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Original article

Design, synthesis and hypolipidemic activity of novel 2-(naphthalen-2-yloxy)propionic acid derivatives as desmethyl fibrate analogs

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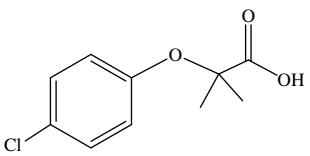
ABSTRACT

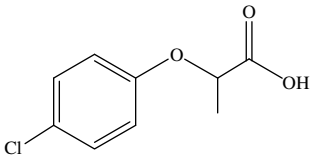
A series of 2-(naphthalen-2-yloxy)propionic acid derivatives were prepared. The hypolipidemic activity of the new compounds as well as the intermediate acid **2** was evaluated in the high cholesterol diet (HCD) fed hyperlipidemic rat model. Interestingly, the *S*-alkylated mercaptotriazole **8b** and the 1,3,4-oxadiazole **9** produced striking reduction of serum levels of total cholesterol (TC), triglycerides (TGs) and low-density lipoproteins (LDLs) and elevation of serum high-density lipoproteins (HDLs) being more active than the reference gemfibrozil. In addition, the 1,2,4-triazole **7a**, the hydroxypyrazoline **10** and the pyrazolone derivative **11** exhibited good hypolipidemic activity on different lipid parameters.

1. Introduction

Hyperlipidemia is the major risk factor for atherosclerosis and atherosclerosis-associated conditions such as coronary heart diseases (CHD), ischaemic cerebrovascular diseases, and peripheral vascular diseases. A 1% drop in serum cholesterol level was reported to reduce the risk for CHD by 2% [1]. The search for effective and safe hypolipidemic agents has engaged the interests of medicinal chemists, biochemists, pharmacologists and clinicians. Fibric acid derivatives (fibrates) represent an important class of lipid modifying agents. The discovery of the biological target of fibrates, peroxisome proliferator-activated receptors (PPARs) specifically the alpha isotype, enabled to explain the diverse lipid and non-lipid effects of fibrates which contribute in their hypolipidemic and antiatherosclerotic benefits [2–4]. Literature references to SAR for this class of drugs are sparse [5]. In order to define the structural requirements for the maximal hypolipidemic properties related to fibrates, several modifications of the fibrate moiety were reported and their biological activities were investigated. From the literature, it is evident that the high lipophilicity is required for the optimal antidyslipidemic effects of fibrates. Although most active fibrates contain a phenoxyisobutyrate moiety [5], it was proven that the desmethyl fibrate analogs (2-phenoxypropionic acid derivatives) e.g. desmethylclofibric acid retained the hypolipidemic activity with fewer side effects [6]. The presence of the acidic functionality is critical for the hypolipidemic action of fibrates [5]. Unfortunately, the free carboxylic group is responsible for the potential unwanted gastrointestinal discomfort which is a frequent side effect associated with fibrate therapy [7,8]. Modification of the carboxylic group to less acidic functions as amides, hydrazides and cyclic derivatives may help to minimize the gastrointestinal upset [9]. Moreover, several compounds containing the 1,2,4-triazole and pyrazole moieties were found to be of value in the management of hyperlipidemia [10,11]. Motivated by these findings, the present work aims at the design, synthesis and hypolipidemic study of novel 2-(naphthalen-2-yloxy)propionic acid derivatives as desmethyl fibrate analogs. The new analogs are designed to be prepared by replacement of the *p*-chlorophenyl moiety in clofibric acid by the lipophilic 2-naphthyl moiety and the carboxyl function by selected carboxylic acid derivatives like amide, hydrazide and some cyclic derivatives (pyrazole, 1,2,4-triazole and their isosteric 1,3,4-oxadiazole) with the aim of exploring the impact of such modifications on the hypolipidemic profile.



Clofibric acid



Desmethylclofibric acid

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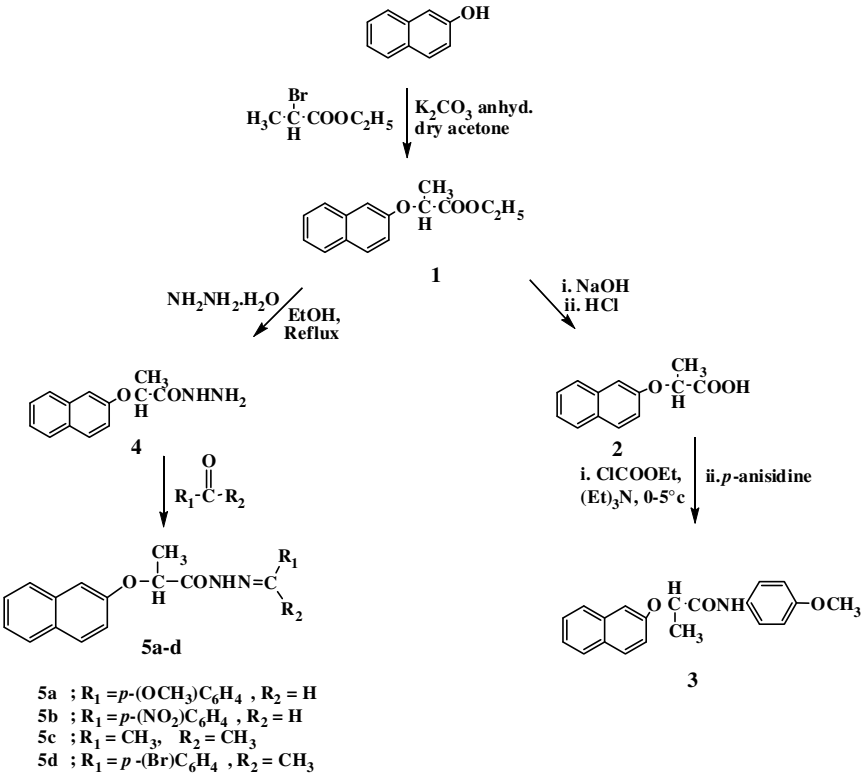
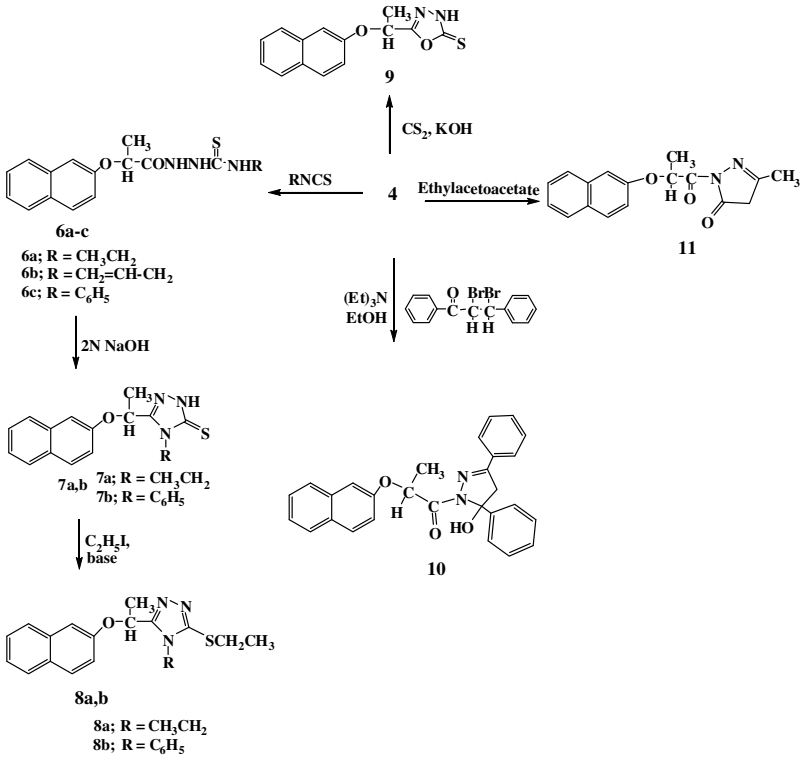
2. Results and discussion

2.1. Chemistry

The syntheses of the designed compounds are outlined in Schemes 1 and 2. The key intermediate, 2-(naphthalen-2-yloxy) propionic acid ethyl ester **1** was prepared in excellent yield by treating β-naphthol with ethyl 2-bromopropionate in boiling dry acetone in the presence of anhydrous potassium carbonate [12–14]. The hydrazide **4** was prepared by treating the ester **1** with hydrazine hydrate in refluxing ethanol for 4 h. Base-catalyzed hydrolysis of the ester **1** using sodium hydroxide afforded the acid **2** that was converted to the corresponding amide **3** by the mixed anhydride method using ethyl chloroformate in the presence of triethylamine as a base at 0–5 °C [15]. The synthesis of the target *N*-alkylidene/arylidene hydrazides **5a**–**d** was accomplished *via* the condensation of equimolar amounts of the hydrazide **4** and the appropriate carbonyl compounds in refluxing ethanol. It is noteworthy that the two methyl groups of the hydrazone **5c** appeared as two separate singlets at δ 2.04 and 2.06 ppm resembling those observed in the ^{1}H NMR spectrum of dimethylformamide [16]. In such cases of restricted rotation due to C═N of the hydrazone moiety, the two methyl groups are magnetically non-equivalent and appear as two separate singlets [17]. Heating equimolar amounts of the hydrazide **4** and alkyl/aryl isothiocyanate in ethanol at reflux afforded the 1,4-disubstituted thiosemicarbazides **6a**–**c**. Intramolecular cyclization of the 1,4-disubstituted thiosemicarbazides **6a**,**c** in the presence of aqueous 2 N NaOH afforded the 1,2,4-triazoline-5-thiones **7a**,**b**. The IR spectra of compounds **6a**,**b** lacked the amidic C═O (1687–1667 cm^{-1}) characteristic for the thiosemicarbazides **6a**,**c**. The ^{1}H NMR spectra of compounds **7a**,**b** lacked the three amidic NH protons characteristic for the thiosemicarbazides **6a**,**c**, but showed a downfield broad singlet resonating at 13.30–13.80 ppm for the triazoline CS–NH. This strong deshielding of CS–NH is probably explained by the strong intermolecular hydrogen bonding as reported [18,19]. These findings in the IR and ^{1}H NMR data clearly provide the evidence for intramolecular cyclization of the thiosemicarbazides into the corresponding 1,2,4-triazoline-5-thiones. Furthermore, The IR spectra of compounds **7a**,**b** indicate that they predominantly exist in the thione form rather than the tautomeric thiol form; there was no absorption of the SH at 2600–2500 cm^{-1} [20], but bands due to NH (3122–3084 cm^{-1}) and N–C═S groups (1356–1350, 1251, 1213–1210, 1177 cm^{-1}) were observed. The two novel thioethers **8a**,**b** were prepared by reacting the 1,2,4-triazoline-5-thiones **7a**,**b** with ethyl iodide in the presence of either anhydrous K_2CO_3 in refluxing acetone [21] or sodium methoxide in methanol [20]. It was noticed that using a stronger base catalyst (sodium methoxide) improved the yield and shortened the reaction time. The disappearance of NH absorption (3122–3084 cm^{-1}) characteristic for the IR spectra of the triazoles **7a**,**b** supported the etherification process. In the ^{1}H NMR spectra of compounds **8a**,**b**, the lack of signals arising from the triazoline CS–NH function at 13.80 and 13.30 ppm, observed with compounds **7a**,**b**, respectively, also provided the evidence for the formation of thioether function. Another support for elucidating the structures of these compounds was the presence of absorptions arising from the ethyl protons at δ 1.55 ppm for CH_3 and δ 4.60 ppm for CH_2. The oxadiazole-2-thione derivative **9** was prepared, according to the reported procedure for the synthesis of analogous compounds [22–24], *via* cyclization of the hydrazide **4** with carbon disulphide in the presence of potassium hydroxide in refluxing ethanol. In the IR spectrum, the absence of C═O band (characteristic for the hydrazide) together with the appearance of vibrational bands at 3297 cm^{-1} (NH), 1625–1597 cm^{-1} (C═N) and 1509, 1361–1331, 1250–1177 cm^{-1} (N–C═S) supports the conversion of the hydrazide **4** to the corresponding 1,3,4-oxadiazole-2-thione **9**. Additionally, the absence of SH absorption at 2600–2500 cm^{-1} and the presence of bands due to NH and N–C═S suggest the existence of compound **9** in the thione



Scheme 1.



Scheme 2.

rather than the thiol form. In the ^{1}H NMR spectrum of compound **9**, the absence of NH and NH_2 absorptions characteristic for the hydrazide moiety and the appearance of a downfield broad singlet resonating at δ 12.80 ppm characteristic for the oxadiazoline CS–NH supports the formation of compound **9**. Clasien–Schmidt condensation of benzaldehyde and acetophenone in the presence of NaOH afforded the corresponding chalcone that was readily brominated to the corresponding dibromo derivative [25]. Reaction of the dibromo derivative with the hydrazide **4** in the presence of triethylamine in refluxing ethanol for 24 h afforded the desired hydroxypyrazoline **10**. The ^{1}H NMR spectrum of compound **10** showed a singlet at 4.99 ppm for the hydroxyl group. In addition, the methylene protons of hydroxypyrazoline ring appeared as two separate doublets centered at 3.47 ppm and 3.73 ppm with a geminal coupling constant ($J = 18.6$ Hz). The appearance of the two doublets clearly reveals the magnetic non-equivalence of the two protons of CH_2 group adjacent to a chiral centre [25]. Heating equimolar amounts of the hydrazide **4** and ethyl acetoacetate in absolute ethanol at reflux afforded the methylpyrazolone **11**. The appearance of two separate doublets for the pyrazolone–CH_2 protons with a strong coupling constant ($J = 16$ Hz) reflects the magnetic non-equivalence of the two protons.

2.2. Antihyperlipidemic activity

The hypolipidemic activity of the synthesized compounds was studied in the high cholesterol diet (HCD) fed hyperlipidemic rat model against hyperlipidemic control [i.e., rats fed with HCD and given drug vehicle (0.5% carboxymethylcellulose)], by oral administration of 20 mg/kg of the tested compounds. Hyperlipidemia was induced by feeding rats with high cholesterol diet (enriched with 2% cholesterol and 1% cholic acid) [26,27]. Rats receiving normal rodent chow and the drug vehicle (0.5% CMC) served as normal control. The results were compared with that obtained by the reference hypolipidemic agent gemfibrozil.

2.2.1. Effect of high cholesterol diet feeding on the lipid profile of adult male rats

The results revealed that feeding rats with high cholesterol diet for 14 days significantly elevated the serum level of total cholesterol, triglycerides and LDL by 59.58%, 71.76% and 102.36% respectively, when compared with normal control rats. Moreover, induction of hyperlipidemia significantly decreased serum HDL level by 34.77% from that of normal control rats.

2.2.2. Effect of the tested compounds and gemfibrozil on serum TC of hyperlipidemic rats

High blood total cholesterol (TC) has been known as the most important risk factor of atherosclerosis [28]. In any population, the incidence of coronary heart diseases (CHD) is directly related to the level of TC [29]. The obtained data showed that the tested compounds produced variable effects on the serum level of TC as compared to the hyperlipidemic control group. The *S*-alkylated mercaptotriazole **8b**, the 1,3,4-oxadiazole **9** and the pyrazolone derivative **11** significantly reduced the serum level of TC of hyperlipidemic rats by 19.44%, 16.18% and 15.89%, respectively and were more active than the reference gemfibrozil which afforded only 4.68% reduction. Moreover, the 1,2,4-triazoline-5-thiones **7a**,**b** and the amide **3** produced mild hypocholesterolemic activity. No significant reduction of serum TC was observed in the groups treated with the hydrazones **5a**–**d** or the 1,4-disubstituted thiosemicarbazides **6a**–**c** (Fig. 1).

2.2.3. Effect of the tested compounds and gemfibrozil on serum TG of hyperlipidemic rats

Elevated serum triglyceride level has been found to increase the risk of developing hypertension and insulin resistance. It may also

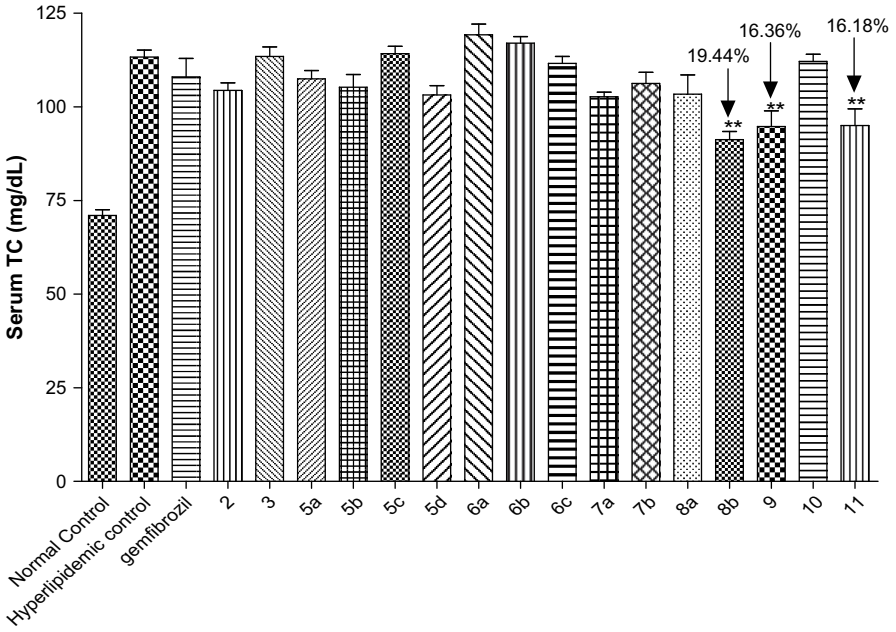


Fig. 1. Effect of the new compounds and intermediate acid **2** on serum TC of hyperlipidemic rats. Significantly different from hyperlipidemic control group at $^{*}P < 0.05$, $^{**}P < 0.01$. Reduction in the level of serum TC is calculated for groups as percentage from the hyperlipidemic control group.

promote atherogenesis by inducing a prothrombic state (i.e., increased platelet agreeability, elevated fibrinogen concentrations, increased plasminogen activator inhibitors [PAI], increased factor VII, and increased factor X clotting activity) [30]. Patients with very high triglyceride concentrations (500 mg/dL or greater) are susceptible to develop acute pancreatitis [30,31]. Therefore, both pharmacological and non-pharmacological measures should be considered in patients with high triglyceride concentrations [30–32]. Results of the present study revealed that the tested compounds produced variable effects on serum TG level of hyperlipidemic rats. Among the tested compounds, the 1,3,4-oxadiazole **9**, the 1,2,4-triazoline-5-thione **7a** and the *S*-alkylated mercaptotriazole **8b** afforded significant hypotriglyceridemic activity ranging from 19.07 to 26.78% reduction in serum level of TG of hyperlipidemic rats being nearly equipotent to gemfibrozil which reduced the serum level of TG by 22.23%. Moreover, the hydrazone **5b**, the 1,2,4-triazoline-5-thione **7b** and the hydroxypyrazoline **10** produced mild activity (Fig. 2).

2.2.4. *Effect of the tested compounds and gemfibrozil on serum HDL of hyperlipidemic rats*

One of the risk factors for atherosclerotic cardiovascular diseases comprises low levels of the good high-density lipoprotein (HDL) cholesterol [33]. Increasing serum concentrations of HDL has been shown to prevent or delay the progression of CHD [34]. One of the reported mechanisms for the protective action of HDL from coronary heart disease may be that HDL collects cholesterol particles from the cells and other circulating lipoproteins which in turn counteract the role of LDL thus preventing the formation of atherosclerotic lesions [35]. Results of the present investigation indicated that significant elevation of serum level of HDL of hyperlipidemic rats ranging from 47.78% to 55.42%

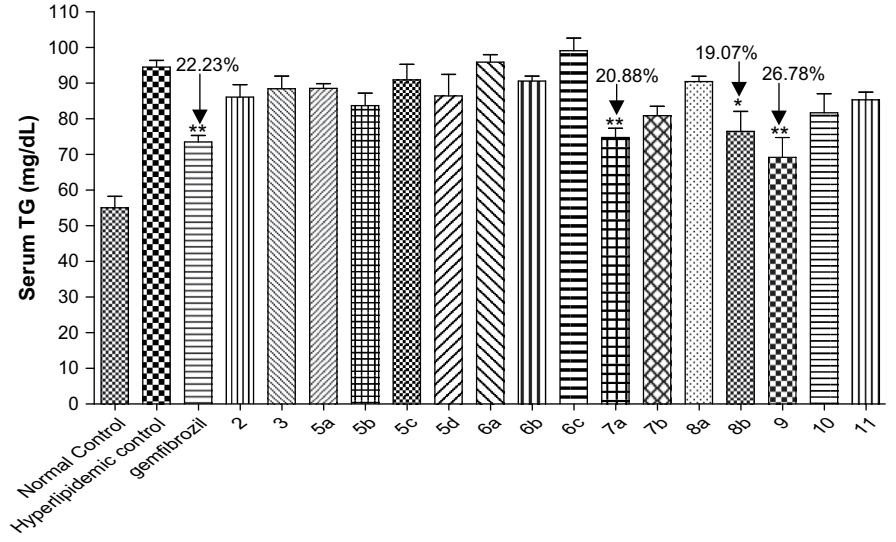


Fig. 2. Effect of the new compounds and intermediate acid **2** on serum TG of hyperlipidemic rats. Significantly different from hyperlipidemic control group at $^{*}P < 0.05$, $^{**}P < 0.01$. Reduction in the level of serum TG is calculated for groups as percentage from the hyperlipidemic control group (HCD fed).

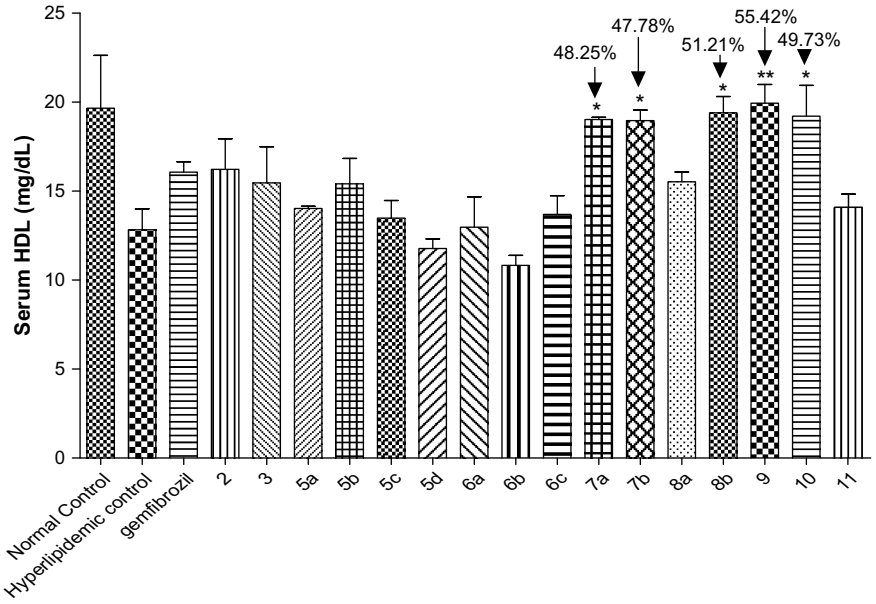


Fig. 3. Effect of the new compounds and intermediate acid **2** on serum HDL of hyperlipidemic rats. Significantly different from hyperlipidemic control group at $^{*}P < 0.05$, $^{**}P < 0.01$. Elevation in the level of serum HDL is calculated for groups as percentage from the hyperlipidemic control group (HCD fed).

was achieved by the 1,3,4-oxadiazole **9**, the 1,2,4-triazoline-5-thiones **7a**,**b**, the *S*-alkylated mercaptotriazole **8b** and the hydroxypyrazoline **10**. The reference gemfibrozil was less active affording only 25.18% elevation of serum HDL. Most of the other compounds afforded moderate improvement of serum HDL (Fig. 3).

2.2.5. *Effect of the tested compounds and gemfibrozil on serum LDL of hyperlipidemic rats*

Elevated serum LDL cholesterol is one of the most powerful and independent risk factors for CHD. The LDL fraction is generally thought to carry cholesterol to the tissues and is responsible for the atherogenesis process [36]. Hypercholesterolemia increases oxidative stress and leads to lipid peroxidation. Lipid peroxidation products are potential causes for oxidative modifications of low-density lipoprotein, which is the key point in the initiation and progression of atherosclerosis [37,38]. The dietary and pharmacological lowering of elevated plasma LDL cholesterol appears to be one of the methods to reduce the development of atherosclerosis. It has been estimated that each 1% reduction in LDL concentration may result in a 1% decrease in the incidence of CHD [1]. Interestingly, results of our study revealed that the pyrazolone derivative **11**, the 1,3,4-oxadiazole **9** and the *S*-alkylated mercaptotriazole **8b** significantly reduced the serum level of LDL of hyperlipidemic rats by percentages ranging from 19.15% to 21.74% being more active than gemfibrozil. In addition, the acid **2**, the 1,2,4-triazoline-5-thiones **7a**,**b** and the *S*-alkylated mercaptotriazole **8a** exhibited moderate activity (Fig. 4).

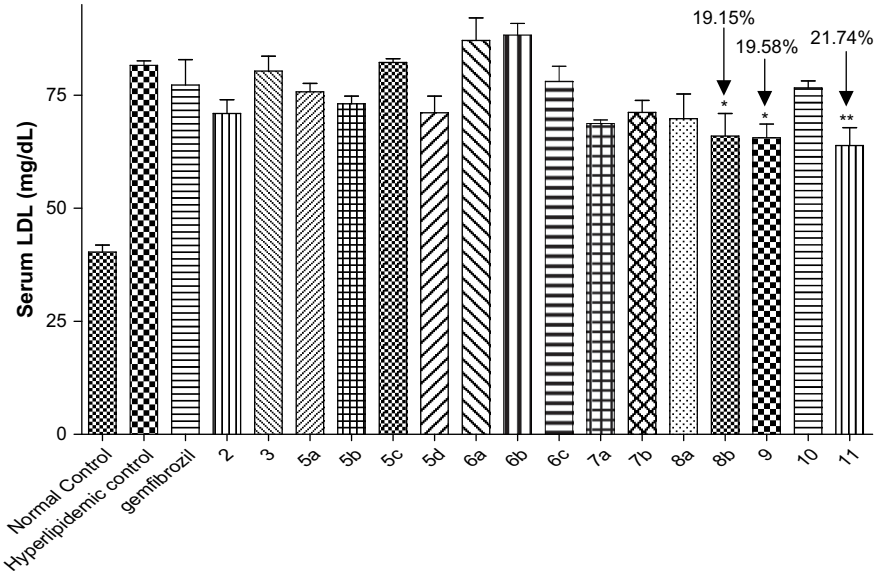


Fig. 4. Effect of the new compounds and intermediate acid **2** on serum LDL of hyperlipidemic rats. Significantly different from hyperlipidemic control group at $^{*}P < 0.05$, $^{**}P < 0.01$. Reduction in the level of serum LDL is calculated for groups as percentage from the hyperlipidemic control group (HCD fed).

2.2.6. Ratios of LDL/HDL for tested compounds and gemfibrozil in hyperlipidemic rats

The HDL fraction leads cholesterol out of the tissue and protects against atherosclerosis [35], whereas the LDL fraction carries cholesterol to the tissues and is responsible for the atherogenesis process [38]. Thus, decreasing the ratio of the plasma level of LDL to that of HDL seems to play an important role in reducing the risk of atherosclerosis. Results (Table 1) illustrate that the oxadiazole **9** recorded the lowest LDL/HDL ratio (3.29). Likewise, the *S*-alkylated mercaptotriazole **8b** and the 1,2,4-triazoline-5-thiones **7a**,**b** afforded low LDL/HDL ratios expressed as 3.40, 3.61, and 3.75, respectively. This valuable finding reflects the role of the mentioned compounds in improving the lipid profile and preventing the progression of atherosclerosis and subsequent cardiovascular complications.

The analysis of the lipid profile data (TC, TG, HDL and LDL) of different groups clearly suggests that some of the synthesized compounds exerted good hypolipidemic activity. The 1,3,4-oxadiazole **9** and the *S*-alkylated mercaptotriazole **8b** appear to be ideal hypolipidemic agents acting *via* several mechanisms. They produced striking reduction of serum levels of TC, TG and LDL and elevation of serum HDL. In addition, the 1,2,4-triazoline-5-thione **7a** afforded pronounced reduction of serum TG levels and increase in HDL. The pyrazolone derivative **11** reduced serum TC and LDL levels. Moreover, the hydroxypyrazoline **10** was effective in elevating HDL levels. From the obtained data, it's obvious that the presence of the carboxylic group or its amide prodrugs is not essential for the hypolipidemic activity. This was evidenced by the good antihyperlipidemic activity of the 1,3,4-oxadiazole **9**, the *S*-alkylated mercaptotriazole **8b** and the pyrazolone derivative **11** which generally exhibited better hypolipidemic activity relative to gemfibrozil. Comparing the effects of the free acid **2** with gemfibrozil, it could be concluded that variation of the aryl moiety produced remarkable changes in the hypolipidemic activity.

3. Experimental

3.1. Chemistry

Melting points were determined on Stuart electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as KBr disks on a Nexus FT-IR spectrometer. ^{1}H NMR spectra were run on a Mercury 300BB NMR spectrometer (300 MHz), on a JEOL EX-270 NMR spectrometer (270 MHz), on a GEMINI-200 NMR spectrometer (200 MHz) and on a Varian EM-360L NMR spectrometer (60 MHz) using TMS as internal standard. Elemental analyses were performed on a Heraeus Vario EL apparatus.

Table 1
Ratios of LDL/HDL for tested compounds and gemfibrozil in hyperlipidemic rats.

Group	LDL/HDL[a]
Normal control	2.05
Hyperlipidemic control	6.36
Gemfibrozil	4.81
3	5.19
5a	5.40
5b	4.74
5c	6.10
5d	6.04
6a	6.71
6b	8.16
6c	5.70
7a	3.61
7b	3.75
8a	4.50
8b	3.40
9	3.29
10	3.99
11	4.54

[a] LDL/HDL ratios are calculated from the mean values of LDL and HDL.

3.1.1. Synthesis of N*-(4-methoxyphenyl)-2-(naphthalen-2-yloxy)propionamide (**3**)*

To a stirred solution of the acid **2** (2.16 g, 10 mmol) in 30 mL dry chloroform at 0–5 °C, triethylamine (1.01 g, 10 mmol) was added, followed by ethyl chloroformate (1.08 g, 10 mmol) in a dropwise manner. The mixture was stirred in the ice bath for 30 min, and then *p*-anisidine (1.23 g, 10 mmol) in dry chloroform was added dropwise. The reaction mixture was stirred for additional 12 h at room temperature. The solvent was evaporated under reduced pressure and the crude product was dissolved in 30 mL chloroform, washed with water (2 × 30 mL), 5% $NaHCO_3$ solution (2 × 20 mL), 1 N HCl (2 × 20 mL), water (2 × 30 mL) and finally with brine (2 × 30 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The product was collected and recrystallized from aqueous ethanol to give (2.1 g, 65%) compound **3** as a white powder, mp 154–155 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.71 (d, 3H, J = 8.1 Hz, $CH\underline{CH_3}$), 3.76 (s, 3H, OCH_3), 4.93 (q, 1H, J = 8.1 Hz, $\underline{CH}CH_3$), 6.82–7.81 (m, 11H, Ar–H), 8.12 (br s, 1H, NH); Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.80; H, 6.00; N, 4.36.

3.1.2. General procedure for the synthesis N*-(alkylidene or arylidene)-2-(naphthalen-2-yloxy)propionic acid hydrazides (**5a**–**d**)*

A mixture of the hydrazide **4** (2.30 g, 10 mmol) and the appropriate carbonyl compound (10 mmol) in absolute ethanol (20 mL) was heated at reflux for 3 h. The reaction mixture was cooled and the precipitated solid was filtered off, dried and recrystallized from ethanol to give the target compounds **5a**–**d**.

3.1.2.1. N*-(4-Methoxybenzylidene)-2-(naphthalen-2-yloxy)propionic acid hydrazide (**5a**).* White powder, 74% yield, mp 187–188 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.75 (d, 3H, J = 6.6 Hz, $CH\underline{CH_3}$), 3.83 (s, 3H, OCH_3), 5.00 (q, 1H, J = 6.6 Hz, $\underline{CH}CH_3$), 6.91–7.83 (m, 11H, Ar–H), 8.06 (s, 1H, azomethine proton), 9.30 (bs, 1H, NH); Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.32; H, 5.56; N, 8.23.

3.1.2.2. N*-(4-Nitrobenzylidene)-2-(naphthalen-2-yloxy)propionic acid hydrazide (**5b**).* Yellow crystals, yield 83%, mp 188–190 °C; ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.80 (d, 3H, J = 7.2 Hz, $CH\underline{CH_3}$), 5.30 (q, 1H, J = 7.2 Hz, $\underline{CH}CH_3$), 7.60–9.00 (m, 11H, Ar–H), 10.70 (s, 1H, azomethine proton), 11.50 (bs, 1H, NH); Anal. Calcd for $C_{20}H_{17}N_3O_4$: C, 66.11; H, 4.72; N, 11.56. Found: C, 66.09; H, 4.51; N, 11.52.

3.1.2.3. N*-Isopropylidene-2-(naphthalen-2-yloxy)propionic acid hydrazide (**5c**).* White powder, yield 65%, mp 128–129 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 11.73 (d, 3H, J = 8.1 Hz, $CH\underline{CH_3}$), 2.04 (s, 3H, N=C–CH_3), 2.06 (s, 3H, N=C–CH_3), 4.99 (q, 1H, J = 8.1 Hz, $\underline{CH}CH_3$), 7.06–7.77 (m, 7H, Ar–H), 9.03 (bs, 1H, NH); Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.12; H, 6.64; N, 10.42.

3.1.2.4. N*-[1-(4-Bromophenyl)ethylidene]-2-(naphthalen-2-yloxy) propionic acid hydrazide (**5d**).* White powder, yield 67%, mp 162–163 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.75 (d, 3H, J = 8.1 Hz, $CH\underline{CH_3}$), 2.08 (s, 3H, N=C–CH_3), 5.04 (q, 1H, J = 7.2 Hz, $\underline{CH}CH_3$), 7.05–8.12 (m, 11H, Ar–H), 9.35 (bs, 1H, NH); Anal. Calcd for $C_{21}H_{19}BrN_2O_2$: C, 61.32; H, 4.66; N, 6.81. Found: C, 61.34; H, 4.59; N, 6.80.

*3.1.3. General procedure for the synthesis of 1-[2-(naphthalen-2-yloxy)propionyl]-4-substituted thiosemicarbazides (**6a**–**c**)*

A mixture of the hydrazide **4** (2.30 g, 10 mmol) and the appropriate alkyl or aryl isothiocyanate (10 mmol) in absolute ethanol

was heated at reflux for 3 h. The mixture was cooled and the precipitated solid was filtered, dried and recrystallized from ethanol to give compounds **6a**–**c**.

*3.1.3.1. 1-[2-(Naphthalen-2-yloxy)propionyl]-4-ethyl thiosemicarbazide (**6a**).* White powder, yield 75%, mp 161–163 °C; IR (cm^{-1}): 3376, 3289 (NH), 3094 (Arom-CH), 2974–2932 (Aliph-CH), 1687 (C═O), 1540, 1251, 1211, 1178 (N–C═S), 1626, 1506, 1460 (C⋯C), 1060, 1094 (C–O–C); ^{1}H NMR (60 MHz, $CDCl_3$): δ 0.90 (t, 3H, $J = 8$ Hz, $CH_2\underline{CH_3}$), 1.80 (d, 3H, $J = 6.6$ Hz, $CH\underline{CH_3}$), 3.60 (q, 2H, $J = 8$ Hz, $\underline{CH_2}CH_3$), 5.40 (q, 1H, $J = 6.6$ Hz, $\underline{CH}CH_3$), 6.80 (bs, 1H, CSNH), 7.70–8.50 (m, 7H, Ar–H), 9.20 (bs, 1H, NHCS), 9.80 (bs, 1H, CONH); Anal. Calcd for $C_{16}H_{19}N_3O_2S$: C, 60.54; H, 6.03; N, 13.24. Found: C, 60.67; H, 6.00; N, 13.29.

*3.1.3.2. 1-[2-(Naphthalen-2-yloxy)propionyl]-4-allyl thiosemicarbazide (**6b**).* White powder, yield 59%, mp 165–166 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.68 (d, 3H, $J = 8.1$ Hz, $CH\underline{CH_3}$), 3.94 (m, 2H, $CSNH\underline{CH_2}$), 5.01 (m, 3H, $\underline{CH}CH_3 + NHCH_2\underline{CH}{=}\underline{CH_2}$), 5.57 (m, 1H, $NHCH_2\underline{CH}{=}CH_2$), 6.39 (bs, 1H, CSNH), 7.19–7.81 (m, 7H, Ar–H), 8.48 (bs, 1H, NHCS), 8.99 (bs, 1H, CONH); Anal. Calcd for $C_{17}H_{19}N_3O_2S$: C, 61.98; H, 5.81; N, 12.76. Found: C, 62.00; H, 5.79; N, 12.72.

*3.1.3.3. 1-[2-(Naphthalen-2-yloxy)propionyl]-4-phenyl thiosemicarbazide (**6c**).* White powder, yield 77%, mp 191–192 °C; IR (cm^{-1}): 3315, 3171 (NH), 3024 (Arom-CH), 2937 (Aliph-CH), 1667 (C═O), 1546, 1215, 1211, 1178 (N–C═S), 1595, 1497, 1468 (C⋯C), 1122, 1050 (C–O–C); ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.70 (d, 3H, $J = 6.4$ Hz, $CH\underline{CH_3}$), 5.00 (q, 1H, $J = 6.6$ Hz, $\underline{CH}CH_3$), 7.22–7.77 (m, 12H, Ar–H), 8.32 (bs, 1H, CSNH), 9.05 (bs, 1H, NHCS), 9.66 (bs, 1H, CONH); Anal. Calcd for $C_{20}H_{19}N_3O_2S$: C, 65.73; H, 5.24; N, 11.50. Found: C, 65.80; H, 5.24; N, 11.48.

*3.1.4. General procedure for the synthesis of 3-[1-(naphthalen-2-yloxy)ethyl]-4-ethyl/phenyl-1,4-dihydro-1,2,4-triazole-5-thione (**7a**,**b**)*

A solution of the thiosemicarbazide derivatives **6a** or **6c** (10 mmol) in aqueous 2 N sodium hydroxide (15 mL) was heated at reflux for 3 h. The solution was cooled and acidified with hydrochloric acid to pH 4.5. The precipitated solid was then filtered, washed with water, dried and recrystallized from aqueous ethanol to give the target compounds **7a**,**b**.

*3.1.4.1. 3-[1-(Naphthalen-2-yloxy)ethyl]-4-ethyl-1,4-dihydro-1,2,4-triazole-5-thione (**7a**).* White powder, yield 47%, mp 150–152 °C; IR data (cm^{-1}): 3122 (NH), 3048 (Arom-CH), 2982–2948 (Aliph-CH), 1596, 1572, 1485 (C═N, C⋯C), 1356, 1251, 1210, 1176 (N–C═S), 1088 (C–O–C); ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.55 (t, 3H, $J = 8$ Hz, $CH_2\underline{CH_3}$), 2.00 (d, 3H, $J = 7.2$ Hz, $CH\underline{CH_3}$), 4.60 (q, 2H, $J = 8$ Hz, $\underline{CH_2}CH_3$), 6.15 (q, 1H, $J = 7.2$ Hz, $\underline{CH}CH_3$), 7.70–8.60 (m, 7H, Ar–H), 13.80 (bs, 1H, NH); Anal. Calcd for $C_{16}H_{17}N_3OS$: C, 64.19; H, 5.72; N, 14.04. Found: C, 64.22; H, 5.72; N, 14.00.

*3.1.4.2. 3-[1-(Naphthalen-2-yloxy)ethyl]-4-phenyl-1,4-dihydro-1,2,4-triazole-5-thione (**7b**).* White powder, yield 58%, mp 214–215 °C; IR data (cm^{-1}): 3084 (NH), 3022 (Arom-CH), 2924–2772 (Aliph-CH), 1596, 1561 (C═N, C⋯C), 1499, 1350, 1251, 1213, 1177 (N–C═S), 1124, 1079 (C–O–C); ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.80 (d, 3H, $J = 7.2$ Hz, $CH\underline{CH_3}$), 5.80 (q, 1H, $J = 7.2$ Hz, $\underline{CH}CH_3$), 7.40–8.50 (m, 12H, Ar–H), 13.30 (bs, 1H, NH). Anal. Calcd for $C_{20}H_{19}N_3OS$: C, 69.14; H, 4.93; N, 12.09. Found: C, 69.22; H, 5.00; N, 12.12.

*3.1.5. General procedure for the synthesis of 3-ethylthio-5-[1-(naphthalen-2-yloxy)ethyl]-4-ethyl/phenyl-4*H*-1,2,4-triazoles (**8a**,**b**)*

Method A: A mixture of the 1,2,4-triazole-5-thiones **7a** or **7b** (10 mmol), ethyl iodide (1.56 g, 10 mmol) and anhydrous potassium carbonate (0.5 g) in dry acetone (20 mL) was heated at reflux for 8 h. The reaction mixture was cooled, poured on ice cooled water and stirred well. The precipitated solid was filtered, washed with water, dried and recrystallized from ethanol to give compounds **8a**,**b**.

Method B: To a mixture of the 1,2,4-triazole-5-thiones **7a** or **7b** (10 mmol) and sodium methoxide [prepared from sodium (0.46 g, 20 mmol) and MeOH (15 mL)], ethyl iodide (1.56 g, 10 mmol) was added dropwise. The reaction mixture was heated at reflux for 1 h, then cooled to room temperature, poured on ice cooled water and stirred well. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol to give the target compounds **8a**,**b**.

*3.1.5.1. 3-Ethylthio-5-[1-(naphthalen-2-yloxy)ethyl]-4-ethyl-4*H*-1,2,4-triazole (**8a**).* White powder, yield 64% (method A), 77% (method B); mp 111–112 °C; IR data (cm^{-1}): 3032 (Arom-CH), 2986–2922 (Aliph-CH), 1623, 1596, 1512, 1487, 1465 (C═N, C⋯C), 1081 (C–O–C), 695, 751 (C–S); ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.35 (t, 3H, $J = 7$ Hz, $SCH_2\underline{CH_3}$), 1.55 (t, 3H, $J = 7$ Hz, $NCH_2\underline{CH_3}$), 2.00 (d, 3H, $J = 7.2$ Hz, $CH\underline{CH_3}$), 3.55 (q, 2H, $J = 7$ Hz, $S\underline{CH_2}CH_3$), 4.40 (q, 2H, $J = 7$ Hz, $N\underline{CH_2}CH_3$), 6.35 (q, 1H, $J = 7.2$ Hz, $\underline{CH}CH_3$), 7.70–8.60 (m, 7H, Ar–H); Anal. Calcd for $C_{18}H_{21}N_3OS$: C, 66.02; H, 6.46; N, 21.83. Found: C, 66.00; H, 6.46; N, 21.78.

*3.1.5.2. 3-Ethylthio-5-[1-(naphthalen-2-yloxy)ethyl]-4-phenyl-4*H*-1,2,4-triazole (**8b**).* White powder, yield 59% (method A), 71% (method B); mp 101–103 °C; IR data (cm^{-1}): 3060 (Arom-CH), 2929–2857 (Aliph-CH), 1627, 1597, 1525, 1498 (C═N, C⋯C), 1180, 1055 (C–O–C), 694, 755 (C–S); ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.35 (t, 3H, $J = 7$ Hz, $SCH_2\underline{CH_3}$), 1.80 (d, 3H, $J = 7.2$ Hz, $CH\underline{CH_3}$), 3.55 (q, 2H, $J = 7$ Hz, $S\underline{CH_2}CH_3$), 6.00 (q, 1H, $J = 7.2$ Hz, $\underline{CH}CH_3$), 7.30–8.50 (m, 12H, Ar–H); Anal. Calcd for $C_{22}H_{21}N_3OS$: C, 70.37; H, 5.64; N, 11.19. Found: C, 70.41; H, 5.72; N, 11.20.

*3.1.6. Synthesis of 5-[1-(naphthalen-2-yloxy)ethyl]-3*H*-1,3,4-oxadiazole-2-thione (**9**)*

To a solution of the hydrazide **4** (2.30 g, 10 mmol) in ethanol (100 mL) was added a solution of KOH (0.84 g, 15 mmol) in ethanol (20 mL), followed by CS_2 (8 mL). The reaction mixture was heated at reflux for 8 h. The solution was concentrated under reduced pressure and acidified with hydrochloric acid. The precipitated solid was filtered off, washed with water, dried and recrystallized from methanol/H_2O to give (1.88 g, 69%) compound **9** as yellowish white crystals, mp 121–122 °C; IR (cm^{-1}): 3297 (NH), 3048 (Arom-CH), 1625, 1597, 1572 (C═N, C⋯C), 1509, 1361–1331, 1250–1177, (N–C═S), 1088 (C–O–C). ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.80 (d, 3H, $J = 7.2$ Hz, $CH\underline{CH_3}$), 5.80 (q, 1H, $J = 7.2$ Hz, $\underline{CH}CH_3$), 7.40–8.50 (m, 7H, Ar–H), 12.80 (bs, 1H, NH). Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 62.00; H, 4.48; N, 10.25.

*3.1.7. Synthesis of 1-(5-hydroxy-3,5-diphenyl-4,5-dihydropyrazol-1-yl)-2-(naphthalen-2-yloxy)propan-1-one (**10**)*

To a solution of the dibromo derivative (3.67 g, 10 mmol) in absolute ethanol (75 mL) were added the hydrazide **4** (2.30 g, 10 mmol) and triethylamine (10 mL). The reaction mixture was heated at reflux for 24 h on a water bath. The volume of the solution was reduced, cooled, poured on crushed ice and kept overnight. The precipitated solid was collected by filtration and recrystallized from methanol to give (2.5 g, 57%) compound **10** as white powder, mp 124–126 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.76 (d, 3H, $J = 6.4$ Hz, $CH\underline{CH_3}$), 3.47 (d, 1H, $J = 18.6$ Hz, pyrazoline–CH_2), 3.73 (d, 1H, $J = 18.6$ Hz, pyrazoline–CH_2), 4.99 (s, 1H, OH), 5.87 (q, 1H, $J = 6.4$ Hz, $\underline{CH}CH_3$), 7.15–7.78 (m, 17H, Ar–H); Anal. Calcd for $C_{28}H_{24}N_2O_3$: C, 77.04; H, 5.54; N, 6.42. Found: C, 77.10; H, 5.42; N, 6.44.

*3.1.8. Synthesis of 3-methyl-1-[2-(naphthalen-2-yloxy)propionyl]-1,4-dihydropyrazol-5-one (**11**)*

A mixture of the hydrazide **4** (2.30 g, 10 mmol) and ethyl acetoacetate (1.30 g, 10 mmol) in absolute ethanol was heated at reflux for 3 h. The reaction mixture was cooled and the formed precipitate was filtered off, dried and recrystallized from acetic acid/H_2O to give (2 g, 67%) compound **11** as white solid, mp 162–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72 (d, 3H, $J = 8$ Hz, $CH\underline{CH_3}$), 2.14 (s, 3H, CH_3 at C-3 of pyrazoline), 3.37 (d, 1H, $J = 16$ Hz, pyrazoline–CH_2), 3.43 (d, 1H, $J = 16$ Hz, pyrazoline–CH_2), 5.00 (q, 1H, $J = 8$ Hz, $\underline{CH}CH_3$), 7.17–7.81 (m, 7H, Ar–H); Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 69.00; H, 5.42; N, 9.52.

3.2. Antihyperlipidemic activities

Male albino rats of Wistar strain weighing 160–180 g were used in this study. Rats were obtained from the animal house of National Research Centre, Dokki, Cairo. The animals were kept for one week in the laboratory under 12 h day and night cycle for accommodation with free access to food and water *ad libitum*. Rats were divided into control (fed normal rodent chow), hyperlipidemic control and hyperlipidemic plus compound treated groups. Each group consisted of six animals. Hyperlipidemia was induced by feeding rats with high cholesterol diet (HCD) for 14 days. The high cholesterol diet was prepared by mixing normal rodent chow with 2% cholesterol (Sigma, USA) and 1% cholic acid (Sigma, USA) [37,38]. Hyperlipidemic rats had a free access to the HCD and water *ad libitum* during the entire period of the experiment. The tested compounds as well as the standard drug gemfibrozil were given orally at a dose of 20 mg/kg using 0.5% CMC as a drug vehicle from day 8 to day 14 (7 days) in the HCD fed rats. Control and hyperlipidemic control rats (fed with HCD) received only the drug vehicle from day 8 to day 14 of the experiment. At the end of experiment, that is, on the 14th day, the animals were fasted for 12 h and the tail blood was collected under mild ether anesthesia. Serum was separated by centrifugation at 3000 rpm for 10 min for measurement of TC, TG and HDL using Randox kits (UK) on a Jenway UV–vis spectrophotometer. Serum levels of LDL in mg/dL were calculated using Friedewald's formula [39].

4. Statistical analysis

The results obtained were expressed as mean ± SD. The difference between groups was evaluated by *one-way* ANOVA test. Mean, standard deviation calculations and ANOVA test were performed using "GraphPad Prism version 4.0" software. A P value < 0.05 was considered significant.

5. Conclusion

The analysis of the lipid profile data (TC, TG, HDL and LDL) of different groups clearly suggests that some of the synthesized compounds exerted good hypolipidemic activity. The 1,3,4-oxadiazole **9** and the *S*-alkylated mercaptotriazole **8b** appear to be ideal hypolipidemic agents acting *via* several mechanisms. They produced striking reduction of serum levels of TC, TG and LDL and elevation of serum HDL. In addition, the 1,2,4-triazoline-5-thione **7a** afforded pronounced reduction of serum TG levels and increase in HDL. The pyrazolone derivative **11** reduced serum TC and LDL levels. Moreover, the hydroxypyrazoline **10** was effective in elevating HDL levels. From the obtained data, it's obvious that the presence of the carboxylic group or its amide prodrugs is not essential for the hypolipidemic activity. This was evidenced by the good antihyperlipidemic activity of the 1,3,4-oxadiazole **9**, the *S*-alkylated mercaptotriazole **8b** and the pyrazolone derivative **11** which generally exhibited better hypolipidemic activity relative to gemfibrozil. Comparing the effects of the free acid **2** with gemfibrozil, it could be concluded that variation of the aryl moiety produced remarkable changes in the hypolipidemic activity.

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