



## Evaluation of Novel Compound Benzoylphenyl-Indole-Carboxamide Effect on Hyperlipidemic and Hyperglycemic Rat

Mahmoud Al-Shawabkeh<sup>1</sup>, Abdulrahim Al Jamal<sup>2\*</sup> and Omaymah Ghaleb Al-Jamal<sup>3</sup>

<sup>1</sup>Applied Sciences University, Faculty of Pharmacy, Amman 19328, Jordan

<sup>2</sup>Al-Hussein Bin Talal University, Faculty of Nursing and Health Sciences, Amman 19328, Jordan

<sup>3</sup>Research Assistant, Al-Albait University, Faculty of Sciences, Department of Biological Sciences, Al Mafraq, Jordan

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### ABSTRACT

Hyperlipidemia is one of the most risk factors involved in the development of cardiovascular disease. As a consequence of hyperlipidemia treatment, a high demand for new oral antihyperlipidemic drugs is required. The present study was designed to investigate the potential effect of a novel compound N-[4-benzoylphenyl]-1H-indole-2-carboxamide on diet-induced hyperlipidemic (prepared by mixing cholesterol 0.5%, 0.25 % cholic acid, 20% fat and 2% corn oil with standard powdered animal food for two months), triton-induced hyperlipidemic (by intraperitoneal injection of Triton WR-1339 250 mg/kg body weight) and alloxan-induced hyperglycemic rats (150 mg/kg body weight injected intraperitoneally). Lipid profiles [Total cholesterol (TC), Triglyceride (TG), Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL)] in all groups showed significant ( $p < 0.05$ ) changes ( $\pm$ ) before treatment. After 24 hrs of treatment with N-[4-benzoylphenyl]-1H-indole-2-carboxamide (15 mg/kg body weight), significant decrease ( $p < 0.05$ ) in serum cholesterol level 60%, triglyceride 33-45%, LDL 32% and increase HDL 58% levels. Nevertheless, antihyperlipidemic fenofibrate - used as standard reference - showed parallel results to the novel compound. In addition, body weight of diet-induced hyperlipidemic rats decreased about 20%. On the other hand, the novel compound showed no significant effect on glucose level of hyperglycemic rats. In conclusion, the results indicate that N-[4-benzoylphenyl]-1H-indole-2-carboxamide possesses significant antihyperlipidemic activity and may conserve a promising potential effect in the treatment of hyperlipidemia correlated to heart diseases.

**Key words:** Hyperlipidemia, Hyperglycemia, [4-Benzoylphenyl]-1H-Indole-2-Carboxamide, Lipid Profiles, Triton, Alloxan.

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### INTRODUCTION

Lipoproteins are large spherical complexes that transport lipids (primarily triglycerides, cholesteryl esters, and fat-soluble vitamins) through body fluids (plasma, interstitial fluid, and lymph) to be exchanged with tissues. Based on relative densities, plasma lipoproteins are classified into five major classes: chylomicrons, very low density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). Most triglyceride is transported by chylomicrons or VLDL, and most cholesterol is carried as cholesteryl esters by LDL and HDL [1].

Abnormal high levels of cholesterol and triglycerides in the blood was identified as hyperlipidemia that can lead to severe health complications like congestive cardiac failure, atherosclerosis, pancreatitis and eventually stroke [2]. Mostly, hyperlipidemia is caused by life style habits (obesity, not exercising, and smoking) or treatable medical conditions (diabetes, kidney disease, pregnancy, and an under active thyroid gland). Other factors such as genetic, sex and age may also contribute to hyperlipidemia [3].

Interestingly, the risky effect of hyperlipidemia was postulated to alleviate vasomotor disturbances due to peroxides and free radical synthesized by metabolic reactions of diet-derived lipids in the arterial wall and serum that hasten the progression of atherosclerosis [4]. Progressively, these compounds induce endothelial cell injury by oxidizing low density lipoproteins (LDLs) that will damage arterial walls [5].

Antihyperlipidemic drugs or lipid-lowering strategy which mainly act as antioxidants, may have a beneficial role in normalizing vascular function and greatly decreasing the frequency of clinical events associated with atherosclerosis. Several classes of drugs are used to treat hyperlipidemia. These classes have different mechanisms of action in reducing type and magnitude of lipids. For example, Statins - the most common group of antihyperlipidemic drugs- lowers cholesterol by interrupting the cholesterol biosynthetic pathway [5, 6]. More or less, Fibrate group decreases fatty acid and triglyceride levels by stimulating the peroxisomal *b*-oxidation pathway [7, 8]. Apart from these drugs, other groups selectively inhibits intestinal cholesterol absorption or esterification [9], microsomal triglyceride transfer protein or sequestering bile acids [10]. Virtually, Triton WR-1339 (Tyloxapol), a non-ionic detergent, has been widely used to induce acute hyperlipidemia in animal models through inhibition the clearance of triglyceride-rich lipoproteins [11]. Since hyperlipidemia is mostly associated with hyperglycemia and both are considered as the major risk factor for the development of cardiovascular diseases [12], researchers are focusing toward discovering new drugs capable to reduce or regulate glucose levels and lipid profile parameters [total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL) and high density lipoproteins (HDL)]. Optimistic attempts of using some medicinal plants such as bay leaves, fenugreek, rosemary and cinnamon were reported to reduce the level of either glucose or/and lipid profiles in mice, rats and human as well [13- 16]

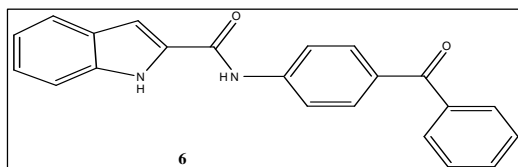
Pharmaceutical reports mention that indole-2-carboxamide derivatives are well-known as hypolipidemic agents [17], and anti-allergics [18] in addition to their potential role as antioxidants [19-21].

The present work is based on the discovery of a novel synthesized benzoylphenylindole carboxamide compound [22-24] to illustrate its effect on hyperlipidemic and hyperglycemic rat models.

## EXPERIMENTAL SECTION

### 2.1. Material preparations

- Hyperlipidemic diet: prepared as described by [25] for induction of hyperlipidemia experimental rats using 2% corn oil, 0.5% cholesterol, 0.25 % cholic acid, and 20% fat.
- Preparation of antihyperlipidemic chemical compound:  
N-[4-benzoylphenyl]-1*H*-indole-2-carboxamide (BIC) was newly prepared by using esterification of Ethyl-1*H*-Indole-2-Carboxylate treated with 4-aminobenzophenone in the presence of sodium ethoxide and DMF. The compound was dissolved in 4% dimethylsulfoxide (DMSO) [21, 22].



- Fenofibrate [(2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic acid isopropyl ester) Sigma-Aldrich, USA] dissolved in 4% DMSO.
- Triton WR-1339 (Tyloxapol, Sigma-Aldrich, USA) dissolved in 4% DMSO.
- Alloxan monohydrate (B.O.H chemical LTD England) dissolved in fresh normal saline.

## 2.2. Animal Models

a. Model of hyperlipidemia: hyperlipidemia in rats was induced either by hyperlipidemic diet 2 months before starting treatment or by Triton WR-1339 administered intraperitoneally as 2.0 ml dose (250 mg/kg body weight) 24 hrs before treatment [22].

b. Model of hyperglycemia: Normal Rats were made hyperglycemic by injecting alloxan intraperitoneally as 1.0 ml dose (150 mg/kg body weight) 24 hrs before treatment [5].

## 2.3. Experimental design:

Adult male Wistar rats weighing 150-180 g obtained from the animal house of Jordan University of Science and Technology were used in this study. The rats were harbored in stainless steel cages under standard laboratory condition. Animals were maintained at 12 h light-dark cycle. Water and food were provided *ad libitum*. Rats were received intraperitoneal injections and distributed into the following groups:

- Control groups received 2.0 ml of normal saline or 2.0 ml of 4% DMSO and fed normally.
- Hyperlipidemic and Hyperglycemic groups were injected either by 2.0 ml of N-[4-benzoylphenyl]-1*H*-indole-2-carboxamide (15 mg/kg body weight) or 2.0 ml of fenofibrate (5 mg/kg body weight).

## 2.4. Experimental analysis

### 2.4.1. Acute oral toxicity study:

Acute oral toxicity assay was performed to estimate lethal dose (LD<sub>50</sub>) concentration of the target compound N-[4-benzoylphenyl]-1*H*-indole-2-carboxamide (BIC) using six different concentrations of the compound (200, 400, 600, 800, 1000 and 1200 mg/kg), which were orally administered to each group of six rats that were carefully and daily recorded over a period of 72 hours.

### 2.4.2. Evaluating the effect of BIC and Fenofibrate (FF) on body weight.

Hyperlipidemic groups rats were injected daily either by 2.0 ml of BIC (15 mg/kg body weight) or 2.0 ml of FF (5 mg/kg body weight) for 4 weeks consequently.

### 2.4.3. Determination of Serum lipid profiles:

Blood samples 2-3 ml were aspirated and collected in non-heparinized tubes from anesthetized rats through the heart puncture and then centrifuged at 3000 rpm for 10 min at room temperature. Serum lipid profile levels of total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL) level were measured by using bio Merieux Kits specified for each parameter (bio Merieux Lab. reagent and product, France).

### 2.4.4. Determination of blood glucose level.

Whole blood samples from the lateral vein of the tail were collected in heparinized capillary tubes before and after 24 hrs of treatment, and the blood glucose levels were determined by strip fast method (Infopia Co., Ltd.Korea). Only rats with blood glucose levels above 200 mg/100 ml were considered and employed in the study.

## 2.5. Statistical analysis:

All data were analyzed by using the Student's t-test and expressed as mean  $\pm$  SD where  $P < 0.05$  were considered statistically significant.

## RESULTS AND DISCUSSION

### 3.1. Lethal dose determination of N-[4-benzoylphenyl]-1*H*-indole-2-carboxamide (BIC):

Acute oral toxicity results in Table 1 showed that the lethal dose (LD<sub>50</sub>) of the target compound N-[4-benzoylphenyl]-1*H*-indole-2-carboxamide (BIC) was estimated to be about 800 mg/kg which is equivalent to  $\approx$  200 mg for a rat weighing 250 g. However, fenofibrate dose was 5 mg/kg based on literature recommendation [6].

**Table 1. Toxicity effect of N-[4-benzoylphenyl]-1H-indole-2-carboxamide on rat survival**

Dose (mg/kg)	Survival rate %
200	100 %
400	100 %
600	83 %
800	50 %
1000	17 %
1200	0 %

### 3.2. Effect of N-[4-benzoylphenyl]-1H-indole-2-carboxamide (BIC) derivative compound and Fenofibrate (FF) on body weight.

Changes in body weight in experimental group are shown in (Table 2). Body weight of diet-induced hyperlipidemic group for two months was increased 25% due to diet. However, after 4 weeks treatment, both BIC and FB showed 23% decrease in body weight of diet-induced hyperlipidemic animals but with no effect on control or Triton groups. In this study, hyperlipidemic-induced animal models showed high levels of lipid profiles. In addition, body weight was significantly increased indicating that a high-fat diet may cause hyperlipidemia which ultimately leads to obesity. These results are parallelly agreed with previous studies who declared that addition of corn oil increase the level of TG and decreased in serum HDL [28]. It was explained that corn oil increases the synthesis and release of LDL and VLDL from the liver into the circulation and decreases the activity of mitochondrial carnitine palmitoyl transferase-1 (PTS-1), which weaken fatty acid oxidation and lipid accumulation [25].

**Table 2. Effect of N-[4-benzoylphenyl]-1H-indole-2-carboxamide (BIC) and Fenofibrate (FF) on body weight of hyperlipidemic rat**

	Normal rat			Diet Hyperlipidemic rat			Triton Hyperlipidemic rat		
	1 <sup>st</sup> day	After 4 weeks	Change %	1 <sup>st</sup> day	After 4 weeks	Change %	1 <sup>st</sup> day	After 4 weeks	Change %
DMSO	182.3 ± 1.8	190.6 ± 1.8	< 1	229.0 ± 3.3*	226.5 ± 4.3*	+ 25	196.2 ± 2.2	192.2 ± 1.6	< 1
BIC	183.4 ± 1.5	195.2 ± 1.6	< 1	215.0 ± 4.6	173.5 ± 4.7**	- 23	192.2 ± 3.4	191.6 ± 1.3	< 1
FF	185.7 ± 1.7	189.6 ± 1.4	< 1	214.6 ± 5.2	172.2 ± 2.0**	- 23	193.8 ± 4.6	190.8 ± 1.6	< 1

> Values are means ± SEM.

> DMSO : dimethylsulfoxide

\* Statistically Significant when compared to control group at  $P < 0.05$ .

\*\* Statistically Significant when compared to Hyperlipidemic group at  $P < 0.05$

### 3.3. Effect of N-[4-benzoylphenyl]-1H-indole-2-carboxamide (BIC) derivative compound and Fenofibrate (FF) on lipid profile parameters:

Results indicate that BIC affects significantly all lipid parameters in both hyperlipidemic model animals. Reduction in level of total cholesterol was 60 % (Table 3), triglyceride 33-45% (Table 4), and low density lipoprotein 32% (Table 5). However, high density lipoprotein increased 58% (Table 5). BIC results showed an improved effect on lipid parameters specially HDL 2.5 folds more when compared with fenofibrate results (Table 6).

It has been reported that administration of Triton WR-1339 to adult rats produces hyperlipidemia in which cholesterol, triglycerides and phospholipids increase to a maximum in about 24 hrs and decrease thereafter in about 20 hrs of treatment with other BIC derivatives [22, 23]. Triton WR-1339 was found to act as a surfactant that suppresses the action of lipase and increase of VLDL secretion by the liver and blocks the uptake of lipoproteins from the circulation by extra hepatic tissues causing increase in the levels of circulating lipid [26]. The present results showed significant increase in lipid profile (TC, TG, and LDL) and significant decrease in HDL in animals 24 hrs after Triton WR-1339 treatment. Interestingly, the results of the present study show that the used dose of N-[4-benzoylphenyl]-1H-indole-2-carboxamide at dose (15 mg/Kg body weight) was able to reverse the drastic effect induced by Triton WR-1339 in rats within 24 hrs treatment. Other lipid-lowering agents were found to exert their outcomes via affecting catabolism of apo-B lipoproteins [27, 29]. Meanwhile, HDL was found to facilitate the mobilization of triglycerides and cholesterol from plasma to liver where it is catabolized and eliminated in the form of bile acids [27]. Hence, this may interpret the inverse relation between LDL and HDL [30]. On the other hand, fenofibrate showed also significant changes of lipid profile as shown in our results. Fenofibrate compound used in our experiment, showed coincide results with previous studies which have examined the effects of fenofibrate on daily food intake, body weight, and lipid profile in rodent models of obesity [27].

**Table 3. Effect of N-[4-benzoylphenyl]-1H-indole-2-carboxamide (BIC) and Fenofibrate (FF) on rat serum Cholesterol**

	Normal rat			Diet Hyperlipidemic rat		Triton Hyperlipidemic rat	
	1 <sup>st</sup> day	After 4 weeks	Change %	After 4 weeks	Change %	After 24 hrs	Change %
DMSO	85.3±3.8	87.3±4.8	< 1	315.4 ±5.5*	+270	313.4 ±5.5*	+268
BIC	83.3±5.5	78.3±3.7	< 1	119.2±3.4**	- 60	116.2±3.4**	- 60
FF	82.3±7.4	79.3±4.4	< 1	97.3±2.4**	- 66	99.3±2.4**	- 66

> Values are means ± SEM.

\* Statistically Significant when compared to control group at  $P < 0.05$ .

\*\* Statistically Significant when compared to Hyperlipidemic group at  $P < 0.05$ .

**Table 4. Effect of N-[4-benzoylphenyl]-1H-indole-2-carboxamide (BIC) and Fenofibrate (FF) on rat serum Triglyceride**

	Normal rat			Diet Hyperlipidemic		Triton Hyperlipidemic	
	1 <sup>st</sup> day	After 4 weeks	Change %	After 4 weeks	Change %	After 24 hrs	Change %
DMSO	82.1±2.2	84.1±2.2	< 1	125.1±4.6*	+ 55	189.1±4.6*	+55
BIC	80.1±3.6	83.1±5.7	< 1	83.1±5.7**	-33	106.5±2.6**	-45
FF	84.1±4.1	84.2±3.3	< 1	87.2±3.3**	30	20.1±602**	- 35

> Values are means ± SEM.

> DMSO: dimethylsulfoxide

\* Statistically Significant when compared to control group at  $P < 0.05$ .

\*\* Statistically Significant when compared to Hyperlipidemic group at  $P < 0.05$ .

**Table 5. Effect of N-[4-benzoylphenyl]-1H-indole-2-carboxamide (BIC) and Fenofibrate (FF) on rat serum Low Density Lipoprotein (LDL)**

	Normal rat			Diet Hyperlipidemic		Triton Hyperlipidemic	
	1 <sup>st</sup> day	After 4 weeks	Change %	After 4 weeks	Change %	After 24 hrs	Change %
DMSO	29.2±1.4	31.1±1.9	< 1	62.3±2.5	< 1	62.3±2.5	< 1
BIC	31.2±1.9	29.4±2.1	< 1	41.3±1.5**	- 32	41.3±1.5**	-32
FF	28.9±1.1	30.1±1.2	< 1	39.7±1.2**	-32	39.7±1.2**	-32

> Values are means ± SEM.

> DMSO: dimethylsulfoxide

\* Statistically Significant when compared to control group at  $P < 0.05$ .

\*\* Statistically Significant when compared to Hyperlipidemic group at  $P < 0.05$ .

**Table 6. Effect of N-[4-benzoylphenyl]-1H-indole-2-carboxamide (BIC) and Fenofibrate (FF) on rat serum High Density Lipoprotein (HDL)**

	Normal rat			Diet Hyperlipidemic rat		Triton Hyperlipidemic rat	
	1 <sup>st</sup> day	After 4 weeks	Change %	After 4 weeks	Change %	After 24 hrs	Change %
DMSO	41.2±1.2	42.1±1.3	< 1	31.2±2.1	< 1	31.2±2.1	< 1
BIC	42.1±1.7	45.3±1.5	< 1	49.5±1.1**	+58	49.5±1.1**	+58
FF	44.3±1.4	42.4±1.1	< 1	40.2±1.4**	+23	36.2±1.4**	+23

> Values are means ± SEM.

> DMSO: dimethylsulfoxide

\* Statistically significant when compared to control group at  $P < 0.05$ .

\*\* Statistically significant when compared to Hyperlipidemic group at  $P < 0.05$ .

### 3.4 Effect of N-[4-benzoylphenyl]-1H-indole-2-carboxamide (BIC) derivative compound and Fenofibrate (FF) on glucose level

Results in Table 7 showed that both BIC and fenofibrate showed no significant change in glucose level in all animal models (hyperlipidemic and hyperglycemic). Alloxan was reported to induce diabetes by damaging the insulin secreting cells of the pancreas leading to hyperglycemia [26, 31, 32]. In the present study, alloxan-induced animals showed hyperglycemic levels. However, our results in this concern showed that N-[4-benzoylphenyl]-1H-indole-2-carboxamide didn't employ any significant changes. Nevertheless, Diabetes mellitus is known to cause hyperlipidemia through various metabolic derangements, in which insulin deficiency has been known to stimulate lipolysis in the adipose tissue and gives rise to hyperlipidemia and fatty liver [33].

**Table 7. Effect of N-[4-benzoylphenyl]-1H-indole-2-carboxamide (BIC) and Fenofibrate (FF) on rat plasma Glucose**

	Normal rat			Diet Hyperlipidemic			Hyperglycemic		
	1 <sup>st</sup> day	After 4 weeks	Change %	1 <sup>st</sup> day	After 4 weeks	Change %	1 <sup>st</sup> day	After 4 weeks	Change %
NS	95.3± 2.5	94.4± 3.5	< 1	95.4± 1.5	97.4± 4.5	< 1	322.4±2.2	325.4±4.2	< 1
DMSO	93.2± 2.4	95.5± 2.5	< 1	94.3± 4.2	96.3± 4.6	< 1	320.4±6.3	323.4±6.3	< 1
BIC	96.3± 3.3	97.4± 4.5	< 1	96.4± 3.5	94.4± 4.5	< 1	331.2±3.7	335.2±3.7	< 1
FF	94.4± 4.5	93.3± 4.6	< 1	98.3± 4.6	99.3± 4.6	< 1	325.4±4.5	328.4±4.7	< 1

> Values are means ± SEM.

> NS: normal saline

> DMSO: dimethylsulfoxide

\* Statistically Significant when compared to control group at  $P < 0.05$ .

\*\* Statistically Significant when compared to Hyperlipidemic group

## CONCLUSION

Hyperlipidemic diet can increase body weight and levels of lipid profile (TC, TG, and LDL) and the newly prepared compound was found to reverse this increase in our animal models without showing any significant effect on hyperglycemic glucose level. Further studies are needed to elucidate and assess the mechanism of action of this newly prepared compound as lipid-lowering agent.

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