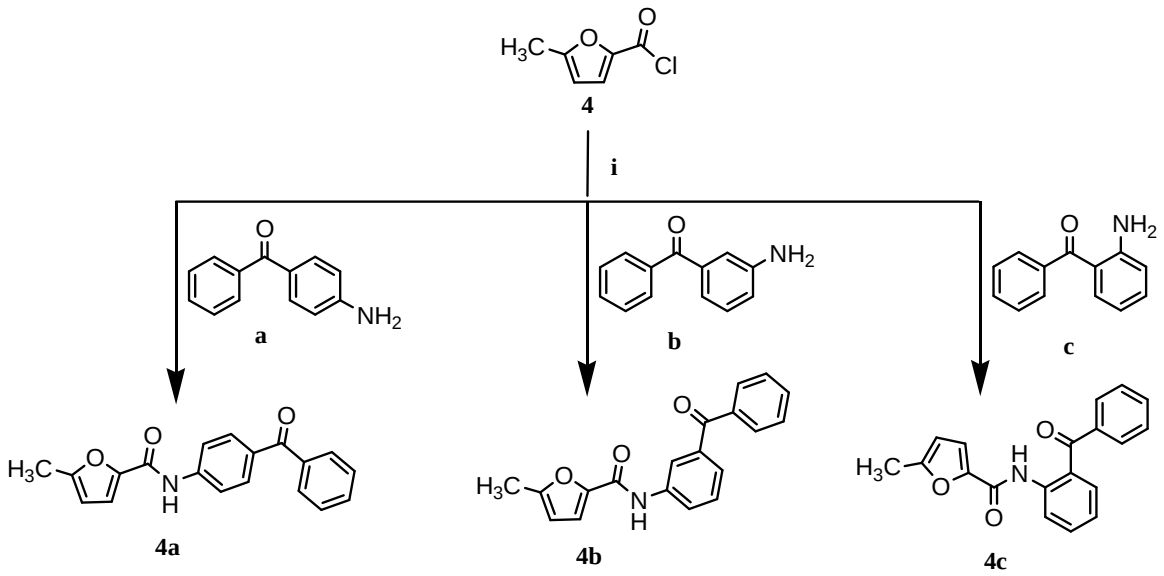
Yield: 38 %: m.p.: 105-106 °C; R_f: 0.55 ($CHCl_3$ /MeOH, 98:2); IR (KBr) cm^{-1}: 3564 (N-H), 3062 (CH3), 1674.21 (CO, ketone), 1674.20(CO, amide), 1597, 1519, 1481, 1427, 1357, 1319, 1288, 1211, 1080, 1018, 964, 902, 871, 786, 725, 586, 509. 1H-NMR (500 Hz, $CDCl_3$) δ(ppm): 8.17 (br, s, 1H, CONH), 8.12 (d, J = 1.0 Hz,1H, Ar-H), 7.93 (s, 1H, Ar-H), 7.84 (d, J = 1.3 Hz, 2H, Ar-H), 7.62 (t, J = 7.4Hz, 1H, Ar-H), 7.57 (d, J = 7.7 Hz,1H, Ar-H), 7.51 (t, J = 7 Hz, 3H, Ar-H), 7.17 (d, J = 3.35 Hz,1H, furan-H), 6.19 (d, J = 2.6 Hz,1H, furan-H), 2.42 ppm (s, 3H, CH_3); 13C-NMR ($CDCl_3$) δ(ppm): 196.2 (1C), 156.3 (1C), 155.2 (1C), 145.8(1C), 138.3 (1C), 137.7 (1C), 137.3 (1C), 132.6 (1C), 130.1 (2C), 129.1 (1C), 128.3 (2C), 125.9(1C), 123.8 (1C), 121.0 (1C), 117.0 (1C), 109.2 (1C), 13.9(1C).

N-(2-Benzoylphenyl)-5-methyl-2-furamide (4c)

Yield: 35 %: m.p.: 102-103 °C; Rf; 0.7 (CHCl3 /MeOH, 98:2); IR (KBr) cm-1: 3317 (N-H), 3124 (CH3), 1674.21 (CO, ketone), 1620.21(CO, amide), 1597, 1519, 1489, 1435, 1357, 1311, 1288, 1211, 1134, 1103, 1018, 925, 871, 802, 748, 694, 632, 516, 447, 385. 1H-NMR (400 Hz, CDCl3) δ(ppm):δ = 11.72 (br, s, 1H,CONH), 8.79 (d, J = 8.0 Hz,1H, furan-H), 7.72 (d, J = 8.0 Hz, 2H, Ar-H), 7.60 (t, J = 12.0 Hz,3H,Ar-H), 7.26 (s, 2H, Ar-H), 7.18 (d, J = 4.0 Hz,1H, Ar-H), 7.10 (t, J = 8.0 Hz, 1H, Ar-H), 6.15 (d, J = 4.0 Hz 1H, furan-H), 2.45 ppm (s, 3H, CH3);13C-NMR (CDCl3) δ(ppm): δ = 199.6 (1C), 156.9 (1C), 155.7 (1C), 146.27 (1C), 140.4 (1C), 138.8 (1C), 134.2 (1C), 133.7 (1C), 132.2 (2C), 129.7 (1C), 128.2 (2C), 123.2(1C), 121.9 (1C), 121.4 (1C), 116.7 (1C), 108.7 (1C), 13.9 (1C).

Anti-hyperlipidemic activity

The plasma total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) levels in hyperlipidemic group (HCG) treated for 18 h are shown in (Figure 2). Triton WR-1339 caused a significant increase in plasma TC, LDL-C ($p < 0.001$), and TG ($p < 0.0001$) levels, and a significant decrease in HDL-C level ($p < 0.001$) in hyperlipidemic control group (HCG) after 18 h of Triton WR-1339 administration in comparison with the normal control group (NCG).



Scheme 2: Synthesis of N-(benzoylphenyl)-5-methyl-2-furamides (4a, 4b and 4c). Reagents and condition: (i): DMAP, DCM/ reflux, 24 h

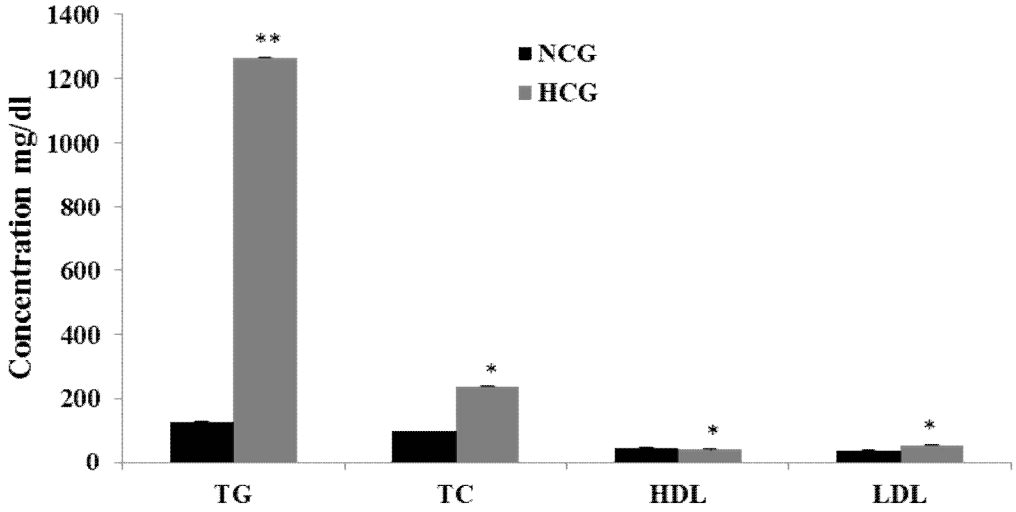


Figure 2: Effect of Triton WR-1339 on plasma lipid profile after 18 h. Values are means ± SEM from eight animals in each group. NCG, control group; HCG, hyperlipidemic control group; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein-cholesterol; LDL-C, low-density lipoprotein cholesterol. HCG is compared to NCG.*$p < 0.001$, .**$p < 0.0001$

The increase of plasma total cholesterol concentration in the HCG was 147 % after 18 h as compared to the NCG. Triglyceride level in the HCG was also elevated by 887 % after 18 h. At the same time, LDL-C level in HCG was also elevated by 49 % after 18 h as compared to the NCG. HDL level in HCG was decreased by 14 % after 18 h as compared to NCG.

Effect of compounds 3b, 4b, 4c and BF on plasma lipid profile in rats

The effect of compounds **3b**, **4b**, **4c** and **BF** on plasma lipid profile on treated rats after 18 h are shown in Table 1. Interestingly, the elevated plasma TG levels produced by the acute injection of Triton WR-1339 were significantly ($p < 0.0001$) decreased by 71 and 67.5 % in compounds **4c** and **BF** respectively and by 56 % in **4b** ($p < 0.001$) after 18 h, in comparison to Triton treated hyperlipidemic control (HCG). Furthermore, total cholesterol levels were significantly ($p < 0.01$) reduced in **4b** by 49 % and in **4c** ($p < 0.001$) by 50 % after 18 h compared to hyperlipidemic control group (HCG).

After 18 h of treatment, LDL-cholesterol levels were lowered by (49 %, $p < 0.0001$) in **4c** and (43.6 % $p < 0.001$) in compound **4b** (Table 1). The HDL-C levels were significantly ($p < 0.001$) increased in compounds **4c** and BF by 34 and 36.5 % respectively and in **4b** by 29 % ($p < 0.01$) after 18 h compared to HCG treated rats. No significant differences in TC, TG, HDL-C and LDL-C levels were observed by compound **3b** in treated rats after 18 h compared to HCG-treated rats.

DISCUSSION

The results of the present study revealed the potential anti-hyperlipidemic activity of novel series of *N*-(benzoylphenyl)-2-furamides using Triton WR-1339-induced hyperlipidemic rats as a model for screening the lipid lowering potential [22].

Table 1: Effect of compounds **3b**, **4b**, **4c** and **BF** on plasma lipid levels in Triton WR 1339 induced hyperlipidemic rats after 18 h

Compound	TG [mg/dl]	TC [mg/dl]	HDL [mg/dl]	LDL [mg/dl]
HCG	1264 ± 22.0	240 ± 9.0	41 ± 2.3	55 ± 1.3
3b	1224 ± 21.0	242 ± 5.0	42 ± 2.7	52 ± 3.5
4b	553 ±12.0 [b]	122 ± 2.0 [a]	53 ± 2.75 [a]	31 ±1.0 [b]
4c	371 ± 5.0 [c]	119 ± 4.0 [b]	55 ± 3.2 [b]	28 ± 2.1[c]
BF	411 ± 3.0 [c]	235 ± 2.0	56 ± 5.0 [a]	52 ± 1.6

Values are means ± SEM from eight animals in each group. NCG: normal control group; HCG: hyperlipidemic control group; 3b: hyperlipidemic plus 3b; 4b: hyperlipidemic plus 4b; 4c: hyperlipidemic plus 4c; BF: hyperlipidemic plus Bezafibrate. TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein

cholesterol; LDL-C: low density lipoprotein cholesterol. 3b, 4b, 4c and BF are compared with HCG [a] $p < 0.01$, [b] $p < 0.001$, [c] $p < 0.0001$

Our results showed that the hyperlipidemia induced by Triton WR-1339 was significantly reduced by compounds **4b**, **4c,** and bezafibrate in comparison with the hyperlipidemic control group after 18 h. It was not surprising that the reduction in triglycerides levels of compounds **4b** and **4c** were significantly greater than the reduction in cholesterol levels; this could be explained by the significant elevation in plasma lipid profile following Triton WR-1339 administration which results mostly from the increase in VLDL (in which the triglycerides portion is several times greater than that of cholesterol) [23]. This result suggests that the compounds are able to restore, at least partially, the catabolism of lipoproteins.

In addition, **4b** and **4c** significantly increased the HDL-C levels after 18 h of Triton WR-1339 administration. Elevated HDL-C is reported to have a preventive action against atherogenesis [24].

The findings of this research work are in agreement with our previous data which indicated that the presence of an aromatic heterocyclic moiety connected to huge lipophilic aromatic rings through a carboxamide linkage is necessary for interaction with proper target(s) for hypolipidemic activity [25,26]. Also, the chemical nature and the electronic effect of the substituents bearing on the heterocycle ring play an important role in the determination of activity.

In the present study, the aromatic heterocycle is represented by furan ring and the aromatic lipophilic rings are benzophenones as shown in compounds **3b**, **4b** and **4c**. Compounds **4b** and **4c** demonstrated much more activity than **3b**. This result may be explained by the chemical nature of the substituent on position 5 of the furan ring. In compounds **4b** and **4c**, the substituent is methyl group, a small lipophilic group while compound **3b** harbors a phenolic group that offers H-bond donor and acceptor motif. The size of the substituent on position 5 is a determinant for the activity and this result may indicate that the adjacent area in the target(s) which receives the furan ring is a small lipophilic site. Therefore, the presence of methyl group provides good hydrophobic interaction in the binding cleft. Interestingly, **4c** exhibited better activity than **4b** and this may be attributed to the possibility of intramolecular H-bond interaction which in turn affects drug/receptor interaction and thus, might infer that the binding site is lipophilic.

At the same time, if compounds **4b** with **4c** are compared, **4c** is more active than **4b** and this may be due to the possibility of intramolecular hydrogen bond formation which means that the amide hydrogen and the oxygen atom of the keto group are not involved in hydrogen bond formation with the target(s); this may suggest that the area in the active site of the target(s) which accommodates the ligand is lipophilic in nature.

CONCLUSION

Compounds 4b and 4c improve lipid profile in Triton-induced hyperlipidemic rats. These findings are in agreement with previous reports, and thus confirm that the presence of lipophilic moiety, carboxamide linkage and a heterocyclic ring (capable of hydrogen bond formation, furan ring) are three important requirements for the hypolipidemic activity of these novel compounds. Thus, there is a need for further investigations to elucidate the exact mechanism of action of these compounds which can serve as lead compounds in the search for therapeutic agents for targeting dyslipidemia and cardiovascular diseases.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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