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HYPOTRIGLYCERIDEMIC AND HYPOCHOLESTEROLEMIC EFFECTS OF NOVEL *N*-(9,10-DIHYDRO-9,10-DIOXOANTHRACEN-1-YL)-1*H*-PYRROLE-2-CARBOXAMIDES IN TRITON WR-1339-INDUCED HYPERLIPIDEMIC RATS

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ABSTRACT

The lipid-lowering effects of novel *N-(9,10-dihydro-9,10-dioxoanthracen-1-yl)-1H-pyrrole-2-carboxamide* derivatives compounds **6** and **7**, were studied *in vivo* by using hyperlipidemic rats as model for experiment, which were induced by Triton-WR-1339. The tested animals were divided into five groups including control groups (NCG) along with hyperlipidemic control group (HCG) in addition to compounds **6**, **7** and bezafibrate (BF) groups. Compounds **6** and **7** in a dose of 15 mg/KgBW significantly decreased raised plasma TG levels by 10% and 30% after 18 h, respectively. Furthermore, a significant increase in high-density lipoprotein-cholesterol levels were observed in compounds **7** ($p < 0.001$). Promisingly, compound **7** were also able to significantly decreased low-density lipoprotein cholesterol level in comparison with HCG after 18 h of treatment. These results show a promising potential for a novel *N*-(9,10-dihydro-9,10-dioxoanthracen-1-yl)-1*H*-pyrrole-2-carboxamides as lipid-lowering agents which may contribute in reducing the risk of atherosclerosis.

Key words: Hypotriglyceridemic, Hypocholesterolemic, *N*-(9,10-dihydro-9,10-dioxoanthracen-1-yl)-1*H*-pyrrole-2-carboxamides, Triton WR-1339, Rats

INTRODUCTION

Hyperlipidemia is one of the major risk factors causing cardiovascular diseases (CVDs). CVDs accounts for one third of total deaths around the world, it is believed that CVDs will turn out to be the main cause of death and disability worldwide by the year 2020 [1-2].

Hyperlipidemia is an increase plasma lipid profile levels, including cholesterol, cholesterol esters, triglycerides and phospholipids and or plasma lipoproteins including very low-density lipoprotein and low-density lipoprotein, and reduced high-density lipoprotein levels [3-4].

Hypercholesterolemia and hypertriglyceridemia are the main cause of atherosclerosis which is strongly related to ischemic heart disease (IHD) [5]. There is a strong relation between IHD and the high mortality rate. Furthermore elevated plasma cholesterol levels cause more than four million deaths in a year.

Atherosclerosis is a process of arteries hardening due to deposition of cholesterol in the arterial wall which causes narrowing of the arteries. Atherosclerosis and atherosclerosis-associated disorders like coronary, cerebrovascular and peripheral vascular diseases are accelerated by the presence of hyperlipidemia [6].

Treatment with fibrates, one of the most widely used lipid-lowering classes, results in a significant reduction in plasma lipid profile including a significant decrease in triglycerides levels and with a modest decrease in low density lipoprotein (LDL), cholesterol, and an increase in high-density lipoprotein (HDL)-cholesterol [7]. Fibrates act mainly by increasing the hydrolysis of triglycerides by stimulating the enzyme lipoprotein lipase and reducing apolipoprotein C-III synthesis [8-9].

A Triton WR-1339-induced hyperlipidemic rat is an important animal model used to investigate potential lipid-lowering agents [10-11]. Triton WR-1339 (a nonionic surfactant) causes an elevation of plasma lipids by inhibiting the uptake of lipoprotein from the circulation by extrahepatic tissues, causing elevation in the levels of circulatory lipoproteins, this effect of triton can lasts for 48 h [12].

In recent years there has been burgeoning interest in developing new pharmacologically active hypolipidemic drugs to overcome the efficacy problems of the current medications and the adverse effects.

Many synthetic drugs containing a pyrrole moiety show significant biological activities such as antiviral [13], antitumor [14], antioxidative [15], anti-inflammatory [16-17] and antihyperlipidemic properties [18-22]. Therefore, highly substituted pyrroles have been one of the major targets in synthetic chemistry.

In the current research, we aimed to synthesize a novel series of *N*-(9,10-dihydro-9,10-dioxoanthracen-1-yl)-1*H*-pyrrole-2-carboxamides and to examine their pharmacological property as lipid-lowering agents using Triton WR-1339.

MATERIALS AND METHODS

Chemical Studies

Stuart Scientific electrothermal melting point apparatus were used to determine the melting points. Both ^{1}H NMR and ^{13}C spectra were recorded by a Bruker DRX 400 MHz-NMR spectrophotometer operating at 400.13 (^{1}H) and 100.61 MHz (^{13}C) using TMS as internal reference standard.

The Infrared (IR) spectra were recorded by KBr pellet (Acros, Belgium) method on an Avatar Thermo Nicolet Impact 400 FTIR spectrophotometer. All the chemicals used were reagent grade purchased from Sigma-Aldrich (St. Louis, MO, USA). Experiments were performed in purified solvents.

Synthesis of N-(9,10-dihydro-9,10-dioxoanthracen-1-yl)-4-amino-1-methyl-1H-pyrrole-2-carboxamide (6).

Methyl-4-amino-1-methyl-1*H*-pyrrole-2-carboxylate hydrochloride **(1)** (1.5 gm, 9.73 mmol) was treated with 10% NaOH. The mixture was stirred at 120 °C for 2 h. Then, the solution was cooled and neutralized by HCl (10%). The crude powder was dissolved in ethanol and filtered. Then, the filtrate was evaporated to afford 4-amino-1-methyl-1*H*-pyrrole-2-carboxylic acid **(3)** as a white solid (0.94 gm, 62.7%).

Next, the 4-amino-1-methyl-1*H*-pyrrole-2-carboxylic acid **(3)** (0.94 gm, 6.10 mmol) was dissolved in DMF (10 ml). DCC (3.71 gm, 15.36 mmol) was added and the reaction was stirred at room temperature for 1 h. Then, 1-aminoanthraquinone **(5)** (2.67 gm, 11.96 mmol) was added to the mixture and left for 4 days at 100 °C. Purification was performed by using dichloromethane (100%) as eluent in column chromatography to afford the targeted compound **(6)** as a fine yellow powder (0.21gm, 9.06%); m.p decomposed over 230 °C; R_f = 0.64 in chloroform : methanol (97:3); ^{1}H-NMR

(500 MHz, DMSO-d*6*): δ =11.84 (br s, IH, CON*H*), 9.02 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 8.29 (m, 2H, Ar-*H*), 7.96 (d, *J* = 7.3 Hz, 1H, Ar-*H*), 7.81 (m, 2H, Ar-*H*), 7.72 (t, *J* = 8.1 Hz, 2H, Ar-*H*), 4.84 (br s, 2H, NH_2), 1.80 (s, 3H, CH_3) ppm; ^{13}C-NMR (500 MHz, DMSO-d*6*): δ = 187.24, 182.88 (CO-ketone), 154.16 (CO-amide), 144.47, 135.67, 134.18, 134.16, 134.12, 133.86, 132.97, 127.11, 127.02, 125.31, 120.90, 116.25, 25.54 ppm; IR (thin film): ν = 3309, 3209, 3147, 3078, 2931, 1666, 1643, 1595, 1560, 1480,1273, 1165, 736 cm^{-1}.

Synthesis of N-(9,10-dihydro-9,10-dioxoanthracen-1-yl)-4-bromo-3,5-dimethyl-1H-pyrrole-2-carboxamide (7).

Ethyl-4-bromo-3,5-dimethyl-1*H*-pyrrole-2-carboxylate **(2)** (1.5 gm, 6.05 mmol) was treated with 10% NaOH. The mixture was stirred at 100 ˚C for 2 h. Then, the reaction was cooled and acidified with HCl (10%). The mixture was filtered to afford 4-bromo-3,5-dimethyl-1H-pyrrole-2-carboxylic acid (**4**) as a dark purple powder (0.78 gm, 58.7 %).

Next, 4-bromo-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid **(4)** (0.78 gm, 3.47 mmol) was dissolved in DMF (10 ml). DCC (1.43 g, 6.94 mmol) was added and stirred at room temperature for 1 h. Then, 1-aminoanthraquinone **(5)** (1.55 gm, 6.94 mmol) was added to the mixture and left for 5 days at 100 ˚C. Purification was performed by using chloroform as eluent in column chromatography to afford the targeted compound **(7)** as dark yellow powder (0.173 gm, 11.53%); m.p 145-150 ˚C; R_f = 0.57 in chloroform : methanol (95:5); ^{1}H-NMR (500 MHz, DMSO-d*6*): δ =11.63 (br s, IH, CON*H*), 9.52 (br s, 1H, pyrrole-N*H*), 8.14 (d, *J* = 7.55 Hz, 2H, Ar-*H*), 7.89 (m, 1H, Ar-*H*), 7.84 (t, *J* = 8.05 Hz, 2H, Ar-*H*), 7.64 (d, *J* = 8.05Hz, 1H, Ar-*H*), 1.96 (s, 3H, CH_3), 1.83 (s, 3H, CH_3) ppm; ^{13}C-NMR (500 MHz, DMSO-d*6*): δ = 187.59, 181.82 (CO-ketone), 154.01 (CO-amide), 141.29, 135.90, 135.15, 134.83, 134.72, 133.52, 132.86, 127.60, 127.43, 122.92, 122.54, 117.63 ppm; IR (thin film): ν = 3410, 3163, 3039, 2931, 2854, 1660, 1635, 1566, 1450, 1334, 1149, 1087, 1049, 894, 740 cm^{-1}.

Animals and Treatment

Forty adult male Wistar rats, weighing around 200-250 gm, were provided *ad libitum* access to tap water throughout the experimental duration. Rats were maintained under standard environmental condition in a 12 h light-dark cycle at temperature of 22 ± 2˚C and 45-50% humidity. All experiments were done

according to protocol approved by the Animal Welfare Committee of the Al-Zaytoonah University, Amman, Jordan.

Triton model of hyperlipidemia

Hyperlipidemia was induced by the intraperitoneal administration of (300 mg/kg body weight) of Triton WR-1339 dissolved in water to the rats [11, 23].

Pharmacological experimental design

The tested animals were divided into five groups including control groups (NCG) along with hyperlipidemic control group (HCG) in addition to compounds **6**, **7** and bezafibrate (BF) groups.

Forty Overnight fasted rats were randomly distributed on five groups of eight animals each. Group one was considered normal control group (NCG) received an intraperitoneal administration of normal saline; group two was considered hyperlipidemic control group (HCG) received an intraperitoneal injection of Triton. Groups three and four received Triton, followed by an intragastric administration of the tested compounds **6** and **7 (**15 mg/kgBW). Group five, bezafibrate (BF), received Triton and was treated with bezafibrate (100 mg/kgBW) [24-25]. After 18 h of treatments, blood was withdrawn from the renal artery and immediately centrifuged (3000 rpm for 10 min). Plasma lipid profile was estimated using an enzymatic method with an automatic analyzer (Model Erba XL-300, Mannheim, Germany).

Statistical Analysis

Data obtained were analyzed using the Student's t-test. The results were expressed as the mean ± SD of six values in each group, and a statistical probability of $p < 0.01$ was considered to be significant.

RESULTS

Chemistry

This study started by synthesizing pyrrole-2-carboxamide derivatives **(6)** and **(7)** as shown in (Fig. 1).

Synthesis of compounds **(6)** and **(7)** started with ester hydrolysis of **(2)** and **(3)** using NaOH (10%). The reaction media was neutralized by HCl (10%). The formation of amide group was afforded using DCC as coupling agent.

Pharmacological Activity

Induction of hyperlipidemia by Triton WR-1339

Triton WR-1339 has been widely used for the induction of acute hyperlipidemia in rats by blocking the clearance of triglyceride-rich lipoproteins through inhibiting the enzyme lipoprotein lipase. It has been used for testing many lipid-

lowering agents. It has been reported that a single parenteral administration of Triton WR-1339 in a dose of 300 mg/kg to adult rats is sufficient to induce hyperlipidemia and the peak plasma triglyceride level was reached at 18 h [26].

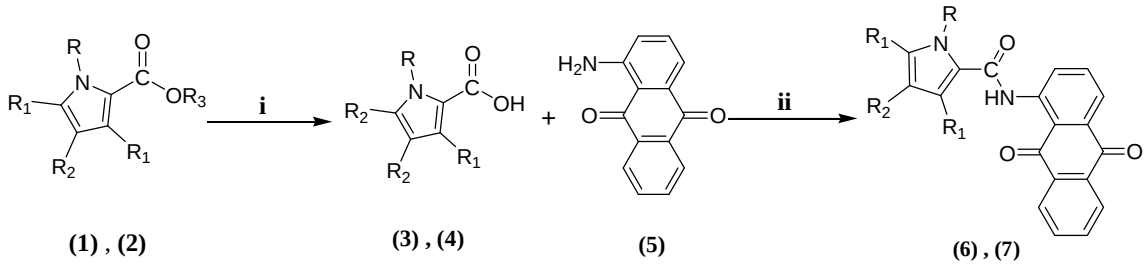
The plasma lipid profile of all treated groups are shown in (Fig. 2) including triglyceride (TG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) levels. The acute injection of Triton resulted in a significant increase in plasma TG, TC and LDL-C ($p < 0.0001$) levels and a significant decrease in HDL-C ($p < 0.0001$) in hyperlipidemic control group (HCG) 18 h following Triton injection compared to normal control group (NCG).

In fact, the triglyceride levels in the HCG were markedly increased by 2378%, which is more than 24 times in comparison with the NCG. The increase in plasma total cholesterol level in the HCG was 887%. At the same time LDL-C level in HCG was also raised by 522% following 18 h of Triton administration in comparison with the normal control group, while a significant reduction in HDL-C level by 36% happened at 18 h after Triton WR-1339 administration.

Effect of compounds 6, 7 and bezafibrate on rat plasma lipid profile

The plasma TG, TC, LDL-C and HDL-C levels of compounds **6, 7** and bezafibrate (**BF**) -treated rats after 18 h of administration are shown in (Table 1). Notably, the elevated plasma TG levels occurred by the single injection of Triton WR-1339 administration were significantly ($p < 0.0001$) reduced in compound **7** by 30% and in **BF**-treated rats by 78.5%. Compound **6** showed a decrease ($p < 0.01$) by 10% with respect (HCG). None of compounds **6, 7** and **BF** groups significantly decreased TC levels following 18 h of Triton administration in comparison with HCG.

Compounds **7** considerably ($P < 0.001$) decreased LDL-C level by 10% compared to HCG. The HDL-C levels were considerably improved after 18h by 92% ($p < 0.0001$) in bezafibrate rats, and 16% ($p < 0.001$) in compound **7**-treated rats compared to HCG (Table 1). No remarkable changes in LDL-C and HDL-C levels were detected in compound **6.**



(1) R= CH_3, R_1= H, R_2= NH_2, R_3= CH_3
(2) R= H, R_1= CH_3, R_2= Br, R_3= C_2H_5
(3) R= CH_3, R_1= H, R_2= NH_2
(4) R= H, R_1= CH_3, R_2= Br
(6) R= CH_3, R_1= H, R_2= NH_2
(7) R= H, R_1= CH_3, R_2= Br

Figure 1: Synthesis of pyrrole-2-carboxamide derivatives (6), (7). *Reagents and conditions*: (i): 1) NaOH (10%), 100-120 ˚C, 2 h, 2) HCl(10%); (ii): DCC, DMF, 100 ˚C, 4-5 days.

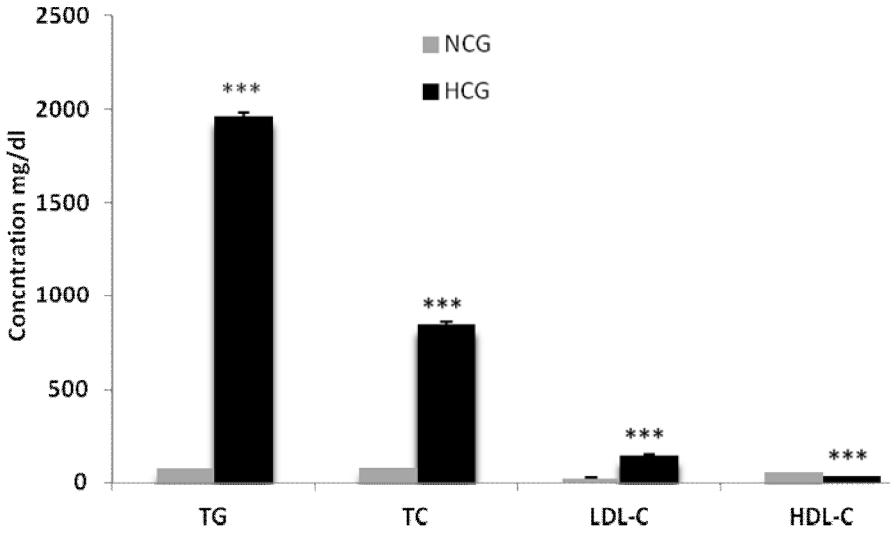


Figure 2: Effect of Triton WR-1339 on plasma lipid levels after 18 h. Values are means ± SD from eight animals in each group. NCG, control group; HCG, hyperlipidemic control group; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol.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

Table 1: Effect of the novel compounds 6, 7 and bezafibrate on plasma lipid levels in TritonWR-1339-induced hyperlipidemic rats after 18 h. Values are means ± SD (n=8 in each group). HCG: hyperlipidemic control group; 6: compound 6; 7: compound 7; BF: bezafibrate; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; 6, 7 and BF are compared with HCG. $^a p < 0.0001$, $^b p < 0.001$, $^c p < 0.01$.

	Lipid Profile			
Groups	**TG (mg/dl)**	**TC (mg/dl)**	**LDL-C (mg/dl)**	**HDL-C (mg/dl)**
HCG	**1965.0 ± 20.14**	**850.0 ± 10.78**	**150.6 ± 6.72**	**35.1 ± 1.74**
6	**1774.2 ± 12.59^c**	**856.3 ± 5.73**	**148.2 ± 2.71**	**35.5 ± 1.34**
7	**1375.3 ± 8.27^a**	**844.0 ± 6.43**	**135.4 ± 1.84^b**	**40.8 ± 1.93^b**
BF	**421.8 ± 5.14 ^{a}**	**860.4 ± 7.28**	**142.4 ± 2.90**	**67.5 ± 2.33 ^{a}**

DISCUSSION

The results of the current study revealed the potential lipid-lowering effect of *N*-(9,10-dihydro-9,10dioxoanthracen-1-yl)-*1H*-pyrrole-2-carboxamide derivatives **6** and **7.** In fact, compounds **7** remarkably decreased TG levels and elevated serum HDL-C after 18 h of Triton administration.

Yamamoto and his colleagues reported that due to the progressive movement of the apo A-1 protein from the HDL surface a large reduction in plasma HDL-C levels resulted due to Triton WR-1339 injection. Meanwhile due to the increase in the secretion of very low-density lipoprotein (VLDL) by the liver in addition to the strong decrease of VLDL and LDL breakdown a large increase in plasma TG levels resulted due to Triton administration [27].

Accordingly, it is not unexpected that the lipid-lowering effect of compounds **7** was remarkably higher for triglycerides than for cholesterol knowing that the proportion of triglyceride in VLDL is many times greater than cholesterol. This result suggests that our novel compounds are capable to restore, at least partially, catabolism of B-lipoproteins as hypothesized by many studies with other anti-hyperlipidemic compounds [28-29].

Promisingly, compounds **7** at a dose of 15 mg/kgBW 18 h following Triton administration had the same potential in reducing TG levels and in elevating HDL-C levels in comparison with bezafibrate at a dose of 100 mg/kgBW, which in this study has been used as standard reference anti-hyperlipidemic drug.

The pharmacological effect of compounds **7** confirmed the essentiality of the presence of the three structural components (aromatic heterocyclic ring capable of hydrogen bond formation, carboxamide linkage and a lipophilic area) for the lipid lowering activity [11, 30].

CONCLUSION

This study has successfully led to the preparation of novel pyrrole-2-carboxiamide derivatives. All compounds were characterized using NMR and IR. All compounds were evaluated for their lipid-lowering activity using Triton WR-1339 induced hyperlipidemic rats.

N-(9,10-dihydro-9,10-dioxoanthracen-1-yl)-*1H*-indole-2-carboxamide derivatives compounds **6** and **7** were shown promising potential in improving many lipid abnormalities such as hypercholesterolemia and

hypertriglyceridemia, and then elevated HDL levels in Triton induced rats, proposing them as possible useful compounds in the management of patients with hyperlipidemia.

The results are highly encouraging but further researches are necessary to elucidate the precise mechanism of action and the safety profile of these novel compounds as lipid-lowering agents.

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