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Synthesis of new *N*-acryl-1-amino-2-phenylethanol and *N*-acyl-1-amino-3-aryloxypropanols and evaluation of their antihyperlipidemic, LDL-oxidation and antioxidant activity

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ABSTRACT

As a part of our drug discovery program, we identified an alkaloidal amide i.e. Aegeline (**V**) isolated from the leaves of *Aegle marmelos* as a dual acting agent (antihyperlipidemic and antihyperglycemic). In continuation of this program, we synthesized new *N*-acyl-1-amino-2-alcohols (*N*-acrylated-1-amino-2-phenylethanol and *N*-acylated-1-amino-3-aryloxypropanols) *via* Ritter reaction and screened for their *in-vivo* antihyperlipdemic activity in Triton induced hyperlipidemia model, LDL-oxidation and antioxidant activity. Compounds **3**, **11** and **13** showed good antihyperlipidemic activity, LDL-oxidation as well as antioxidant activity and comparable activity with marketed antidyslipidemic drug.

1. Introduction

Hyperlipidemia is an elevation of lipids in the bloodstream and these lipids include fats, fatty acids, cholesterol, cholesterol esters, phospholipids, and triglycerides. An increase in plasma lipids, particularly cholesterol, is a common feature of atherosclerosis, a condition involving arterial damage, which may lead to ischaemic heart disease, myocardial infarction, and cerebrovascular accidents. These conditions are responsible for one-third of deaths in industrialized nations [1]. In 1984, it was demonstrated for the first time that there exists a link between serum cholesterol levels and risk to coronary heart disease (CHD) [2]. CHD is caused by the narrowing of the artery that supplies nutrients and oxygen to the heart. A 1% drop in serum cholesterol reduces the risk for CHD by 2% [3]. In addition to this, cholesterol lowering drugs treatments can significantly reduce morbidity from CHD, thus providing a causal role for cholesterol in coronary events. The discovery of new drugs from traditional medicine is not a new phenomenon (Fig. 1). Metformin (**I**) is currently used as antidiabetic agent in the treatment of type 2 diabetes (Fig. 1). Metformin (**I**) and its analogues [4] were synthesized on the basis of a natural product lead, that is, galegine (**II**) [5]. The synthetic cholesterol lowering statins such as fluvastatin (**III**) [6], cerivastatin [7] were synthesized on the basis of natural product lead, that is, mevastatin (**IV**) [8]. The plant derived saponin derivative, pamaqueside (CP-148623) [9], has been reported for cholesterol absorption up to 35–40% and the fish oils, which contain fatty acids such as eicosapentaenoic acid and docosahexenoic acids, have been reported for their lowering activity on triglycerides and cholesterol [10]. Christophe et al. [11] discovered glucose induced insulin secretion *in vitro* and *ex vivo* of 4-hydroxyisoleucine. Furthermore, in type 2 diabetic rat model the compound was active and partly corrected hyperglycemia and glucose tolerance. Our group had reported the lipid lowering activity in phytoconstituents such as 4-hydroxyisoleucine, [12] amyrin derivatives [13], lupeol derivatives [14], calophyllic acid and isocalophyllic acid [15], canophyllic acid [15], amentoflavone [15], and furanoflavonoids [16] etc. On the other hand, interesting lipid lowering activities of synthetic hybrid benzofuranebisindole derivatives [17], 2,5,6-Trisubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles [18], and 2-(4-[(2-hydroxybenzyl) amino]-phenyl aminomethyl)-phenol [19] etc are also found in literature.

The plant *Aegle marmelos* is commonly known as 'bael' in India [20], belongs to the family of Rutaceae, widely used in Indian Ayurvedic medicine for the treatment of diabetes mellitus. In addition

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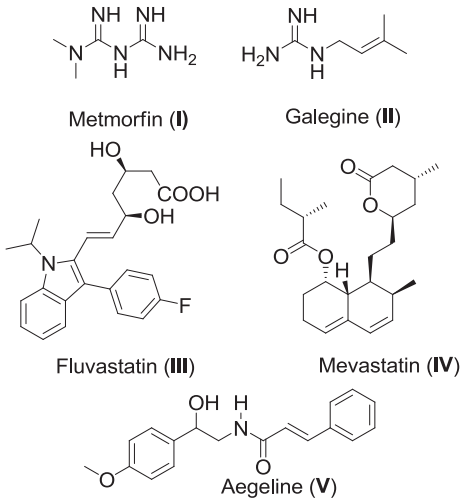


Fig. 1. Naturally occurring and synthetic Antidiabetic and Antidyslipdemic agents.

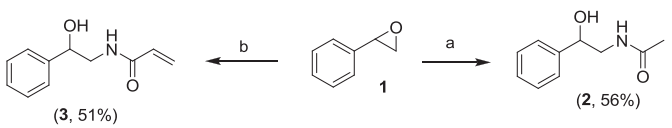
to this our group has discovered the antidyslipidemic activity in the leave's of alcoholic extract and its chloroform fraction and bioactivity-guided fractionation and isolation work led to discovery of Aegeline (Fig. 1), as an antihyperglycemic and antidyslipidemic principle [21].

Aegeline is a naturally occurring *N*-acylated-1-amino-2-alcohol. Recently our group synthesized few *N*-acylated-1-amino-2-alcohols, as Aegeline analogues, which showed antidyslipidemic and antioxidant activity in Triton induced hyperlipidemia model [22]. In continuation of this program, we synthesized new *N*-acylated-1-amino-2-alcohols (*N*-acrylated-1-amino-2-phenylethanol and *N*-acylated-1-amino-3-aryloxypropanols) *via* Ritter reaction to evaluate their antihyperlipidemic, LDL-oxidation and antioxidant activity. Further we have studied the dose dependent lipid lowering activity, lipoprotein triglycerides level, LPL activity, antioxidant and LDL oxidation.

2. Chemistry

The synthesis of *N*-acylated-1-amino-2-alcohols *via* Ritter reaction, was started with the ring opening reaction of commercially available styrene oxide **1** in acetonitrile in the presence of BF3*OEt2, which led to *N*-(2-hydroxy-2-phenylethyl)acetamide (**2**) in good yield (Scheme 1). Encouraged by these results similar reaction on styrene oxide **1** was performed using acrylonitrile and obtained respective *N*-(2-hydroxy-2-phenyl-ethyl)acrylamide (**3**) in good yield (Scheme 1). Compound **2** and **3** are close structural analogues of aegeline (**V**).

After the successful results with styrene oxide (**1**), oxiranes (**4**–**7**) were used to generate *N*-acylated-1-amino-3-aryloxy-2-propanols (*N*-acyl-1-amino-3-aryloxy-2-propanols) to extend the scope and the generality of this reaction. 2-[(4-tert-Butylphenoxy) methyl]oxirane (**4**), 2-[(3-methoxyphenoxy)methyl]oxirane (**5**), 2-[(4-chlorophenoxy)methyl]oxirane (**6**) and 2-(*m*-tolyloxymethyl) oxirane (**7**) were prepared in very good yields from 4-tert-Butylphenol, 3-methoxyphenol, 4-chlorophenol and 3-methylphenol respectively by refluxing with epichlorohydrin in dry acetone in presence of potassium carbonate at 60 °C for 4 h.



Scheme 1. Synthesis of *N*-acylated-1-amino-2-alcohols **2** and **3**. *Reagents and conditions*: (a) BF3*OEt2 (0.2 mmol), CH_3CN (1 ml), 80 °C, 12 h. (b) BF3*OEt2 (0.2 mmol), CH_2=CHCN (1 ml), 80 °C, 12 h.

2-[(4-tert-Butylphenoxy)methyl]oxirane (**4**), 2-[(3-methoxyphenoxy)methyl]oxirane (**5**) and 2-[(4-chlorophenoxy) methyl]oxirane (**6**) were treated respectively with BF3*OEt2 in nitriles (acetonitrile, acrylonitrile, benzonitrile and 4-methoxybenzonitrile) under similar reaction condition as shown in Scheme 1, which provided *N*-[3-(4-tert-Butylphenoxy)-2-hydroxy-propyl]acetamide (**8**), *N*-[3-(4-tert-Butylphenoxy)-2-hydroxypropyl]acrylamide (**9**), *N*-[3-(4-tert-Butylphenoxy)-2-hydroxypropyl]benzamide (**10**) and *N*-[3-(4-tert-Butylphenoxy)-2-hydroxypropyl]-4-methoxybenzamide (**11**), *N*-[2-hydroxy-3-(3-methoxyphenoxy)-propyl]acetamide (**12**), *N*-[2-hydroxy-3-(3-methoxyphenoxy)propyl]acrylamide (**13**), *N*-[2-hydroxy-3-(3-methoxyphenoxy)propyl]benzamide (**14**) and *N*-[2-hydroxy-3-(3-methoxyphenoxy)propyl]-4-methoxybenzamide (**15**), *N*-[3-(4-chlorophenoxy)-2-hydroxypropyl]acetamide (**16**), *N*-[3-(4-chlorophenoxy)-2-hydroxypropyl]acrylamide (**17**), *N*-[3-(4-chlorophenoxy)-2-hydroxypropyl]benzamide (**18**) and *N*-[3-(4-chlorophenoxy)-2-hydroxypropyl]-4-methoxybenzamide (**19**) with good yields (Scheme 2).

After verifying the Ritter reaction with three different oxiranes, 2-(*m*-tolyloxymethyl)oxirane (**7**) was also treated with BF3*OEt2 in nitriles (acetonitrile and acrylonitrile) under same experimental condition as shown in Scheme 1, which gave *N*-[2-hydroxy-3-(*m*-tolyloxy)propyl]acetamide (**20**) and *N*-[2-hydroxy-3-(*m*-tolyloxy)-propyl]acrylamide (**21**) in good yields (Scheme 3).

The yields of N-acylated-1-amino-2-alcohols indicate that the transformation seems to be general; thus the reaction can be carried out easily on oxiranes with different nitriles such as aliphatic and aromatic. The known compounds were identified by spectroscopic data and compared with those data reported in literatures. Further structure elucidation of new compounds was performed by different NMR spectroscopic and Mass spectrometry techniques.

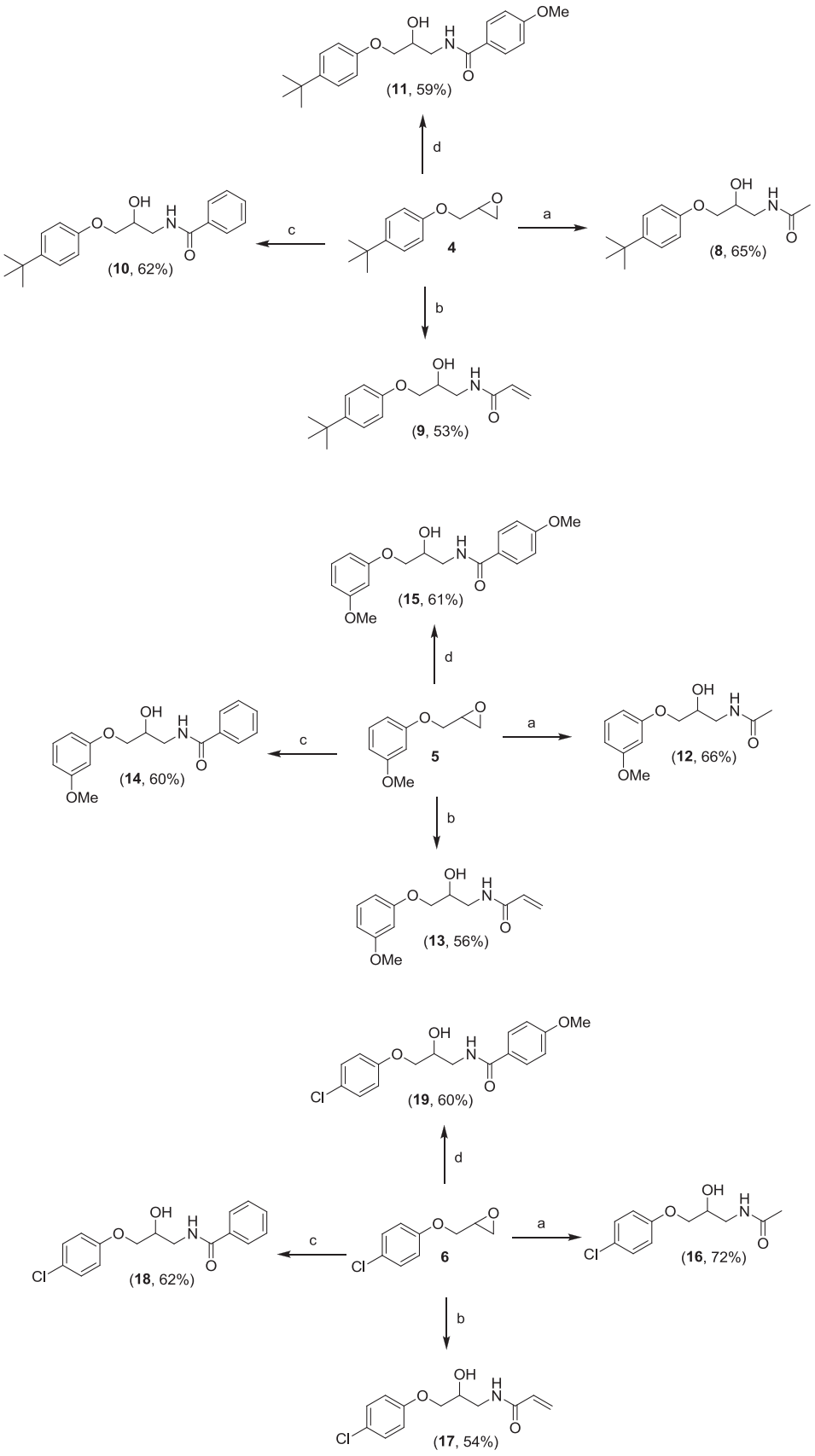
3. Pharmacology study

3.1. Animals used

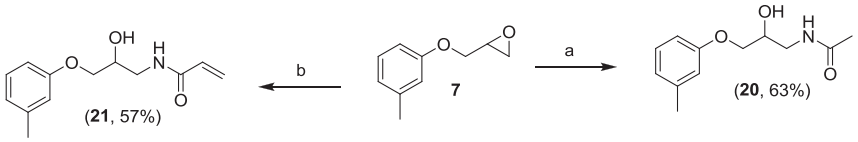
Rats (Charles foster strain, male, adult, body weight 200–225 g) were kept in a room with controlled temperature (25–26 °C), humidity (60–80%) and12/12 h light/dark cycle (light on from 8.00 A.M. to 8.00 P.M.) under hygienic conditions. Animals, which were acclimatized for one week before starting the experiment, had free access to the normal diet and water.

3.2. Lipid lowering and post heparin lipolytic activity

Rats were divided into groups, control, triton-induced, triton + compound (**2**,**3** and **8**–**21**) and Gemfibrozil (Gem) (100 mg/kg) treated groups containing six rats in each group. In this experiment of 18 h, hyperlipidemia was developed by administration of triton WR-1339 (Sigma chemical company, St. Louis, MO, USA) at a dose of 400 mg/kg b.w. intraperitoneally to animals of all the groups except the control. These derivatives were macerated with gum acacia (0.2% w/v), suspended in water and fed simultaneously with triton with a dose of 100 mg/kg, p.o. to the animals of treated group and the diet being withdrawn. Animals of control and triton group without treatment with compounds (**2**,**3** and **8**–**21**) were given same amount of gum acacia suspension (vehicle). After 18 h of treatment the animals were anaesthetized with thiopentone solution (50 mg/kg, b.w.) prepared in normal saline and then 1.0 ml blood was withdrawn from retro-orbital sinus using glass capillary in EDTA coated Eppendorf tube (3.0 mg/ml blood). The blood was



Scheme 2. Synthesis of *N*-acylated-1-amino-3-aryloxy-2-propanols **8**–**19**. *Reagents and conditions*: (a) BF3*OEt2 (0.2 mmol), CH_3CN (1 ml), 80 °C, 12 h. (b) BF3*OEt2 (0.2 mmol), CH_2=CHCN (1 °ml), 80 °C, 12 h. (c) BF3*OEt2 (0.2 mmol), C_6H_5CN (1 ml), 80 °C, 12 h. (d) BF3*OEt2 (0.2 mmol), 4-$OCH_3C_6H_5$ (1 ml), 80 °C, 12 h.



Scheme 3. Synthesis of *N*-[2-hydroxy-3-(*m*-tolyloxy)propyl]acetamide (**20**) and *N*-[2-hydroxy-3-(*m*-tolyloxy)-propyl]acrylamide (**21**). Reagents and conditions: (a) BF3*OEt2 (0.2 mmol), CH_3CN (1 ml), 80 °C, 12 h. (b) BF3*OEt2 (0.2 mmol), CH_2=CHCN (1 ml), 80 °C, 12 h.

centrifuged at 4 °C for 10 min and plasma was separated. Plasma was diluted with normal saline (ratio of 1:3) and used for analysis of total cholesterol (TC), triglycerides (TG) and phospholipids (PL) by standard enzymatic methods [23] and post-heparin lipolytic activity (PHLA) were assayed using spectrophotometer and Beckmann auto-analyzer and standard kits purchased from Beckmann Coulter International, USA [24].

3.3. Lipoprotein measurement in blood plasma of triton induced hyperlipidemic rats

Plasma was fractionated into very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) by poly anionic precipitation methods. Plasma and lipoproteins were analyzed for their total cholesterol (TC), phospholipid (PL), and triglyceride (TG) by standard procedures reported earlier [25].

3.4. Lipoprotein lipase activity in liver of triton induced hyperlipidemic rats

Liver was homogenized (10%, w/v) in cold 100 mM phosphate buffer pH 7.2 and used for the assay of total lipolytic activity of lipoprotein lipase (LPL) [24].

3.5. Antioxidant activity (generation of free radicals)

Superoxide anions (O^{-2}) were generated enzymatically by xanthine (160 mM), xanthine oxidase (0.04 U) and nitroblue tetrazolium (320 μM) in absence or presence of compounds (200 μg/ml) in 100 mM phosphate buffer (pH 8.2) [26]. Fractions were sonicated well in phosphate buffer before use. The reaction mixtures were incubated at 37 °C and after 30 min the reaction was stopped by adding 0.5 ml glacial acetic acid. The amount of formazone formed was measured at 560 nm on a spectrophotometer. Percentage inhibition was calculated taking absorption coefficient of formazone as 7.2 × 103 M/cm. In another set of experiment, an effect of compounds on generation of hydroxyl radicals (OH•) was also studied by non-enzymic reactants [27]. Briefly (OH•) were generated in a non-enzymic system comprised of deoxy ribose (2.8 mM), $FeSO_4 \cdot 7H_2O$ (2 mM), sodium ascorbate (2.0 mM) and H_2O_2 (2.8 mM) in 50 μM KH_2PO_4 buffer, pH 7.4 to a final volume of 2.5 ml. The above reaction mixtures in the absence or presence of compounds (200 μg/ml) were incubated at 37 °C for 90 min. Reference samples and reagent blanks were also run simultaneously. Malondialdehyde (MDA) content in both experimental and reference samples were estimated spectrophotometrically by thiobarbituric acid method as mentioned above [23,28].

3.6. LDL oxidation

Serum was separated from the blood of normolipemic donors who were fasted overnight and fractionated into very low-density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) by ultracentrifugation [29]. The lipoproteins preparations were dialyzed against 150 mM NaCl containing EDTA (0.02% w/v) in presence of N_2 gas in cold. The purity of LDL was checked on polyacrylamide gel electrophoresis. LDL (0.71 mg) and $CuCl_2 \cdot 2H_2O$ (10 μM) in the absence or presence of compound 2 in 50 mM phosphate buffer saline (pH 7.4) to a final volume of 1.5 ml, was incubated at 37 °C for 16 h. The level of lipid peroxides in unoxidised LDL, oxidised LDL with Cu^{++} in the absence or presence of compounds was assayed as thiobarbituric acid reactive substances (TBARS). Briefly the reaction mixture contained 0.5 ml SDS (8% w/v), 0.5 ml glacial acetic acid, 1.5 ml TBA (0.8% w/v) was heated in a boiling water bath for one hour. After cooling up to room temperature optical density of reaction mixture was read at 532 nm with respective reagent blank. The level of lipid peroxide as nmol of Malondialdehyde formed was calculated by taking absorption coefficient of MDA as 1.78 × 105 cm^{-1} M^{-1} mg protein.

4. Results and discussion

4.1. Effect of synthesized compounds on blood plasma lipids profile in triton induced hyperlipidemic rat

All the synthesized compounds (**2**,**3** and **8**–**21**) were screened in Triton-induced hyperlipidemic rats [17,30] at dose of 100 mg/kg (Table 1). Compounds **3**, **11** and **13** showed good lipid lowering activity (Table 1). Compound **3** lowered the total cholesterol (TC) by 28%, triglycerides (TG) by 28%, phospholipids (PL) by 26%, reactivation of post heparin lipolytic activity (PHLA) by 17%, compound **11** lowered the TC by 26%, TG by 25% PL by 27%, reactivation of PHLA by 15%, compound **13** lowered the TC by 24%, TG by 23%, PL by 26%, reactivation of PHLA by 6% (Table 1). Marketed drug Gemfibrozil (Gem) lowered the TC by 33%, TG by 31% PL by 35%, reactivation of PHLA by 18% (Table 1). Whereas, compounds **2**, **10**, **19,** and **20** showed moderate antihyperlipidemic activity (Table 1). Compound **2** lowered the TC by 20%, TG by 21%, PL by 22%, and reactivation of PHLA by 12%. Compound **10** lowered the TC by 17%, TG by 16%, PL by 15%, and reactivation of PHLA by 10%. Compound **19** lowered the TC by 14%, TG by 14%, PL by 13%, and reactivation of PHLA by 8%. Compound **20** lowered the TC by 16%, TG by 14%, PL by 14%, and reactivation of PHLA by 6%.

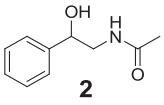
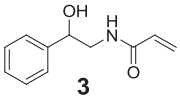
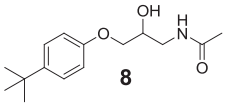
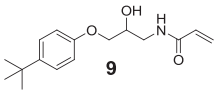
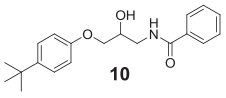
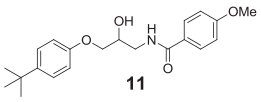
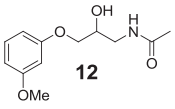
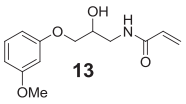
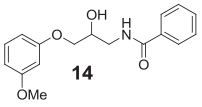
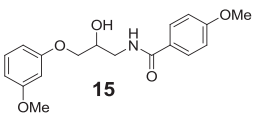
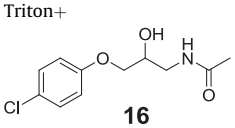
4.2. Effect of compounds *3*, *11* and *13* on lipid lowering at different doses in triton induced hyperlipidemic rat

After the confirmation of most active compounds in primary screening we further, evaluated the dose dependent efficacy of most active compounds **3**, **11** and **13** in triton-induced hyperlipidemic rats at different doses of 50, 100 and 150 mg/kg body weight. The dose dependent activity results are shown in Table 2. Compound **3** lowered the TC by 21%–28%, PL by 22%–27% and TG by 20%–30% followed by increase in PHLA level by 12%–18%. Compound **11** lowered the TC by 18%–29%, PL by 16%–28%, and TG by 18%–27% followed by increase in PHLA level by 11%–16% similarly compound **13** lowered the TC by 14%–25%, PL by 17%–28%, and TG by 16%–26% followed by increase in PHLA level by 10%–15% respectively.

4.3. Effect of compounds *3*, *11* and *13* on plasma lipoprotein lipids in triton induced hyperlipidemic rats

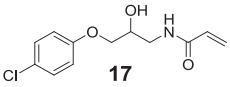
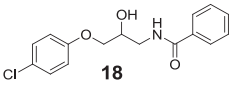
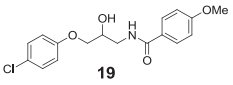
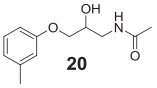
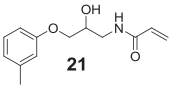
The most active compounds **3**, **11** and **13** were also tested for their effect on plasma lipoprotein lipids. As shown in Fig. 2, the analysis of

Table 1
Percentage (%) change of plasma lipids with the treatment of compounds in Triton-induced hyperlipidemic rats at dose of 100 mg/kg body weight.

Animal groups	Lipids profile			PHLA (nmol of free fatty acids formed/h/ml of plasma)
	TC (mg/dl)	PL (mg/dl)	TG (mg/dl)	
Control	78.53 ± 5.13	82.64 ± 4.71	79.43 ± 6.08	18.86 ± 1.37
Triton	244.27 ± 16.84^{C} (+3.110 Fold)	269.23 ± 19.82^{C} (+3.257 Fold)	239.38 ± 16.38^{C} (+3.013 Fold)	11.59 ± 0.93^{C} (−38.54%)
Triton+  2	195.41 ± 12.33** (−20%)	212.69 ± 16.36** (−21%)	189.11 ± 14.28** (−21%)	12.98 ± 0.93* (+12%)
Triton+  3	175.87 ± 10.56*** (−28%)	199.23 ± 13.78*** (−26%)	172.35 ± 11.99*** (−28%)	13.56 ± 1.18* (+17%)
Triton+  8	219.84 ± 17.26* (−10%)	239.61 ± 13.67* (−11%)	208.26 ± 18.61* (−13)	12.05 ± 0.73^{NS} (+4%)
Triton+  9	217.40 ± 14.83* (−11%)	242.30 ± 15.48* (−10%)	210.65 ± 12.96* (−12)	13.32 ± 1.2^{NS} (+4%)
Triton+  10	202.74 ± 15.91* (−17%)	226.15 ± 14.26* (−16%)	203.47 ± 18.21* (−15)	12.74 ± 0.91* (+10%)
Triton+  11	180.75 ± 13.49*** (−26%)	196.53 ± 16.11*** (−27%)	179.53 ± 13.73*** (−25)	11.93 ± 0.52* (+15%)
Triton+  12	212.51 ± 18.27* (−13%)	242.30 ± 17.91* (−10%)	210.65 ± 14.52* (−12)	12.28 ± 0.88^{NS} (+6%)
Triton+  13	185.64 ± 11.63*** (−24%)	199.23 ± 16.19*** (−26%)	184.32 ± 11.85*** (−23)	13.21 ± 1.11* (+14%)
Triton+  14	217.40 ± 16.62* (−11%)	242.30 ± 21.68* (−10%)	215.44 ± 17.33* (−10)	12.16 ± 0.63^{NS} (+5%)
Triton+  15	222.28 ± 29.35^{NS} (−9%)	247.69 ± 15.82^{NS} (−8%)	217.83 ± 13.29^{NS} (−9)	11.93 ± 0.71^{NS} (+3%)
Triton+  16	224.72 ± 18.69^{NS} (−8%)	253.07 ± 19.47^{NS} (−6%)	220.22 ± 18.46^{NS} (−8)	12.63 ± 0.66^{NS} (+3%)

(*continued on next page*)

Table 1 (*continued*)

Animal groups	Lipids profile			PHLA (nmol of free fatty acids formed/h/ml of plasma)
	TC (mg/dl)	PL (mg/dl)	TG (mg/dl)	
Triton+  **17**	214.95 ± 17.32* (−12%)	242.30 ± 17.83* (−10%)	213.04 ± 17.83* (−11)	11.93 ± 0.79^{NS} (+9%)
Triton+  **18**	227.17 ± 12.87^{NS} (−7%)	255.76 ± 22.31^{NS} (−5%)	220.22 ± 15.39^{NS} (−8)	12.51 ± 0.96^{NS} (+3%)
Triton+  **19**	210.07 ± 14.63* (−14%)	231.53 ± 18.72* (−14%)	208.26 ± 16.26* (−13)	13.67 ± 0.51^{NS} (+8%)
Triton+  **20**	205.18 ± 13.81* (−16%)	231.53 ± 18.39* (−14%)	205.86 ± 17.38* (−14%)	12.28 ± 0.82^{NS} (+6%)
Triton+  **21**	214.95 ± 18.92* (−12%)	242.30 ± 12.79* (−10%)	208.26 ± 18.34* (−13%)	12.05 ± 0.77^{NS} (+4%)
Triton + Gemfibrozil	163.66 ± 11.38*** (−33%)	185.76 ± 11.66*** (−31%)	155.59 ± 10.72*** (−35)	13.67 ± 0.51* (+18%)

Each parameter represents pooled data from 6 rats/group and values are expressed as mean ± S.D. $^{c}P < 0.001$, Triton treated group compared with control group and $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ Triton plus compounds groups compared with Triton treated group only. NOTE: ^{NS} (non significant) and F (Fold change over control group).

hyperlipidemic plasma of triton administered rats showed marked increase in the level of lipoprotein TG and these effects were pronounced for VLDL-TG and LDL-TG followed by a decrease in HDL-TG as compared to control rats. Interestingly, compounds **3**, **11** and **13**, significantly reversed the levels of VLDL-TG, LDL-TG and HDL-TG, the complete lipid profile results are shown in Fig. 2.

4.4. Effect of compounds *3*, *11* and *13* on hepatic-LPL activity in triton induced hyperlipidemic rats

Further the compounds **3**, **11** and **13** were studied for hepatic-LPL activity in triton induced hyperlipidemic rats. Administration of triton in rats markedly decreased LPL activity in liver as shown in Fig. 3. After treatment with compounds **3**, **11** and **13** significantly decreased the level of FFA followed by increase in LPL, complete activity results are shown in Fig. 3.

4.5. Antioxidant activity

Recent studies have demonstrated that the generation of large quantities of reactive oxygen species can cause activation of lipid peroxidation, protein modification, which leads to cardiovascular diseases (CVD) [31]. Therefore all the synthesized compounds (**8**–**21**) were screened for their antioxidant activity (Table 3). The compounds **3**, **10**, **11** and **13** exhibited antioxidant activity (Table 3), among them **3**, **11** and **13** are also active in hyperlipidemia studies. A significant decrease in superoxide anions (26%, 27%, 33% and 25%) and hydroxyl radicals (23%, 29%, 35% and 23%) were observed

Table 2
Percentage (%) change of plasma lipids with the treatment of compounds **3**, **11** and **13** in triton-induced hyperlipidemic rats at different doses.

Animal groups	Lipids profile			PHLA (nmol of free fatty acids formed/h/ml of plasma)
	TC (mg/dl)	PL (mg/dl)	TG (mg/dl)	
Control	83.26 ± 5.82	80.19 ± 6.31	79.68 ± 4.83	20.03 ± 1.61
Triton	263.33 ± 20.08^{c} (+3.16 Fold)	251.69 ± 16.59^{c} (+3.13Fold)	248.92 ± 18.23^{c} (+3.12Fold)	13.11 ± 1.22^{c} (−34.54%)
Triton + 3				
50 mg/kg	208.03 ± 13.36** (−21%)	196.31 ± 11.83** (−22%)	199.13 ± 13.61** (−20%)	14.68 ± 1.08* (+12%)
100 mg/kg	189.59 ± 11.23*** (−28%)	186.25 ± 13.66*** (−26%)	179.22 ± 11.76*** (−28%)	15.33 ± 1.14* (+17%)
150 mg/kg	189.03 ± 15.44***,# (−28%)	183.73 ± 15.73***,# (−27%)	174.24 ± 14.59***,# (−30%)	15.46 ± 1.12*,# (+18%)
Triton + 11				
50 mg/kg	215.93 ± 16.22* (−18%)	211.41 ± 13.38* (−16%)	204.11 ± 14.16* (−18%)	14.55 ± 1.26* (+11%)
100 mg/kg	194.86 ± 14.31*** (−26%)	183.73 ± 12.49*** (−27%)	186.69 ± 12.27*** (−25%)	15.05 ± 1.20* (+15%)
150 mg/kg	186.96 ± 11.86***,# (−29%)	181.21 ± 13.92***,# (−28%)	181.71 ± 13.28***,# (−27%)	15.20 ± 1.09*,# (+16%)
Triton + 13				
50 mg/kg	226.46 ± 15.88* (−14%)	208.90 ± 15.64* (−17%)	209.09 ± 12.82* (−16%)	14.42 ± 1.28* (+10%)
100 mg/kg	200.13 ± 16.19*** (−24%)	186.25 ± 14.38*** (−26%)	191.66 ± 15.22*** (−23%)	14.94 ± 1.21* (+14%)
150 mg/kg	197.49 ± 13.21***,# (−25%)	181.16 ± 15.18***,# (−28%)	184.20 ± 14.46***,# (−26%)	15.07 ± 1.33*,# (+15%)

Each parameter represents pooled data from 6 rats/group and values are expressed as mean ± S.D. $^{c}P < 0.001$, Triton treated group compared with control group and $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ Triton plus compounds groups compared with Triton treated group only. NOTE: $^{\#}$ non significant between 100 and 150 mg/kg doses in treated groups of compounds; F (Fold change over control group).

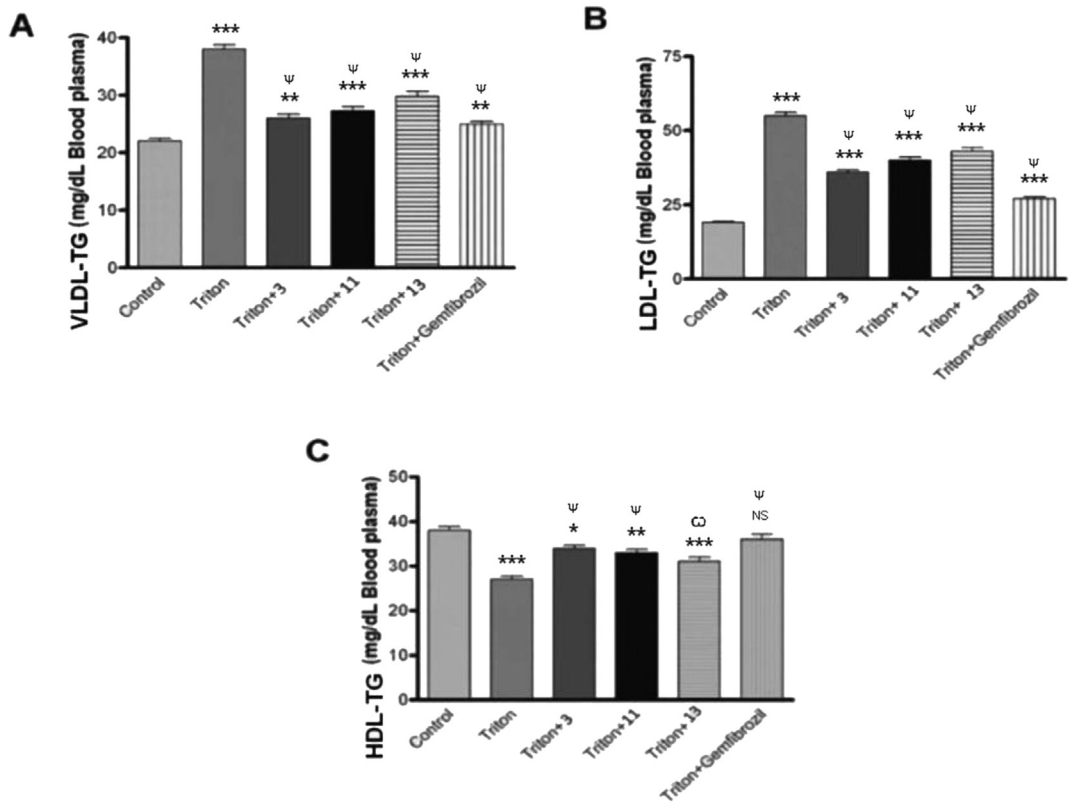


Fig. 2. Effect of compounds **3**, **11** and **13** on lipoprotein metabolism in triton induced hyperlipidemic rats. Blood was drawn after 18 h of hyperlipidemia was developed by administration of triton WR-1339 with and without compounds **3**, **11** and **13** and gemfibrozil (100 mg/kg). Compounds **3**, **11** and **13** and gemfibrozil (Gem) improve lipoprotein TG level in triton induced hyperlipidemic rats. Values are expressed as the mean ± SD ($n = 6$). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; ^{NS} (non significant) compared to triton treated only and $^{\omega}P < 0.01$; $^{\psi}P < 0.001$ comparison triton and triton plus compound treated groups.

respectively by compounds **3**, **10**, **11** and **13**. Furthermore, compounds **3**, **10**, **11** and **13** at 200 μg/ml reduced 25%, 26%, 34% and 23% of the microsomal lipid per-oxidation respectively.

4.6. *Effect of compounds **3**, **10**, **11** and **13** on LDL oxidation*

Aerobic oxidation of LDL even in the absence of metal ions caused formation of TBARS (nmol MDA/mg protein), which were increased by 10–15 folds in presence of Cu^{+2}. Compounds **3**, **10**, **11** and **13** at 200 μg/ml concentrations in above reaction mixture protected LDL against oxidative changes (Fig. 4).

5. Conclusion

In conclusion a new series of *N*-acyl-1-amino-2-alcohols (*N*-acrylated-1-amino-2-phenylethanol, **3** and *N*-acylated-1-amino-3-aryloxypropanols, **8**–**21**) have been synthesized in one step *via* Ritter reaction on the basis of natural product lead i.e. aegeline and evaluated their antihyperlipidemic, LDL-oxidation and antioxidant activity. From this series, compounds **3**, **11** and **13** are turned out to be active in antihyperlipidemic studies and also exhibited LDL-oxidation and antioxidant activity. Further work is in progress in our laboratory for lead optimization to develop a potent anti-hyperlipidemic agent.

6. Experimental protocols

6.1. *General materials and instrumentations*

All reagents were purchased from commercial suppliers and used without further purification. IR spectra of the compounds were recorded on Perkin–Elmer AC-1 spectrometer. ^{1}H NMR and ^{13}C spectra were run on Bruker Advance DPX 300 MHz spectrometer in $CDCl_3$ and TMS was used as internal standard. ESI mass spectra were recorded on JEOL SX 102/DA-6000. Silica gel 60–120 mesh was used as stationary phase to isolate the compounds. Melting points were uncorrected and were recorded on a Buchi B-54 melting point apparatus.

6.2. *Synthesis*

6.2.1. *General procedure for the preparation of N-acyl-1-amino-2-alcohols (**2**–**3** & **8**–**21**)*

To a stirred solution of the corresponding epoxide **1** or oxiranes **4**–**7** (0.2 mmol) in the corresponding nitrile (1 ml) was added BF3*OEt2 (0.025 ml, 0.2 mmol) at room temperature. After that the mixture was stirred at 80 °C for 12 h. An aqueous saturated solution of sodium bicarbonate (5 ml) was added and the mixture was stirred at room temperature for 5 min. Then, the aqueous phase was extracted with ethyl acetate (3 × 5 ml), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. Column chromatography on silica gel (60–120 mesh) using chloroform/methanol (10:1) as eluent provided the desired compounds **2**–**3** and **8**–**21**.

*6.2.1.1. N-(2-Hydroxy-2-phenylethyl)acetamide (**2**).* White solid; m.p.: 125–127 °C (lit. [32] m.p. 125–126 °C); IR (KBr): ν_{max} 3301, 3082, 1650, 1548, 1296 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43–7.33 (m, 5H), 5.29 (t, $J = 4.1$ Hz, 1H), 3.89–3.85 (m, 1H), 3.56–3.52 (m, 1H), 1.88 (s, 3H); ^{13}C NMR (75 MHz): δ 173.2 (C), 143.1 (C), 128.6 (2CH), 127.2 (2CH), 126.5 (CH), 72.3 (CH), 46.1 (CH_2), 23.7 (CH_3); MS (ESI): $m/z = 180.1$ $(M+H)^+$, 162.1 $(M\text{-}H_2O+H)^+$.

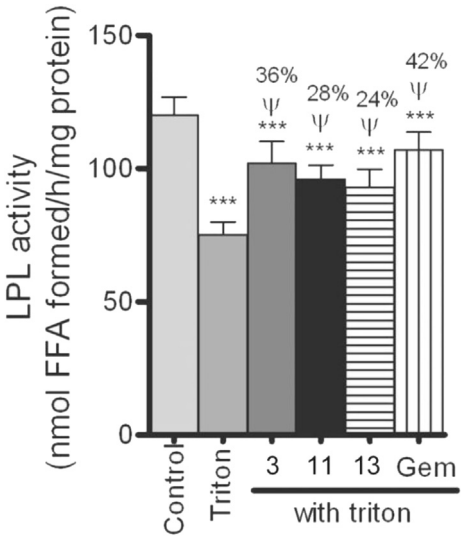


Fig. 3. Compounds **3**, **11** and **13** at dose of 100 mg/kg, re-activate hepatic LPL activity by 36%, 28% and 24% in triton induced hyperlipidemic rats. Each parameter represents pooled data from 6 rats/group and values are expressed as mean ± S.D. $^{***}P < 0.001$ between control and triton, triton plus compound treated rats groups gemfibrozil (100 mg/kg) taken as standard drug. $^{\psi}P < 0.001$ between triton and triton plus compound treated rats groups gemfibrozil (Gem).

6.2.1.2. N-(2-Hydroxy-2-phenylethyl)acrylamide (***3***). Pale yellow oil; IR (Neat): ν_{max} 3310, 3090, 1648, 1615, 1448, 1298 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.41–7.32 (m, 5H), 6.24–6.18 (m, 2H), 5.68–5.60 (m, 1H), 5.26–5.22 (m, 1H), 3.57–3.55 (m, 1H), 3.33–3.31 (m, 1H); ^{13}C NMR (75 MHz): δ 168.0 (C), 143.3 (C), 128.6 (CH), 127.7 (2CH), 127.3 (2CH), 126.7 (CH), 126.3 (CH_2), 72.1 (CH), 44.2 (CH_2); MS (ESI): m/z = 192.1 $(M+H)^+$, 174.1 $(M\text{-}H_2O+H)^+$.

6.2.1.3. N-[3-(4-t-Butylphenoxy)-2-hydroxypropyl]acetamide (***8***). Yellow oil; IR (Neat): ν_{max} 3315, 2955, 1658, 1550, 1480, 1395, 1268 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 4.35–3.98 (m, 2H), 3.85–3.84 (m, 1H), 3.36–3.33 (m, 1H), 3.29–3.26 (m, 1H), 1.86 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (75 MHz): δ 166.0 (C), 156.3 (C), 144.2 (C), 126.5 (2CH), 114.3 (2CH), 71.7 (CH_2), 69.5 (CH), 44.8 (CH_2), 34.3 (C), 31.7 ($3CH_3$), 23.3 (CH_3); MS (ESI): m/z = 266.1 $(M+H)^+$, 248.1 $(M\text{-}H_2O+H)^+$.

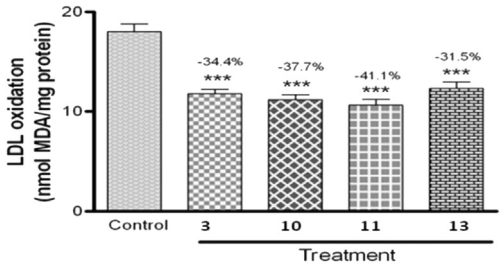


Fig. 4. Compounds **3**, **10**, **11** and **13** reduced the LDL-oxidation at dose of 200 μg/ml in normal donor blood sample. Data expressed as mean ± S.D. $^{***}P < 0.001$compared to treated values with Control.

6.2.1.4. N-[3-(4-t-Butylphenoxy)-2-hydroxypropyl]acrylamide (***9***). Yellow oil; IR (Neat): ν_{max} 3325, 3077, 2970, 2940, 1652, 1590, 1450, 1380 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 6.17–5.99 (m, 2H), 5.66–5.56 (m, 1H), 4.36–4.22 (m, 2H), 4.01–3.95 (m, 1H), 3.38–3.35 (m, 1H), 3.35–3.23 (m, 1H), 1.37 (s, 9H); ^{13}C NMR (75 MHz): δ 170.2 (C), 157.6 (C), 144.5 (C), 131.7 (CH), 127.9 (CH_2), 126.1 (2CH), 114.5 (2CH), 72.9 (CH_2), 67.2 (CH), 43.3 (CH_2), 34.6 (C), 31.5 ($3CH_3$); MS (ESI): m/z = 278.2 $(M+H)^+$, 260.2 $(M\text{-}H_2O+H)^+$.

6.2.1.5. N-[3-(4-t-Butylphenoxy)-2-hydroxypropyl]benzamide (***10***). Yellow oil; IR (Neat): ν_{max} 3322, 3065, 2960, 2915, 2845, 1651, 1610, 1510, 1385 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.01–7.99 (m, 2H), 7.53–7.28 (m, 2H), 5.12–5.03 (m, 1H), 4.35–3.89 (m, 4H), 1.34 (s, 9H); ^{13}C NMR (75 MHz): δ 164.1 (C), 156.3 (C), 144.1 (C), 131.4 (CH), 128.3 (2CH), 128.3 (2CH), 127.6 (C), 126.3 (2CH), 114.2 (2CH), 76.5 (CH_2), 69.4 (CH), 57.4 (CH_2), 34.1 (C), 31.5 ($3CH_3$); MS (ESI): m/z = 328.2 $(M+H)^+$, 310.2 $(M\text{-}H_2O+H)^+$.

6.2.1.6. N-[3-(4-t-Butylphenoxy)-2-hydroxypropyl]-4-methoxybenzamide (***11***). Yellow oil; IR (Neat): ν_{max} 3320, 3070, 2965, 2925, 2855, 2830, 1650, 1605, 1515, 1395 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.90 (d, J = 8.7 Hz, 2H), 7.44 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 4.48–4.20 (m, 2H), 4.05–3.98 (m, 1H), 3.79 (s, 3H), 3.53–3.51 (m, 2H), 1.35 (s, 9H); ^{13}C NMR (75 MHz): δ 168.4 (C), 159.7 (C), 155.5 (C), 143.5 (C), 130.6 (CH), 128.3 (2CH), 126.7 (2CH), 114.4 (2CH), 113.3 (2CH), 72.3 (CH_2), 68.5 (CH), 56.5 (CH_3), 44.4 (CH_2), 34.3 (C), 31.5 ($3CH_3$); MS (ESI): m/z = 358.2 $(M+H)^+$, 340.2 $(M\text{-}H_2O+H)^+$.

Table 3
Effect of compounds on generation of superoxide anions, hydroxyl radicals and lipid-peroxidation.

Series of compounds	Dose (μg/ml)	Superoxide anions (%) (nmol formazone formed/minute)	Hydroxyl radicals (%) (nmol MDA formed/h/mg protein)	Lipid-peroxidation (%) (nmol MDA formed/h/mg protein)
2	200	−17*	−14*	−18*
3	200	−26***	−23***	−25***
8	200	−11*	−13*	−14*
9	200	−14*	−12*	−13*
10	200	−27***	−29***	−26***
11	200	−33***	−35***	−34***
12	200	−17*	−15*	−19*
13	200	−25***	−23***	−23***
14	200	−14*	−17*	−15*
15	200	−17*	−19*	−19*
16	200	−11*	−10*	−12*
17	200	−21**	−20***	−21**
18	200	−16*	−18*	−15*
19	200	−20**	−20**	−22**
20	200	−13*	−10*	−15*
21	200	−16*	−12*	−17*
Standards	200	−43*** (Allopurinol)	−47*** (Mannitol)	−50*** (α-tocopherol)

Each value is mean ± SD of six values, $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ experimental values compared with control values. NOTE: ^{NS} (non significant).

*6.2.1.7. N-[2-Hydroxy-3-(3-methoxyphenoxy)propyl]acetamide (**12**).* Yellow oil; IR (Neat): ν_{max} 3365, 3230, 2815, 1648, 1600, 1570, 1280 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.14–7.09 (m, 1H), 6.48–6.43 (m, 3H), 4.05–3.87 (m, 3H), 3.71 (s, 3H), 3.55–3.51 (m, 1H), 3.33–3.29 (m, 1H), 1.95 (s, 3H); ^{13}C NMR (75 MHz): δ 172.1 (C), 160.7 (C), 159.6 (C), 129.9 (CH), 106.7 (CH), 106.5 (CH), 101.1 (CH), 69.6 (CH_2), 69.2 (CH), 55.2 (CH_3), 42.9 (CH_2), 22.9 (CH_3); MS (ESI): *m/z* = 240.1 $(M+H)^+$, 222.1 $(M-H_2O+H)^+$.

*6.2.1.8. N-[2-Hydroxy-3-(3-methoxyphenoxy)propyl]acrylamide (**13**).* Yellow oil; IR (Neat): ν_{max} 3335, 3080, 2977, 2945, 2830, 1645, 1595, 1450, 1382 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.20–7.14 (m, 1H), 6.55–6.49 (m, 3H), 6.18–6.00 (m, 2H), 5.67–5.57 (m, 1H), 4.10–3.93 (m, 3H), 3.77 (s, 3H), 3.67–3.62 (m, 1H), 3.39–3.34 (m, 1H); ^{13}C NMR (75 MHz): δ 172.3 (C), 160.9 (C), 159.8 (C), 130.1 (CH), 127.5 (CH), 121.3 (CH_2), 106.8 (2CH), 101.3 (CH), 69.8 (CH_2), 69.4 (CH), 55.4 (CH_3), 43.1 (CH_2); MS (ESI): *m/z* = 252.1 $(M+H)^+$, 234.1 $(M-H_2O+H)^+$.

*6.2.1.9. N-[2-Hydroxy-3-(3-methoxyphenoxy)propyl]benzamide (**14**).* Yellow oil; IR (Neat): ν_{max} 3342, 3085, 2960, 2915, 2845, 2830, 1642, 1612, 1512, 1386 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.99–7.96 (m, 2H), 7.48–7.38 (m, 3H), 7.20–7.15 (m, 1H), 6.55–6.51 (m, 3H), 5.06–5.01 (m, 1H), 4.24–3.93 (m, 4H), 3.76 (s, 3H), 3.67–3.54 (m, 1H); ^{13}C NMR (75 MHz): δ 164.1 (C), 160.8 (C), 159.7 (C), 131.1 (CH), 131.3 (CH), 129.9 (CH), 128.3 (CH), 128.2 (CH), 127.4 (CH), 126.8 (CH), 107.0 (CH), 106.6 (CH), 101.2 (CH), 76.8 (CH_2), 69.2 (CH), 57.1 (CH_2), 55.2 (CH_3); MS (ESI): *m/z* = 302.1 $(M+H)^+$, 284.1 $(M-H_2O+H)^+$.

*6.2.1.10. N-[2-Hydroxy-3-(3-methoxyphenoxy)propyl]-4-methoxybenzamide (**15**).* Yellow oil; IR (Neat): ν_{max} 3342, 3090, 2985, 2935, 2855, 2835, 1640, 1605, 1515, 1395 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.04 (d, *J* = 8.6 Hz, 2H), 7.34–7.17 (m, 3H), 7.04–6.85 (m, 2H), 6.55–6.43 (m, 2H), 4.07–4.02 (m, 1H), 3.88 (s, 2H), 3.78 (s, 3H), 3.55 (s, 2H); ^{13}C NMR (75 MHz): δ 173.4 (C), 163.7 (C), 160.8 (C), 159.5 (C), 132.1 (CH), 130.5 (CH), 129.9 (CH), 126.4 (C), 114.4 (CH), 113.6 (CH), 106.8 (CH), 106.6 (CH), 101.1 (CH), 74.2 (CH_2), 69.5 (CH), 55.3 ($2CH_3$), 42.6 (CH_2); MS (ESI): *m/z* = 332.2 $(M+H)^+$, 314.2 $(M-H_2O+H)^+$.

*6.2.1.11. N-[3-(4-Chlorophenoxy)-2-hydroxypropyl]acetamide (**16**).* Yellow oil; IR (Neat): ν_{max} 3355, 3080, 2945, 2870, 2810, 1655, 1600, 1580, 1280, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.22 (d, *J* = 7.3 Hz, 2H), 6.84 (d, *J* = 7.1 Hz, 2H), 4.32–4.18 (m, 2H), 3.90–3.84 (m, 1H), 3.34–3.29 (m, 1H), 3.15–3.11 (m, 1H), 1.89 (s, 3H); ^{13}C NMR (75 MHz): δ 170.6 (C), 157.8 (C), 129.4 (2CH), 125.8 (C), 115.7 ($2CH_2$), 72.3 (CH_2), 68.3 (CH), 42.1 (CH_2), 23.1 (CH_3); MS (ESI): *m/z* = 244.1 $(M+H)^+$, 226.1 $(M-H_2O+H)^+$.

*6.2.1.12. N-[3-(4-Chlorophenoxy)-2-hydroxypropyl]acrylamide (**17**).* Yellow oil; IR (Neat): ν_{max} 3335, 3085, 2978, 2940, 2830, 1649, 1598, 1450, 1382, 1280, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.23 (d, *J* = 7.5 Hz, 2H), 6.79 (d, *J* = 7.4 Hz, 2H), 6.22–6.07 (m, 2H), 5.62–5.58 (m, 1H), 4.41–4.32 (m, 1H), 4.17–4.11 (m, 1H), 3.92–3.86 (m, 1H), 3.28–3.21 (m, 1H), 3.02–2.96 (m, 1H); ^{13}C NMR (75 MHz): δ 167.8 (C), 157.6 (C), 131.1 (CH), 129.4 (2CH), 127.2 (CH_2), 125.3 (C), 115.4 (2CH), 72.3 (CH_2), 68.5 (CH), 43.6 (CH_2); MS (ESI): *m/z* = 256.1 $(M+H)^+$, 238.1 $(M-H_2O+H)^+$.

*6.2.1.13. N-[3-(4-Chlorophenoxy)-2-hydroxypropyl]benzamide (**18**).* Yellow oil; IR (Neat): ν_{max} 3362, 3095, 2965, 2915, 2855, 2830, 1642, 1612, 1510, 1386, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.94 (d, *J* = 7.5 Hz, 2H), 7.47–7.27 (m, 2H), 6.85 (d, *J* = 7.5 Hz, 2H), 5.06–4.97 (m, 1H), 4.22–3.91 (m, 4H); ^{13}C NMR (75 MHz): δ 167.2 (C), 159.6 (C), 134.6 (2CH), 131.3 (2CH), 130.6 (2CH), 129.3 (2CH), 128.3 (2CH), 125.6 (C), 117.9 (2CH), 72.4 (CH_2), 68.1 (CH), 57.4 (CH_2); MS (ESI): *m/z* = 306.1 $(M+H)^+$, 288.1 $(M-H_2O+H)^+$.

*6.2.1.14. N-[3-(4-Chlorophenoxy)-2-hydroxypropyl]-4-methoxybenzamide (**19**).* Yellow oil; IR (Neat): ν_{max} 3344, 3090, 2988, 2930, 2855, 2845, 1640, 1605, 1525, 1395, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.22–7.14 (m, 4H), 6.84 (d, *J* = 8.3 Hz, 2H), 6.74 (d, *J* = 8.2 Hz, 2H), 4.04–3.99 (m, 1H), 3.86–3.82 (m, 2H), 3.78 (s, 3H), 3.53 (s, 2H), 3.45–3.33 (m, 1H); ^{13}C NMR (75 MHz): δ 173.3 (C), 158.8 (C), 157.6 (C), 130.4 (2CH), 129.3 (2CH), 126.6 (C), 125.9 (C), 115.8 (2CH), 114.3 (2CH), 69.9 (CH_2), 69.1 (CH), 55.2 (CH_3), 43.0 (CH_2); MS (ESI): *m/z* = 336.1 $(M+H)^+$, 318.1 $(M-H_2O+H)^+$.

*6.2.1.15. N-[2-Hydroxy-3-(m-tolyloxy)propyl]acetamide (**20**).* Yellow oil; IR (Neat): ν_{max} 3325, 2950, 2855, 1656, 1550, 1483, 1395, 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.25–7.19 (m, 1H), 6.86–6.67 (m, 3H), 4.33–4.16 (m, 2H), 3.95–3.88 (m, 1H), 3.25–3.24 (m, 1H), 3.18–3.14 (m, 1H), 2.39 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (75 MHz): δ 172.1 (C), 159.6 (C), 139.5 (C), 130.0 (CH), 122.1 (CH), 117.5 (CH), 113.5 (CH), 73.2 (CH_2), 69.3 (CH), 43.0 (CH_2), 22.8 (CH_3), 21.3 (CH_3); MS (ESI): *m/z* 224.1 $(M+H)^+$, 206.1 $(M-H_2O+H)^+$.

*6.2.1.16. N-[2-Hydroxy-3-(m-tolyloxy)propyl]acrylamide (**21**).* Yellow oil; IR (Neat): ν_{max} 3335, 3078, 2970, 2945, 2862, 1652, 1590, 1450, 1380 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.20–7.15 (m, 1H), 6.83–6.76 (m, 3H), 6.24–6.06 (m, 2H), 5.61–5.57 (m, 1H), 4.42–4.37 (m, 1H), 4.36–4.07 (m, 1H), 3.78–3.71 (m, 1H), 3.25–3.21 (m, 1H), 3.00–2.95 (m, 1H), 2.25 (s, 3H); ^{13}C NMR (75 MHz): δ 166.3 (C), 158.6 (C), 139.3 (C), 131.2 (CH), 129.9 (CH), 126.5 (CH_2), 121.1 (CH), 115.6 (CH), 113.7 (CH), 72.3 (CH_2), 67.4 (CH), 44.3 (CH_2), 22.1 (CH_3); MS (ESI): *m/z* 236.1 $(M+H)^+$, 218.1 $(M-H_2O+H)^+$.

6.3. Statistical evaluation

Data were analyzed using student's *t*-test and one way ANOVA (Newman–Keuls Multiple Comparison test). The hyperlipidemic groups were compared with control drug treated groups. $P < 0.05$ was considered to be significant.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.04.020.

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