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Novel Pyrrole Derivatives as Potent lipid-Lowering Agents in Triton-WR-1339-Induced Hyperlipidemic Rats

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***SUMMARY*. Hyperlipidemia is nowadays one of the main risk factors for cardiovascular diseases. Therefore, synthesis of new compounds with potential lowering effect on blood lipid profiles became a major concern for many researchers. In this study, we were able to synthesize, characterize and validate new series of novel pyrrole derivatives and evaluate their potency as lipid-lowering agents on animal model. Hyperlipidemia was induced in rats using Triton WR-1339 (Tyloxapol). After 18 h and at a dose of 15 mg/kg body weight, C5, C7 and bezafibrate (100 mg/kg) significantly ($p < 0.0001$) reduced the elevated plasma TG as well as that of plasma total cholesterol and LDL levels compared to the hyperlipidemic control group. Promisingly, C5 and C7 were also able to increase HDL level compared to the hyperlipidemic control group. These results insights potential hypolipidemic effects which consequently may contribute as protective agents against atherosclerosis and cardiovascular diseases.**

RESUMEN. La hiperlipidemia es hoy en día uno de los principales factores de riesgo de enfermedades cardiovasculares. Por lo tanto, la síntesis de nuevos compuestos con potencial efecto reductor de los perfiles de lípidos en sangre se convirtió en una gran preocupación para muchos investigadores. En este estudio, hemos sido capaces de sintetizar, caracterizar y validar una nueva serie de derivados de pirrol novedosos y evaluar su potencial como agentes reductores de lípidos en modelo animal. La hiperlipidemia fue inducida en ratas utilizando Triton WR-1339 (Tiloxapol). Después de 18 h y a una dosis de 15 mg/kg de peso corporal, C5, C7 y bezafibrato (100 mg/kg) redujo significativamente ($p < 0,0001$) el elevado nivel de TG en plasma, así como los niveles de colesterol total y LDL en comparación con el grupo de control hiperlipidémico. C5 y C7 también fueron capaces de aumentar el nivel de HDL en comparación con el grupo control hiperlipidémico. Estos resultados de compuestos con potenciales efectos hipolipemiantes podrían contribuir como agentes protectores contra la aterosclerosis y las enfermedades cardiovasculares.

INTRODUCTION

Elevated blood lipids concentration (hyperlipidemia) is currently considered as one of the main risk factors for cardiovascular diseases (CVDs) which contribute to almost one third fatalities worldwide [1,2]. Hyperlipidemia is characterized by an increase of one or more of lipid profile components including cholesterol, triglycerides along with different types of lipoproteins such as, very low density lipoproteins (VLDL) and low density lipoprotein (LDL), while high density lipoproteins (HDL) level is reduced [3].

In addition, many reports have correlated hypercholesterolemia and hypertriglyceridemia to atherosclerosis which is known for its strong relation to ischemic heart disease (IHD) [4]. Atherosclerosis is a process by which the arteries get hardening because of cholesterol deposition in the wall of arteries leading to narrowing of the arteries. This process along with atherosclerosis-associated disorders such as coronary, cerebrovascular and peripheral vascular diseases are augented in patients with hyperlipidemia [4].

The treatment regimen for hypertriglyceridemia is mainly by using fibrates, which is one of the most widely used anti-hyperlipidemic

KEY WORDS: Hyperlipidemia, Triton WR-1339, Pyrrole derivatives, Rat.

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agents, results in a profound decrease in triglycerides levels in addition to a modest decrease in low density lipoprotein (LDL), cholesterol as well as increase in high density lipoproteins (HDL) [5]. Fibrates mainly work by activating lipoprotein lipase which increases the hydrolysis of circulating triglycerides. In parallel, it inhibits the synthesis of Apolipoproteins C-III, which inhibits lipoprotein lipase [6,7] .

To study the effect of potential compounds as anti-hyperlipidemic agents, hyperlipidemic rats induced by Triton WR-1339, are used as animal model [8,9]. The mechanism by which Triton WR-1339 (a nonionic surfactant) causes an elevation of plasma lipids is mainly by inhibiting the uptake of circulation lipoprotein by extrahepatic tissues, leading to accumulation of circulatory lipoproteins, taking into consideration that the effect of Triton can lasts for 48 h when designing the experiments [10-12].

To overcome the adverse effects and efficacy problems related to the existing medications used to treat hyperlipidemia, researchers became interested in developing novel pharmacologically active anti-hyperlipidemic drugs. Many reports on synthetic drugs with pyrrole moiety showed promising biological activities as antiviral [13], antitumor [14], antioxidative [15], anti-inflammatory [16,17] and antihyperlipidemic properties [18-22], Therefore, substituted pyrroles have been one of the major targets in synthetic chemistry. In this current research, we intended to synthesize novel pyrrole derivatives and to investigate their pharmacological property as lipid-lowering agents using induced hyperlipidemic rat model.

MATERIALS AND METHODS

Chemical studies

All starting materials were purchased from Siga-Aldrcih (St. Louis, MO, USA) and used without further purification. Experiments were performed in purified solvents. Melting points were determined using a Stuart Scientific electrothermal melting point apparatus and were uncorrected. Nuclear magnetic resonance (NMR) 1H NMR and 13C spectra were acquired by a Bruker DRX 400 MHz instrument operating at 400.13 (1H) and 100.61 MHz (13C) 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.

Synthesis of the targeted compounds

4-Bromo-1H-pyrrole-2-carboxylic acid (9,10-dioxo-9,10-dihydro-anthracen-1-yl)-amide (5)

Ethyl-4-bromopyrrole-2-carboxylate (**1**) (1.5 g, 6.88 mmol) was treated with 10% NaOH. The mixture was stirred at 100 °C for 2 h. Then, the solution was cooled and acidified with HCl (10%). The mixture was filtered to afford 4-bromopyrrole-2-carboxylic acid (**2**) as a white powder (1.20 g, 92 %).

Next, 4-bromopyrrole-2-carboxylic acid (**2**) (1.00 g, 5.26 mmol) was dissolved in dried dichloromethane. Oxalyl chloride (0.92 mL, 10.54 mmol) was added and the reaction mixture was refluxed for 2 days at 40-50 °C. Then dichloromethane was evaporated and the product was washed with toluene (2 × 10 mL) to give 4-bromopyrrole-2-carbonyl chloride (**3**) as a white solid (1 g, 91.7%).

Next, 4-bromopyrrole-2-carbonyl chloride (**3**) (1 g, 4.79 mmol) was dissolved in dried dichloromethane (10 mL). Then 4-(dimethylamino)pyridine (1.17 g, 9.58 mmol) was added and stirred at room temperature for 30 min. 1-aminoanthraquinone (**4**) (2.14 g, 9.58 mmol) was added to the mixture and refluxed for 2 days at 40-50 °C. Dichloromethane was removed by evaporation and the residue was purified by column chromatography using chloroform: cyclohexane (70:30) as eluent to afford the targeted compound (**5**) as a fine yellow solid (0.23 g, 12.10%); m.p decomposed over 270 °C; R_f = 0.5 in dichloromethane : n-hexane (90:10); ^{1}H-NMR (500 MHz, DMSO-d*6*): δ = 12.83 (br s, IH, CON*H*), 12.43 (br s, 1H, pyrrole-N*H*), 9.06 (s, 1H, Ar-*H*), 8.35 (s, 1H, Ar-*H*), 8.21 (s, 1H, Ar-*H*), 7.93-8.00 (m, 4H, Ar-*H*), 7.28 (s, 1H, pyrrole-*H*), 7.04 (s,1H, pyrrole-*H*) ppm; ^{13}C-NMR (500 MHz, DMSO-d*6*): δ = 187.53, 182.67 (CO-ketone), 158.66 (*C*ONH), 142.10, 136.41, 135.29, 127.79, 127.08, 126.99, 124.65, 122.19, 118.08, 112.94 ppm; IR (thin film): ν = 3448, 1735, 1675, 1643, 1589, 1473, 1411, 1280, 1033, 671 cm^{-1}.

4-(9,10-Dioxo-9,10-dihydro-anthracen-1-ylsulfamoyl)-3,5-dimethyl-1H-pyrrole-2-carboxylic acid ethyl ester (7)

Ethyl-4-(chlorosulfonyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (**6**) (0.50 g, 1.88 mmol) was dissolved in dried DMF (5 mL) and 4-dimethyl amino pyridine (0.46 g, 3.76 mmol) was added and stirred at room temperature for 30 min. Then, 1-aminoanthraquinone (4) (0.84 g, 3.76

mmol) was added to the mixture and stirred for 3 days at 80 °C. DMF was removed by evaporation under reduced pressure and the residue was purified by column chromatography using chloroform : cyclohexane → chloroform (70:30) → (100) as gradient eluent to afford the targeted compound (**7**) as an orange solid (0.175 g, 20.6%); m.p 253-255 °C; R_f = 0.58 in chloroform: methanol (99:1); ^{1}H -NMR (500 MHz, DMSO-d*6*): δ =12.20 (br s, IH, SO_2NH), 8.99 (br s, 1H, pyrrole-N*H*), 8.34 (d, *J* = 8.40 Hz, 1H, Ar-*H*), 8.29 (d, *J* = 6.30 Hz, 1H, Ar-*H*), 8.01 (d, *J* = 7.55 Hz, 1H, Ar-*H*), 7.91 (d, *J* = 8.40 Hz, 1H, Ar-*H*), 7.82 (m, 2H, Ar-*H*), 7.68 (t, *J* = 8.1 Hz, 2H, Ar-H), 4.29 (q, *J* = 7.05 Hz, 2H, OCH_2CH_3), 2.62 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 1.58 (t, 3H, OCH_2CH_3) ppm; ^{13}C-NMR (500 MHz, DMSO-d*6*): δ = 161.80 ($CO_2C_2H_5$), 141.55,138.30, 135.36, 134.53, 134.44, 133.78, 129.15, 127.51, 127.10, 122.71, 122.04, 60.77, 30.04, 29.36, 10.66 ppm; IR (thin film): ν = 3456, 3286, 3255, 3093, 2962, 1674, 1643, 1589, 1481, 1342, 1265, 1165, 1087, 1018, 894, 802, 709 cm^{-1}.

In vivo antihyperlipidemic testing

Drug and chemicals

Triton WR-1339 (Tyloxapol) was purchased from Siga-Aldrich, USA. All other chemicals were of analytical grade and obtained locally.

Animals and treatment

Forty five adult male Wistar rats, weighing around 200-250 g, bred in the animal care center of Faculty of Pharmacy, Al-Zaytoonah University, Amman, Jordan, were provided *ad libitum* access only to tap water throughout the experimental duration (24 h). Rats were maintained in a 12 h light-dark cycle under constant humidity and temperature (22 ± 2 °C). All experiments were performed in accordance with the guidelines of Animal Welfare Committee of the University.

Triton model of hyperlipidemia

Triton WR-1339 was dissolved in water and administered intraperitoneally to the rats at a dose of (300 mg/kg body weight) in order to induce hyperlipidemia [23,24].

Pharmacological experimental design

Overnight, the 45 fasted rats were randomly divided into five groups of nine animals each. The first group, serving as normal control group (NCG) received an intraperitoneal administration of normal saline; the second hyperlipidemic group (HCG) received an intraperitoneal injection of Triton (dissolved in distilled water). In the third and fourth groups, rats were intraperitoneally injected with Triton, followed by an intragastric administration of (1 mL) of C**5** and C**7** (15 mg/kg body weight) dissolved in 4% DMSO. The last group, bezafibrate (BF), was also intraperitoneally injected with Triton and intragastrically treated with bezafibrate (100 mg/kg body weight) dissolved in 4% DMSO [25,26]. After 18 h of treatments, animals were anaesthetized with diethyl ether and blood was collected from renal artery. 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 automatic analyzer (Model Erba XL-300, Germany, 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.

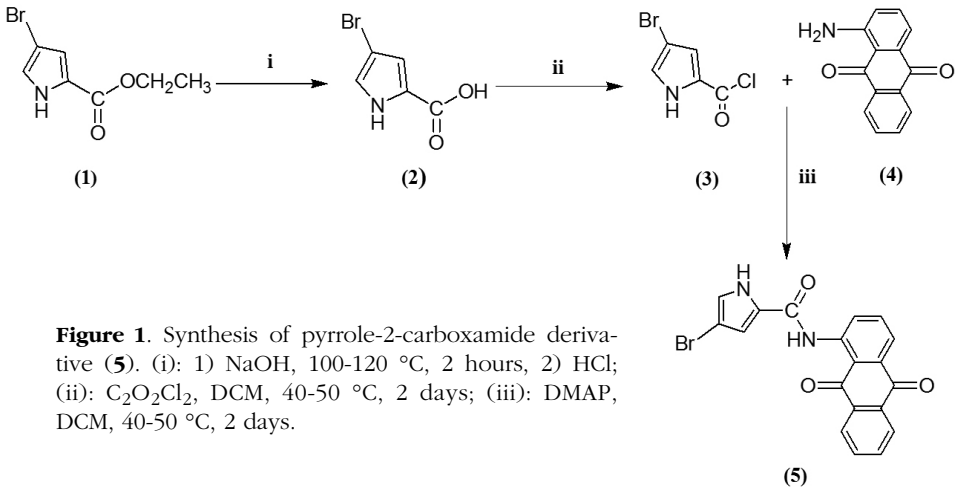

Figure 1. Synthesis of pyrrole-2-carboxamide derivative (**5**). (i): 1) NaOH, 100-120 °C, 2 hours, 2) HCl; (ii): $C_2O_2Cl_2$, DCM, 40-50 °C, 2 days; (iii): DMAP, DCM, 40-50 °C, 2 days.

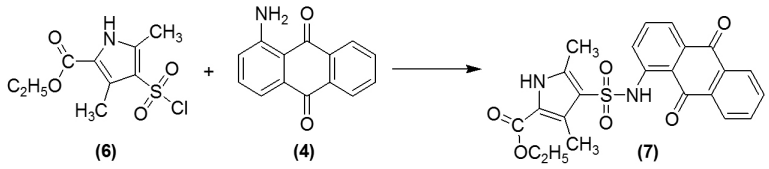

Figure 2. Synthesis of compound (**7**). DMAP, DMF, 80 °C, 3 days. The low yield of synthesizing compounds could be anticipated to the weak nucleophilicty of anthraquinone ring.

RESULTS

Chemistry

Synthesis of compound (**5**) (Fig. 1), was started using (**1**) to prepare the carboxylic derivative (**2**) by using NaOH, after that the activated acyl chloride derivative (**3**) reacted with (**4**) to afford (**5**) using DMAP as a catalyst and a base.

Surprisingly, the reaction of compound (**6**) with (**4**) gave (**7**) (Fig. 2), with a relative good yield comparing to (**5**). The electrophilicity of sulfonyl chloride enhanced the reaction with 1-aminoanthraquinine (**4**) using DMAP.

Hypolipidemic activity

Pyrrole-2-carboxamide derivative of 1-aminoanthraquinone compound **5** and pyrrole-4-sulfonamide derivative of 1-aminoanthraquinone (**7**) were successfully synthesized and tested *in vivo* for their hypolipidemic activity, at a dose of 15 mg/kg body weight. Compounds (**5**) and (**7**) have shown significant reduction in plasma triglyceride levels in Triton WR-1339 induced hyperlipidemic rats. It is therefore reasonable to assume that compounds (**5**) and (**5**) may have a promising potential in the treatment of hyperlipidemia and atherosclerosis.

Induction of hyperlipidemia by Triton WR-1339

Triton WR-1339 has been widely used to block clearance of triglyceride-rich lipoproteins by inhibiting the enzyme lipoprotein lipase to induce acute hyperlipidemia in several animals including rats. It has been used for screening natural or chemical hypolipidemic drugs [27]. It has been reported that hyperlipidemia could be induced by parenteral administration of Triton WR-1339 to adult rats. The peak plasma triglyceride level was reached at 18 h [28,29].

The plasma total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C) levels of all groups treated for 18 h are shown in (Table 1). The acute injection of Triton WR-1339 caused 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 after Triton injection in comparison with the normal control group (NCG).

In fact, the triglyceride levels in the HCG were markedly increased by 2378%, which is more than 24 times after 18 h as compared to the NCG. The increase of plasma total cholesterol concentration in the HCG was 887% after 18 h as compared to the NCG. At the same time LDL-C level in HCG was also elevated by 522% after 18 h as compared to the NCG, while a significant decrease in HDL-C level by 36% occurred at 18 h after Triton WR-1339 injection.

Effect of compounds 5, 7 and bezafibrate on rat plasma lipid profile

The plasma TG, TC, LDL-C and HDL-C levels of compounds **C5**, **C7** and bezafibrate (**BF**) - treated rats 18 h are shown in Figs. 3-6. Importantly, the elevated plasma TG levels produced by the acute injection of Triton WR-1339 administration were significantly ($p < 0.0001$) suppressed in **C5** by 90%, in **C7** by 83% and in **BF**-treated rats by 78.5% after 18 h, with respect to Triton treated hyperlipidemic control group (HCG, Fig. 3).

After 18 h of treatment, TC levels were sig-

Group	Lipid profile			
	TG (mg/dL)	TC (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)
NCG	79.3 ± 1.26	86.1 ± 2.03	24.2 ± 1.20	54.8 ± 1.57
HCG	1965.0 ± 20.14 [a]	850.0 ± 10.78 [a]	150.6 ± 6.72 [a]	35.1 ± 1.74 [a]

Table 1. Effect of Triton WR-1339 on plasma lipid levels after 18 h. Values are means ± SD from nine animals in each group. NCG, normal control group; HCG, hyperlipidemic control group; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol. [a] $p < 0.0001$.

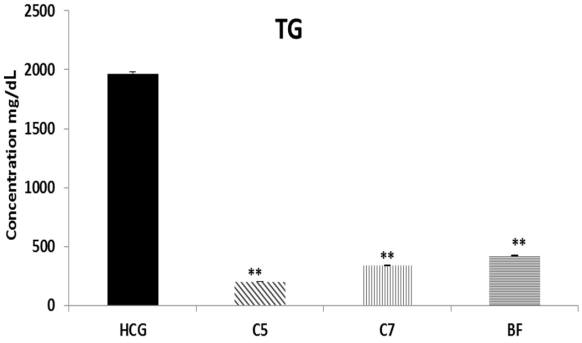

Figure 3. Effect of novel compounds on triglycerides (mg/dl) after 18 h. Values are means ± SD from nine animals in each group. HCG: hyperlipidemic control group; **C5**: C5+ 4% DMSO; **C7**: C7 + 4% DMSO; BF: bezafibrate + 4% DMSO; TG, triglyceride; C5, C7 and BF are compared with HCG. * $p < 0.01$; ** $p < 0.0001$.

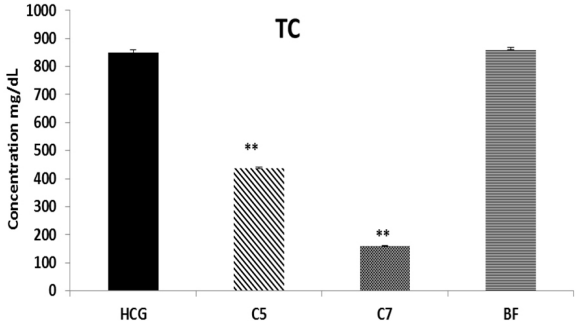

Figure 4. Effect of novel compounds on total cholesterol (mg/dl) after 18 h. Values are means ± SD from nine animals in each group. HCG: hyperlipidemic control group; **C5**: C5+ 4% DMSO; **C7**: C7 + 4% DMSO; BF: bezafibrate + 4% DMSO; TC, total cholesterol; C5, C7 and BF are compared with HCG. * $p < 0.01$; ** $p < 0.0001$.

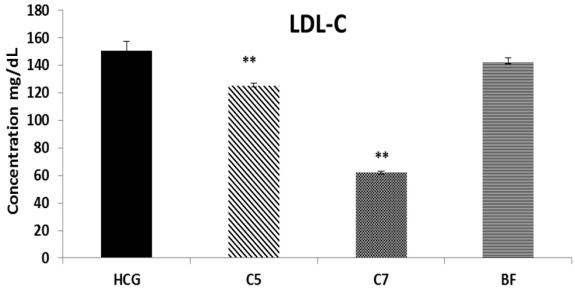

Figure 5. Effect of novel compounds on low-density lipoprotein (mg/dl) after 18 h. Values are means ± SD from nine animals in each group. HCG: hyperlipidemic control group; **C5**: C5+ 4% DMSO; **C7**: C7 + 4% DMSO; BF: bezafibrate + 4% DMSO; LDL-C, low-density lipoprotein-cholesterol; C5, C7 and BF are compared with HCG. * $p < 0.01$; ** $p < 0.0001$.

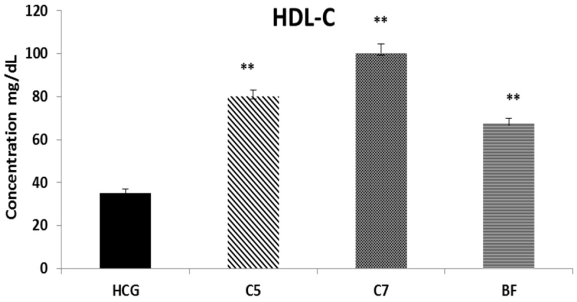

Figure 6. Effect of novel compounds on high-density lipoprotein (mg/dl) after 18 h. Values are means ± SD from nine animals in each group. HCG: hyperlipidemic control group; **C5**: C5+ 4% DMSO; **C7**: C7 + 4% DMSO; BF: bezafibrate + 4% DMSO; HDL-C, high density lipoprotein-cholesterol; C5, C7 and BF are compared with HCG. * $p < 0.01$; ** $p < 0.0001$.

nificantly lowered ($p < 0.0001$) by 48.5% in **C5** and 81% in **C7** compared to HCG. No significant changes were observed in TC levels after 18 h compared to HCG in **BF** treated group (Fig. 4).

Compounds **C5** and **C7** showed similar trend on meditating plasma LDL-C level after 18 h of Triton administration compared to HCG. Actually, compounds **C5** and **C7** significantly ($p < 0.0001$) reduced LDL-C level by 17% and 59% respectively compared to HCG (Fig. 5).

The HDL-C levels were significantly increased after 18h by 128%, 185% and 92% ($p < 0.0001$) in **C5**, **C7** and **BF**-treated rats respectively compared to HCG (Fig. 6).

DISCUSSION

The outcomes of this study revealed that 4-bromo-1*H*-pyrrole-2-carboxylic acid (9,10-dioxo-9,10-dihydro-anthracen-1-yl)-amide derivatives (**C5**) and 4-(9,10-Dioxo-9,10-dihydro-anthracen-1-ylsulfamoyl)-3,5-dimethyl-1H-pyrrole-2-carboxylic acid ethyl ester derivative (**C7**) have promising hypolipidemic effect. Actually, significant reduction of serum TG and increased serum HDL-C after 18 h of Triton administration were observed after administration of **C5** and **C7**.

The observed increase in plasma triglyceride in triton treated rats is mainly due to an increase of the secretion of very low density lipoproteins (VLDL) by the liver paralleled to reduction of VLDL and LDL catabolism. Furthermore, the observed large decrease in plasma HDL levels in Triton treated animal results mostly from progressive displacement of apolipoprotein A-1 from the HDL surface without loss of lipid [30].

Consequently, while taking into consideration that most of the lipids in VLDL are triglyceride while cholesterol represent a minor proportion of VLDL, it is not unexpected that the hypolipidemic activity of **C5** was significantly higher for triglycerides than for cholesterol. This observation suggests that our compound is able to recover, at least partially, the catabolism of B-lipoproteins and this hypothesis was suggested by many works with other lipid-lowering agents [31].

In comparison to bezafibrate at a dose of 100 mg/kg body weight, **C5** and **C7** at a dose of 15 mg/kg body weight 18 h after Triton injection showed the same potential in reducing TG levels and in increasing HDL-C levels.

The pharmacological effect of **C5** 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 [9, 23,32-34].

On the other hand, **C7**, with the presence of the pyrrole (H-bond donar) linked by a sulfonamide linkage to the anthraquinone moiety (lipophilic component), was found to be more effective than compound **C5**. This higher potency could be due the presence of sulfonamide link in **C7** but not in **C5** which might increase the binding at the target site. Also, additional H-bonds are provided by sulfonamide and ester moiety which also may in turn increase the binding affinity.

CONCLUSION

In the course of this research, novel pyrrole-2-carboxiamide derivatives were successfully prepared and then characterized and validated using NMR and IR. The hypolipidemic activities of these compounds were tested using Triton WR-1339 induced hyperlipidemic rats.

4-Bromo-1*H*-pyrrole-2-carboxylic acid (9,10-dioxo-9,10-dihydro-anthracen-1-yl)-amide derivative (**C5**) and 4-(9,10-Dioxo-9,10-dihydro-anthracen-1-ylsulfamoyl)-3,5-dimethyl-1H-pyrrole-2-carboxylic acid ethyl ester compound (**C7**) were shown to improve lipid abnormalities such as hypertriglyceridemia and hypercholesterolemia, and then elevated HDL levels in Triton induced hyperlipidemic rats. Interestingly, compounds **5** and **7** were found to be 6 times more potent in reducing plasma triglycerides levels than bezafibrate, suggesting them as possible useful candidates in the treatment of patients with lipid abnormalities.

In sum, the findings of this research are highly promising but more studies are required to elucidate the exact mechanism of action and the safety profile of these novel compounds as anti-hyperlipidemic agents.

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