Pharmacological Evaluation of Novel Indole-2-carboxamides As Potent Lipid-Lowering Agents in Triton-WR-1339-Induced Hyperlipidemic Rats

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The lipid-lowering effects of two novel antihyperlipidemic agents, BMI2C [*N*-(4-benzoylphenyl)-5-methoxy-1*H*-indole-2-carboxamide] and DDMI2C [*N*-(9,10-dihydro-9,10-dioxoanthracen-2-yl)-5-methoxy-1*H*-indole-2-carboxamide], were studied using hyperlipidemic rats as an experimental model; hyperlipidemia was developed by intraperitoneal injection of Triton WR-1339 (200 mg/kg body weight). At a dose of 15 mg/kg body weight, BMI2C and DDMI2C significantly reduced elevated plasma triglyceride levels after 7 and 24 h. Furthermore, BMI2C and DDMI2C significantly reduced elevated plasma total cholesterol levels after 24 h. Interestingly, high-density lipoprotein-cholesterol levels were significantly increased in all treated groups. These findings indicate that the two studied novel compounds have a promising potential in the treatment of hyperlipidemia and atherosclerosis.

Key words: BMI2C [*N*-(4-Benzoylphenyl)-5-methoxy-1*H*-indole-2-carboxamide], DDMI2C [*N*-(9,10-Dihydro-9,10-dioxoanthracen-2-yl)-5-methoxy-1*H*-indole-2-carboxamide], Antihyperlipidemic Activity

Introduction

Hyperlipidemia is one of the important risk factors involved in the development of cardiovascular disease (Frishman, 1998). Treatment of hyperlipidemia consists of diet control, exercise, and the use of lipid-lowering drugs (Stone, 1996). However, some patients cannot tolerate the adverse effects from these oral drugs (Bhatnagar, 1998). As a consequence, there continues to be a high demand for new oral antihyperlipidemic drugs.

Triglycerides (TG) are energy-rich compounds, primarily stored in the 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 carry TG from the liver. Overproduction of VLDL is associated with a number of disease states that result in an increased risk of cardiovascular heart disease; this has renewed the interest in factors that affect hepatic TG production (Ginsberg, 2001).

In the early 1950 s, it was noted that intravenous injection of certain nonionic detergents resulted in milky serum that lasted up to 48 h (Kellner *et al.*, 1951). This was later shown to be due to the inhibition of TG hydrolysis by lipoprotein lipase (LPL) (Schotz *et al.*, 1957). Since then, lipolysis inhibition has been used to determine hepatic TG production rates, with Triton WR-1339 (also known as tyloxapol) being widely used. Using this technique, the TG production rate is calculated from the increase in TG over time following detergent injection.

Fibrate derivatives are among the most widely used antihyperlipidemic drugs in the world and have been shown to be effective in preventing coronary heart diseases in hyperlipidemic patients (Frick *et al.*, 1987), and in patients with a low level of high-density lipoprotein-cholesterol (HDL-C) and normal or low levels of low-density lipoprotein-cholesterol (LDL-C) (Rubins *et al.*,

1999). The major pharmacological mechanism of fibrates, including bezafibrate, in hyperlipidemia is supposed to be a decreased production of VLDL as a result of the decreased synthesis of TG and an increased hydrolysis of TG by the induction of lipoprotein lipase and reduction of apolipoprotein C-III synthesis (Schoonjans *et al.*, 1996).

In spite of extensive research and development of numerous drugs, the antiyperlipidemic therapy is still deprived of efficacy, safety and thorough knowledge of the exact mechanisms of the real cause of hyperlipidemia.

Indole derivatives are known to exhibit antihyperlipidemic activity. Furthermore benzophenone and anthraquinone derivatives are also investigated as antihyperlipidemic agents (Bosies *et al.*, 1980; Sher and Ellsworth, 2004; Kopin *et al.*, 2006; Dasseux and Oniciu, 2002). The present research was conducted to prepare BMI2C [*N*-(4-benzoylphenyl)-5-methoxy-1*H*-indole-2-carboxamide] and DDMI2C [*N*-(9,10-dihydro-9,10-dioxoanthracen-2-yl)-5-methoxy-1*H*-indole-2-carboxamide] containing indole-2-carboxamide and benzophenone/anthraquinone, as shown in Fig. 1, and to clarify whether BMI2C and DDMI2C improve lipid abnormalities. In addition we investigated the possibility that BMI2C and DDMI2C may increase the blood HDL level.

Material and Methods

Chemical studies

A novel series of 5-methoxy-1*H*-indole-2-carboxamide derivatives (BMI2C, DDMI2C; Fig. 1) were prepared in the course of this work. Ethyl-5-methoxy-1*H*-indole-2-carboxylate was treated with the appropriate amine in DMF in the presence of sodium methoxide as a base. The coloured solid targets were produced in satisfactory yields (up to 65%) and were fairly pure except for BMI2C which was further purified using a silica gel plate (Rf = 0.68, major).

All targets were characterized and there structures were confirmed by MS, IR, NMR and elemental analyses.

Preparation of N-(4-benzoylphenyl)-5-methoxy-1H-indole-2-carboxamide (BMI2C)

Ethyl-5-methoxy-1*H*-indole-2-carboxylate (4.5 mol) was treated with 4-aminobenzophenone (3.0 mol, equivalent) in the presence of sodium meth-
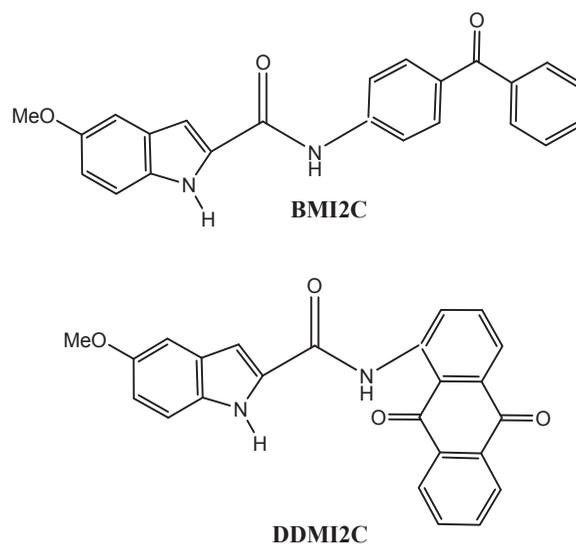

Fig. 1. Chemical structures of BMI2C [*N*-(4-benzoylphenyl)-5-methoxy-1*H*-indole-2-carboxamide] and DDMI2C [*N*-(9,10-dihydro-9,10-dioxoanthracen-2-yl)-5-methoxy-1*H*-indole-2-carboxamide].

oxide (1.0 mol, equivalent) and *N,N*-dimethylformamide (10 ml). The mixture was refluxed for 4 h, then it was cooled (ice bath), and the resultant solid was filtered off, washed with H_2O and dried to give BMI2C as yellow solid (0.98 g, 64%). – M.p. 233 °C. – ^{1}H NMR (DMSO-d_6): δ = 3.78 (3H, s, OCH$_3$), 6.90 (1H, d, J = 2.4, 8.7 Hz, 6-H), 7.16 (1H, d, J = 2.4 Hz, 4-H), 7.36–7.42 (2H, m, 3-H/7-H), 7.55–7.60 (2H, m, Ar-H), 7.66–7.82 (6H, m, Ar-H), 8.02 (1H, s, Ar-H, 1'-H), 8.05 (major) and 8.55 (1H, br s, CONH, rotamers), 10.63 (major) and 11.82 (1H, br s, N$_1$-H, rotamers). – IR (KBr): ν = 1689, 1715, 1660 (C=O), 3410 (NH), 1211, 1024 cm^{-1} (C–O). – MS: *m/z* = 370.40070 [M$^+$]. – MS (CI/ESI negative mode): *m/z* (%) = 371 (6), 370 (21), 369 (100), 307 (3), 306 (12), 293 (8), 265 (30), 221 (9), 190 (23). – C$_{23}$H$_{18}$N$_2$O$_3$: calcd. C 74.58, H 4.90, N 7.56; found C 74.44, H 4.78, N 7.72.

Preparation of N-(9,10-dihydro-9,10-dioxoanthracen-2-yl)-5-methoxy-1H-indole-2-carboxamide (DDMI2C)

Ethyl-5-methoxy-1*H*-indole-2-carboxylate (4.5 mol) was treated with 1-aminoanthraquinone (3.0 mol, equivalent) in the presence of sodium methoxide (1.0 mol, equivalent) and *N,N*-dimethylformamide (10 ml). The mixture was refluxed for 4 h,

then it was cooled (ice bath), and the resultant solid was filtered off, washed with H_2O and dried to give DDMI2C as red solid (1.1 g, 62%). – M.p. > 350 °C (decomposition). – ^1H NMR (DMSO-d_6): δ = 3.72 (3H, s, OCH$_3$), 6.47 (1H, br s, 3-H), 6.66 (1H, d, J = 2.0, 8.8 Hz, 6-H), 6.96 (1H, br s, J = 2 Hz, 4-H), 7.23 (2H, d, J = 8.6 Hz, 7-H/Ar-H, 4'-H), 7.36–7.56 (2H, 2 m, Ar-H, 2'-H/3'-H), 7.82–7.93 (2H, m, Ar-H, 6'-H/7'-H), 8.13–8.23 (2H, 2 m, Ar-H, 5'-H/8'-H), 8.53 (major) and 8.78 (1H, br s, CO-NH, rotamers), 10.73 (major) and 12.50 (1H, br s, N$_1$-H, rotamers). – IR (KBr): v = 1690, 1715 (C=O), 3475, (NH), 1222 cm^{-1} (C–O). – MS: m/z = 396.11101 [M$^+$]. – MS (CI/ESI negative mode): m/z (%) = 403 (4), 400 (1), 396 (1), 393 (1), 3382 (2), 381 (4), 265 (5), 191 (10), 190 (100), 146 (10). – C$_{24}$H$_{16}$N$_2$O$_4$: calcd. C 72.72, H 4.07, N 7.07; found C 72.92, H 4.19, N 7.01.

Pharmacological studies

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

Animals and treatments

54 adult male Wistar rats, weighing around 180 g, bred in the animal care centre 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 at (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 DMSO and administered intraperitoneally to the rats (200 mg/kg body weight) in order to induce hyperlipidemia.

Experimental design

Overnight fasted rats were randomly divided into five groups of six animals each. The first group, serving as normal control group (NCG) received an intraperitoneal administration of normal saline; the second hyperlipidemic plus DMSO control group (TDCG) received an intra-peritoneal injection of Triton WR-1339 and was gavaged with 4% DMSO (in distilled water). In the third group (BMI2C) animals were intraperitoneally injected with Triton W-1339, followed by an intragastric administration of BMI2C (15 mg/kg body weight) dissolved in 4% DMSO. The rats of the fourth group (DDMI2C) were also intraperitoneally injected with Triton WR-1339, followed by an intragastric administration of DDMI2C (15 mg/kg body weight) dissolved in 4% DMSO. The last group (TDFG) was also intraperitoneally injected with Triton WR-1339 and intragastrically treated with bezafibrate (100 mg/kg body weight) dissolved in 4% DMSO.

After 7 h and 24 h of treatments, 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 automatic analyzer (Model Erba XL-300, Mannheim, Germany).

Statistical analysis

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

Results

Induction of hyperlipidemia by Triton WR-1339

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 7 h and 24 h are shown in Figs. 2A and B, respectively. Triton WR-1339 caused a significant increase in plasma total cholesterol ($p < 0.05$) and triglyceride ($p < 0.0001$) levels in the hyperlipidemic + DMSO control group (TDCG), at both 7 h and 24 h after Triton administration in comparison with the normal control group (NCG). In fact, the increases of plasma total cholesterol concentration in the TDCG were 13% and 69% after 7 h and 24 h, respectively, as compared to the NCG. Triglyceride levels in the TDCG were also elevated by 444% and 312% after 7 h and 24 h, respectively.

Neither at 7 h nor at 24 h the LDL-C level was significantly changed in the TDCG with respect to the NCG. While a significant ($p < 0.05$) de-
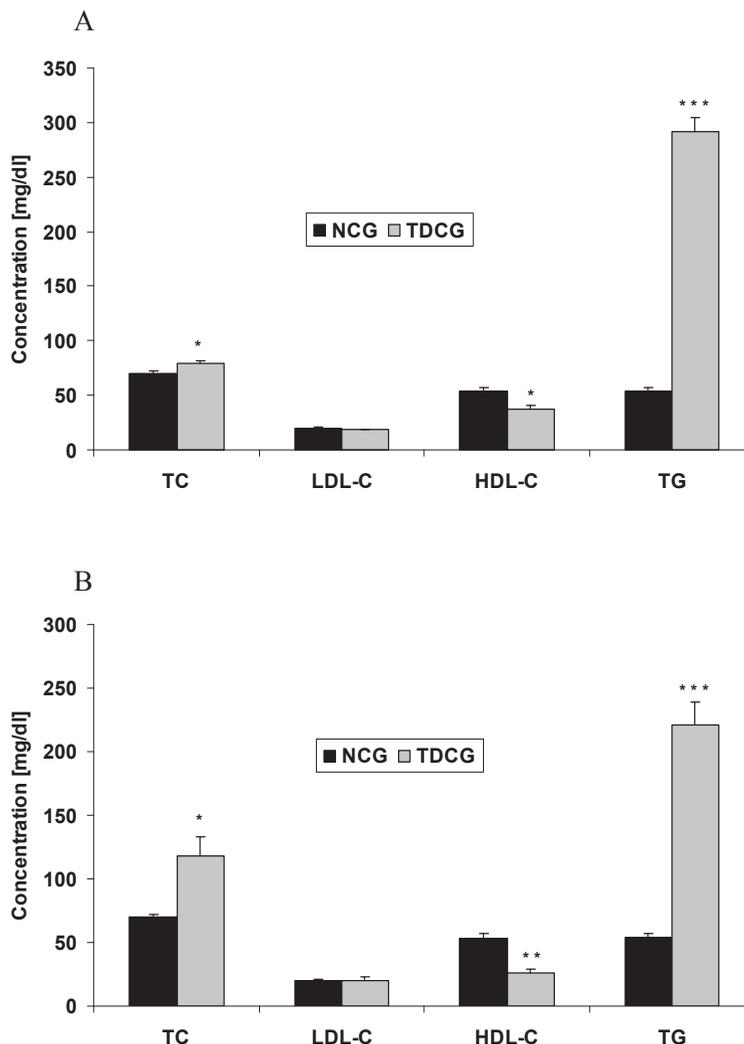
Fig. 2. Effect of Triton WR-1339 on the lipid profile after (A) 7 h and (B) 24 h. Values are means ± SEM from six animals in each group. NCG, normal control group; TDCG, hyperlipidemic control group; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TG, triglyceride. TDCG is compared to NCG. * $p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$.

crease in the HDL-C levels occurred at 7 h and was maintained until 24 h after Triton injection.

Effect of BMI2C, DDMI2C, and bezafibrate on the rat plasma lipid profile

The plasma total cholesterol, triglyceride, high-density lipoprotein-cholesterol and low-density lipoprotein-cholesterol levels of TDFG-, BMI2C- and DDMI2C-treated rats after 7 h and 24 h are shown in Table I. Importantly, the elevated

plasma TG levels produced by Triton WR-1339 administration after 7 h were significantly ($p <$ 0.0001) suppressed by 68% in TDFG-, by 80% in BMI2C-, and by 78% in DDMI2C-treated rats with respect to the hyperlipidemic control (TDCG). However, the reductions of the TG levels after 24 h were not considered highly significant ($p < 0.05$), with 47% in TDFG-, 27% in BMI2C-, and 26% in DDMI2C-treated rats compared to TDCG-treated rats.

Table I. Effect of the novel agents BMI2C and DDMI2C on plasma lipid levels in Triton-WR-1339-induced hyperlipidemic rats after 7 h and 24 h.

Lipid profile	TC [mg/dl]	TG [mg/dl]	HDL-C [mg/dl]	LDL-C [mg/dl]
7 h				
TDCG	79.2 ± 3.01	292 ± 12.81	37.3 ± 3.47	18.2 ± 0.95
BMI2C	76.7 ± 2.49	57.8 ± 5.70 [d]	70.7 ± 1.87 [c]	15.2 ± 1.11
DDMI2C	81.8 ± 5.14	64.3 ± 4.44 [d]	59.3 ± 3.48 [d]	14.3 ± 1.94
TDFG	73.3 ± 1.70	94.7 ± 6.29 [d]	59.8 ± 1.70 [c]	18.8 ± 2.67
24 h				
TDCG	118 ± 15.06	221 ± 18.08	25.7 ± 3.19	19.8 ± 3.31
BMI2C	67.5 ± 4.20 [b]	161 ± 19.47 [c]	41.3 ± 1.09 [a]	16.8 ± 1.53
DDMI2C	67.5 ± 3.73 [b]	164 ± 13.10 [a]	35.5 ± 2.82 [c]	14.8 ± 1.85
TDFG	63.7 ± 6.57 [b]	117 ± 4.10 [a]	40.8 ± 3.65 [a]	15.3 ± 1.82

Values are means ± SEM from six animals in each group. TDCG, hyperlipidemic + 4% DMSO control group; BMI2C, BMI2C + 4% DMSO; DDMI2C, DDMI2C + 4% DMSO; TDFG, bezafibrate + 4% DMSO; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.
BMI2C, DDMI2C, and TDFG are compared with TDCG.
[a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$; [d] $p < 0.0001$.

The HDL-C levels significantly increased after 7 h of Triton administration, by 59% and 60% ($p < 0.001$) in TDFG- and DDMI2C-treated rats, respectively, and 90% ($p < 0.0001$) in BMI2C-compared to TDCG-treated rats. However, the increase in the HDL-C levels after 24 h were not considered highly significant, with 59% and 38% ($p < 0.05$) in TDFG- and DDMI2C-treated rats, respectively, and 61% ($p < 0.001$) in BMI2C-treated rats compared to TDCG-treated rats.

After 7 h of treatment, no significant differences in plasma total cholesterol levels between any treated group (TDFG, BMI2C and DDMI2C) were observed (Table I). In contrast, 24 h after treatment, in all treated groups the plasma total cholesterol levels significantly ($p < 0.01$) reduced, by 46%, 43% and 43% in TDFG-, BMI2C-, and DDMI2C-treated rats, respectively.

Neither after 7 h nor after 24 h did all treated groups significantly decrease the LDL-C level compared to the TDCG-treated group.

Discussion

Triton WR-1339 has been widely used to induce acute hyperlipidemia in several animal models by blocking the clearance of triglyceride-rich lipoproteins (Frishman, 1998). This model has been widely used in rats to investigate natural or chemical hyperlipidemic drugs for a number of different reasons; it is convenient in terms of the length of the treatment period and handling (Fiser *et al.*,

1974; Kalopissis *et al.*, 1980). Schurr *et al.* (1972) demonstrated that parenteral administration of a dose of Triton WR-1339 to adult rats induced hyperlipidemia. The maximum plasma triglyceride and total cholesterol levels were reached at 20 h, followed by a decrease to normal values. Similar results were described by Lauk *et al.* (1989) and by Khanna *et al.* (1992). In our hand, the same model gave a similar pattern of lipid profile changes either at 7 or 24 h after Triton administration. Fig. 2 demonstrates the feasibility of using it as a model of acute hyperlipidemia to assess the hypolipidemic activity of BMI2C, DDMI2C and bezafibrate on the rat plasma lipid profile.

The results of the present work clearly show that BMI2C and DDMI2C reduce the level of plasma triglycerides 7 h and 24 h after being applied (Table I). The large increase in plasma cholesterol and triglyceride levels due to Triton WR-1339 injection results mostly from an increase of VLDL secretion by the liver accompanied by a strong reduction of VLDL and LDL catabolism (Otway and Robinson, 1967). Triton has also been shown to cause dissociation of apolipoprotein A-I (apoA-I) and apoC-II from HDL (Ishikawa and Fidge, 1979). Thus, since the portion of triglyceride in VLDL is several times greater than of cholesterol, it is not surprising that the hyperlipidemic action of BMI2C and DDMI2C was markedly higher for triglycerides than for cholesterol. This result suggests that the compounds are able to restore, at least partially, the catabolism of li-

poproteins. The underlying mechanism of this activity is not elucidated by our present study, however, as hypothesized by others (Campillo *et al.*, 1994; P´erez *et al.*, 1999), the restoration of the catabolic metabolism of VLDL could be due to an increased stimulation of the lipolytic activity of plasma lipoprotein lipase.

The reduction of the total plasma cholesterol level by BMI2C and DDMI2C after 24 h was associated by a decrease of its LDL fraction (Table I), which is the target of several antihyperlipidemic drugs. This result suggests that the cholesterol-lowering activity of BMI2C and DDMI2C can be a result of the rapid catabolism of LDL-C through its hepatic receptors for the final elimination in the form of bile acids (Khanna *et al.*, 2002). Therefore, further studies are necessary to elucidate the exact mechanisms of these compounds by an experimental study.

At 7 and 24 h after Triton injection, the entity of plasma triglycerides decrease induced by bezafibrate, which in this study has been used as standard reference hyperlipidemic drug, was similar to the reduction induced by BMI2C and DDMI2C (Table I). It is also of interest to note that bezafibrate reduced the LDL-C level after 24 h (Table I), but not after 7 h. Furthermore, other plasma lipid levels were not significantly changed indicating that bezafibrate has an acute lowering activity only on plasma triglycerides and LDL-C. This is concomitant with the mechanism of action of fibrates (Fujiwara *et al.*, 1997; Yamada, 1997; Norioka *et al.*, 2000; Nagai *et al.*, 2000; Hikita *et al.*, 2000) whose LDL-C-lowering activity is not strongly marked, but their triglycerides-decreasing effect is very spectacular especially by stimulation of gene expression of lipoprotein lipase leading to enhanced catabolism of VLDL, synthesis of fatty acids and reduced VLDL secretion.

Both compounds showed a protective action by an increase of the HDL-C levels, which is well known for its preventive action against atherogenesis since there is an independent inverse relationship between HDL-C levels and cardiovascular risk incidence (Malloy and Kan, 1994). HDL-C is very important in mobilizing cholesterol from the plasma to the liver where it is eliminated in the form of bile acids. This effect may be due to the stimulation of lecithin cholesteryl acyl transferase which may lead to a rapid catabolism of blood lipids through extrahepatic tissues (Anila and Vijayalakshmi, 2002).

In conclusion, the indole-2-carboxamide derivatives BMI2C and DDMI2C improve lipid abnormalities such as hypertriglyceridemia and hypercholesterolemia, and then elevate the HDL levels in Triton-induced hyperlipidemic rats, suggesting that BMI2C and DDMI2C may be useful in the treatment of patients with lipid abnormalities. The results found are encouraging for further assessments to elucidate the exact mechanism of action of these novel compounds as lipid-lowering agents.

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