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Preliminary communication

Antidyslipidemic and antioxidative activities of 8-hydroxyquinoline derived novel keto-enamine Schiffs bases

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ABSTRACT

8-Hydroxyquinoline when subjected to Duff reaction resulted in the formation of unexpected 7-methylaminomethylene-8-oxo-7, 8-dihydroquinoline-5-carbaldehyde **2**, which existed in the keto-enamine form, in which the aromaticity of the relevant ring was disrupted, which upon subsequent treatment with various primary amines resulted in its nucleophilic substitution of aliphatic methyl amine. These interesting novel derivatives were evaluated in vitro for their antioxidant and in vivo for their antidyslipidemic and post-heparin lipolytic activities. Compound **6** was found to be most active antidyslipidemic and antioxidative agent in this series, respectively, and thus represent a new class of promising lead.

1. Introduction

Atherosclerosis, the principal contributor to the pathogenesis of myocardial and cerebral infarction, is known to be one of the leading causes of morbidity and mortality worldwide. Elevated plasma concentration of cholesterol, especially low-density lipoprotein (LDL) and triglyceride is recognized as a leading cause in the development of atherosclerosis and coronary heart disease [1–6].

Several drugs are being used in the treatment of dyslipidemia. The drugs can intervene by lowering cholesterol (LDL and total cholesterol) or by lowering triglyceride levels in plasma. Treatment of hyperlipidemia using statins has been used to lower serum levels of cholesterol and triglyceride. Statins such as atorvastatin, lovastatin, fluvastatin, simvastatin and pravastatin are HMG CoA reductase inhibitors which act by inhibiting cholesterol synthesis and upregulate LDA receptors in livers. However, common side effects of Statins are myositis, arthralgias, gastrointestinal upset and elevated liver function tests. Thus, there is a need for the therapeutic benefits of several antidyslipidemic drugs while simultaneously reducing the severe side effects.

The involvement of hydroxyl free radicals ($OH^{\bullet}$) has been found to be a major causative factor for peroxidative damage to lipoproteins which is responsible for inhibition and progression of atherosclerosis in hyperlipidemic subject [7]. Hyperlipidemia may also induce other abnormalities like oxidation of fatty acids, leading to the formation of ketone bodies as well as masking liver and muscle resistance to insulin which initiates the progress of diabetes in patients [8]. Furthermore, due to hyperglycemia, increase in non-enzymic glycosylation occurs, accompanied with glucose oxidation and these reactions being catalyzed by Cu^{2+} and Fe^{2+}, resulting in formation of $O_2^{\bullet}$ and $OH^{\bullet}$ radicals which further accelerates the risk of cardiac diseases in dyslipidemic patients [9]. In order to overcome these ailments, a drug having multifold properties such as antioxidant, anti-diabetic and lipid lowering activities is in great demand.

Towards an ongoing drug discovery programme for developing new antidyslipidemic drugs, wherein we have recently synthesized a series of Schiff bases from dicarbaldehyde of benzocoumarin as potential lipid lowering agents [10]. In continuation of our efforts, we embarked on the synthesis of Schiff bases from 8-hydroxyquinoline as potential antidyslipidemic agents.

The quinoline nucleus occurs in several natural compounds (cinchona alkaloids) and pharmacologically active substances displaying a broad range of biological activity [11]. Quinoline moiety is present in many classes of biologically active compounds. A number of them have been clinically used as antifungal, antibacterial, and antiprotozoic drugs.

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It has found to posses antiasthmatic, anti-inflammatory, and antihypertensive properties as well as antineoplastics [12]. Styrylquinoline derivatives have gained strong attention recently due to their activity as perspective HIV integrase inhibitors [13–16]. The compounds containing 8-hydroxyquinoline pharmacophore seem especially interesting. According to the results reported recently, some new 8-hydroxyquinoline derivatives possess interesting antifungal and herbicidal activities [17].

Thus, we found it interesting to evaluate the Schiff base derivatives of 8-hydroxyquinoline for their antioxidant behaviour and for their antidyslipidemic activity. The structure of our derivatives combines in addition to the biological active quinoline nucleus, possesses amine moiety and extended conjugation that is responsible for its highly fluorescent nature and its antioxidant nature.

2. Chemistry

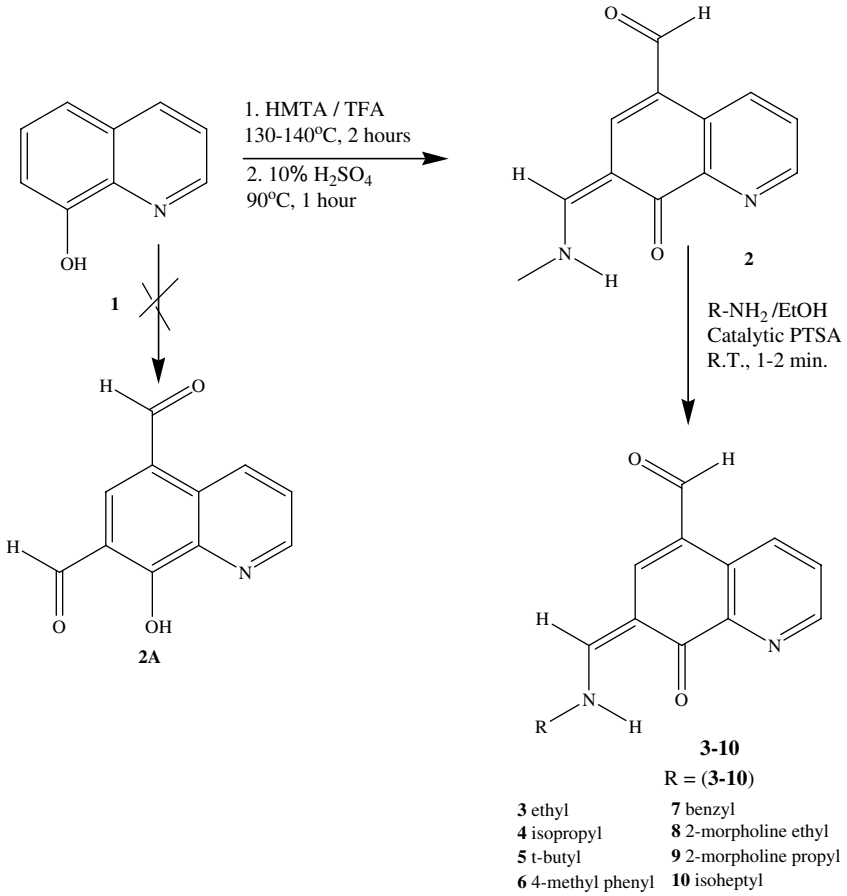
In our efforts to synthesize the quinoline derivatives for potential leads, we started with Duff formylation [18] to get the dialdehydes of 8-hydroxyquinoline **2A**. But surprisingly we got compound **2** (Scheme 1) that on careful examination by 2D NMR spectroscopic experiments such as HSQC and HMBC revealed that the compound was present in the keto-enamine form at room temperature. The ESI-Mass spectrum of **2** gave a molecular ion at m/z 215 $[M+H]^+$indicated the presence of even number of nitrogens. ^{1}H NMR spectrum showed unexpected signals at δ 3.5 and at δ 9.86 suggesting the presence of N–CH_3 group and the free aldehyde, respectively. The ^{13}C NMR spectrum apart from other signals showed two unusual signals at δ 193.76 (CHO) and 181.91 (CO) and this led us to speculate that the product had a keto-enamine structure. In ^{1}H–^{1}H COSY spectrum, the NH proton (δ 13.41) gave correlations with the protons present at δ 3.5 and δ 7.9. Furthermore, In the HMBC spectrum, the enamine proton (δ 7.9) gave long-range correlations with signals at (CO), (C-2), (C-3), and (N–CH_3) (Scheme 2). The final analysis with all the spectral data confirmed the structure as **2**.

It is important to mention that the unlike 7-hydroxyl-4-methylbenzo(*h*)chromene-2-one and 1-hydroxy-napthalene which when subjected to Duff reaction furnished their respective dialdehydes [19] 8-hydroxyquinoline gave only compound **2**.

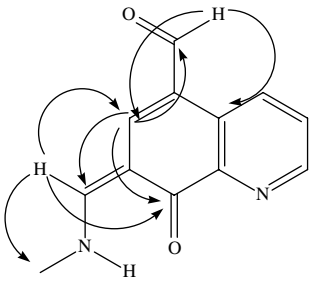
To the best of our knowledge we are first to report this unusual Duff formylation. It is interesting to note that our efforts to synthesize the dialdehyde of 8-hydroxyquinoline failed with changing the, molar ratio, reaction solvent (glacial acetic acid instead of TFA) and also increasing the reaction temperature, also we ended up with the same product when the hydrolysis of the reaction was performed with HCl instead of sulfuric acid. To compound **2** when treated with different amines resulted in the respective Schiffs bases quinoline derivatives (**3**–**10**) through nucleophilic substitution [20]. The most plausible mechanism of this reaction would be nucleophilic attack of the amine at the enamine moiety of the push–pull system, as this site is the most electrophilic. The synthesis (Scheme 1) and detailed NMR characterization of the derivatives are given in Table 1.

2.1. Typical procedure for the synthesis of compound *2*

To a stirred solution of 8-hydroxyquinoline (500 mg, 3.5 mmol) in TFA (2 ml) was added HMT (970 mg, 6.8 mmol) and the reaction mixture maintained at 130–140 °C for 2 h and then hydrolysis was



Scheme 1.



Scheme 2. Selected $^{1}H–^{13}C$ HMBC correlations of **2** in $CDCl_3$.

done by adding 10% H_2SO_4 (2 ml) under stirring with reaction temperature at around 90 °C for 1 h. After completion of reaction (TLC monitoring) the reaction mixture was poured into $NaHCO_3$ solution and extracted with chloroform, dried over Na_2SO_4 and removal of solvent afforded crude compound. The crude product was purified by column chromatography (MeOH:$CHCl_3$, 5:95) over silica gel to provide pure enamine **2** in high yield.

3. General experimental procedure for the synthesis of compounds 3–10

To a mixture of compound **2** (2 mmol) and *p*-toluidine (2 mmol) was added catalytic amount of PTSA, in absolute ethanol (10 ml) and reaction mixture stirred at room temperature for 1–2 min. Completion of reaction was monitored by TLC, the reaction mixture was poured in to aqueous $NaHCO_3$ and extracted with chloroform and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography over silica gel to provide pure enamine **6** in high yield.

4. Biological activity

4.1. 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.

4.2. Lipid lowering and post-heparin lipolytic activity

Rats were divided into 12 Groups control, triton-induced, triton plus **2–10**, and Gemfibrozil (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

Table 1
Spectral data of compounds (**2–10**)

Compound no.	ESIMS (M^{+1})	IR (ν_{max}) ν_{NH} (KBr cm^{-1})	$\nu_{H-C=O}$	^{1}H NMR, 300 MHz	Yield (%)	MP °C
2	215	3441	1649	($CDCl_3$): δ 13.41 (s, 1H, –NH, exchangeable), 9.86 (s, 1H, –CHO), 9.58 (dd, J = 1.6, 8.4 Hz, 1H, C_4–Ar–H), 8.89 (dd, J = 1.6, 4.3 Hz, 1H, C_2–Ar–H), 7.98 (d, J = 11.8 Hz, 1H, C_{11}–H), 7.59–7.56 (m, 2H, C_3–Ar–H, C_6–Ar–H), 3.5 (d, J = 2.4 Hz, 3H, C_{12}–H)	90	215–216
3	229	3427	1638	($CDCl_3$): δ 13.49 (d, J = 1.5 Hz, 1H, –NH, exchangeable), 9.87 (s, 1H, –CHO), 9.60 (d, J = 6.8 Hz, 1H, C_4–Ar–H), 8.90 (s, 1H, C_2–Ar–H), 8.05 (s, 1H, C_{11}–H), 7.60–7.57 (m, 2H, C_3–Ar–H, C_6–Ar–H), 3.79–3.71 (m, 2H, C_{12}–H), 1.49 (t, J = 7.0 Hz, 3H, C_{13}–H)	80	210–211
4	243	3385	1637	($CDCl_3$): δ 13.61 (s, 1H, –NH), exchangeable, 9.79 (s, 1H, –CHO), 9.54 (dd, J = 1.0, 8.3 Hz, 1H, C_4–Ar–H), 8.84 (s, 1H, C_2–Ar–H), 8.06 (d, J = 12.2 Hz, 1H, C_{11}–H), 7.57 (s, 1H, C_6–Ar–H), 7.53 (dd, J = 4.2, 8.4 Hz, 1H, C_3–Ar–H), 3.91–3.87 (m, 1H, C_{12}–H), 1.45 (d, J = 6.5 Hz, 2H, C_{13}–H, C_{14}–H)	85	237–238
5	257	3441	1634	($CDCl_3$): δ 14.09 (s, 1H, –NH, exchangeable), 9.87 (s, 1H, –CHO), 9.59 (dd, J = 1.5, 8.4 Hz, 1H, C_4–Ar–H), 8.89 (d, J = 3.1 Hz, 1H, C_2–Ar–H), 8.1 (d, J = 3.2 Hz, 1H, C_{11}–H), 7.65 (s, 1H, C_6–Ar–H), 7.57 (dd, J = 4.3, 8.5 Hz, 1H, C_3–Ar–H), 1. 56 (s, 9H, C_{13}–H, C_{14}–H, C_{15}–H)	85	234–235
6	291	3423	1629	($CDCl_3$): δ 15.49 (s, 1H, –NH, exchangeable), 9.91 (s, 1H, –CHO), 9.57 (dd, J = 1.0, 8.34 Hz), 8.92 (d, J = 2.9 Hz, 1H, C_4–Ar–H), 8.49 (s, 1H, C_{11}–H), 7.72 (s, 1H, C_6–Ar–H), 7.59 (dd, J = 4.2, 8.5 Hz, 1H, C_3–Ar–H), 7.28 (s, 4H, C_{13}–Ar–H, C_{14}–Ar–H, C_{16}–Ar–H, C_{17}–Ar–H), 2.41 (s, 3H, C_{18}–H)	80	255–256
7	291	3425	1638	($CDCl_3$): δ 13.93 (d, J = 7.6 Hz, 1H, –NH, exchangeable), 9.87 (s, 1H, –CHO), 9.59 (dd, J = 1.4, 8.4 Hz, 1H, C_4–Ar–H), 8.90 (d, J = 2.3 Hz, 1H, C_2–Ar–H), 8.03 (s, 1H, C_{11}–H), 7.61–7.58 (m, 2H, C_3–Ar–H, C_6–Ar–H), 7.46–7.37 (m, 5H, C_{14}–Ar–H, C_{15}–Ar–H, C_{16}–Ar–H, C_{17}–Ar–H, C_{18}–Ar–H), 4.87 (s, 2H, C_{12}–H)	75	Liquid
8	314	3404	1647	($CDCl_3$): 13.19 (s, 1H, –NH, exchangeable), 9.75 (s, 1H, –CHO), 9.49 (dd, J = 1.4, 8.4 Hz, 1H, C_4–Ar–H), 8.79 (d, J = 3.0 Hz, 1H, C_2–Ar–H), 7.94 (s, 1H, C_{11}–H), 7.53 (s, 1H, C_6–Ar–H), 7.53–7.47 (m, 1H, C_3–Ar–H), 3.70–3.63 (m, 6H), 2.88 (s, 2H), 2.80 (s, 2H), 2.68–2.64 (m, 2H)	65	Liquid
9	328	3432	1641	($CDCl_3$): δ 13.39 (s, 1H, –NH, exchangeable), 9.84 (s, 1H, –CHO), 9.56 (dd, J = 1.0, 8.3 Hz, 1H, C_4–Ar–H), 8.86 (s, 1H, C_2–Ar–H), 8.03 (s, 1H, C_{11}–H), 7.56 (m, 2H, C_3–Ar–H, C_6–Ar–H), 3.72 (t, J = 4.3 Hz, 6H), 2.47 (t, J = 7.3 Hz, 6H), 1.94 (t, J = 6.0 Hz, 2H)	65	172–173
10	299	3445	1638	($CDCl_3$): δ 13.68 (s, 1H, –NH, exchangeable), 9.86 (s, 1H, –CHO), 9.58 (dd, J = 1.6, 8.4 Hz, 1H, C_4–Ar–H), 8.87 (dd, J = 1.3, 4.1 Hz, 1H, C_2–Ar–H) 8.03 (d, J = 12.4 Hz, 1H, C_{11}–H), 7.62 (s, 1H, C_6–Ar–H), 7.57 (dd, J = 4.2, 8.4 Hz, 1H, C_3–Ar–H), 3.70 (m, 1H, C_{12}–H), 1.76–1.68 (m, 2H, C_{14}–H), 1.49 (s, 2H, C_{16}–H), 1.46 (s, 3H, C_{16}–H), 1.33–1.3 (m, 6H, C_{15}–H, C_{17}–H), 0.90 (t, J = 6.7 Hz, 3H)	85	Liquid

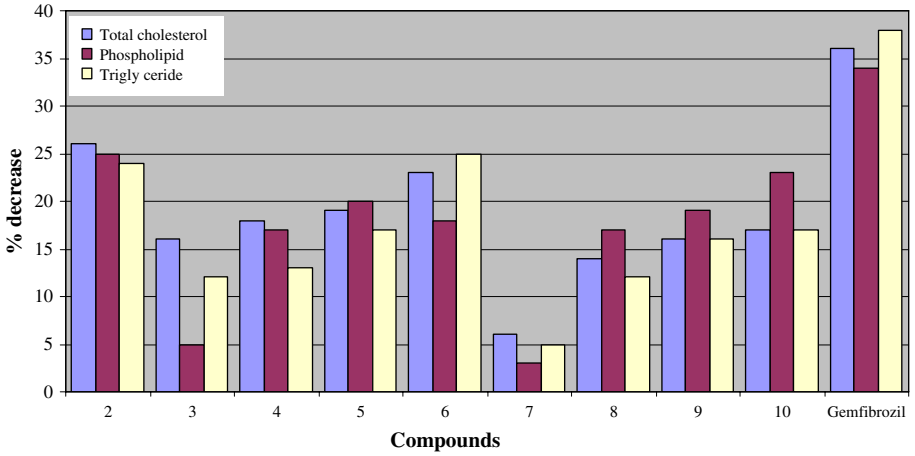


Fig. 1. Showing the lipid lowering activity of different quinoline Schiffs base derivatives (100 mg/kg) in triton treated hyperlipimedic rats. Triton treated group with control and drug treated group compared with triton group (Units – mg/dl for Tc, Pl, and Tg).

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 quinoline compounds 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 centrifuged (at 2500 g) 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 [21] and post-heparin lipolytic activity (PHLA) were assayed (Wing and Robinson, 1968) using spectrophotometer and Beckmann auto-analyzer and standard kits purchased from Beckmann Coulter International, USA.

4.3. Antioxidant activity (generation of free radicals)

Superoxide anions were generated enzymatically [22] by xanthine (160 mM), xanthine oxidase (0.04 U) and nitroblue tetrazolium (320 μM) in the absence or presence of compounds (100 μg/ml) in 100 mM phosphate buffer (pH 8.2). 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 7.2×10^3 M/cm. In another set of experiment, an effect of compounds on generation of hydroxyl radicals ($OH^{\bullet}$) was also studied by non-enzymic reactants [23]. Briefly $OH^{\bullet}$ was 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 mM 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 (100 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 [24].

4.4. Statistical evaluation

Data were analyzed using Student's *t*-test. The hyperlipidemic groups were compared with control drug treated groups. Similarly the generations of oxygen free radicals with different benzocoumarin derivatives were compared with that of their formation without compounds. $P < 0.05$ was considered to be significant.

5. Results and discussion

5.1. Effect of quinoline derivatives on hyperlipidemia and its post-heparin lipolytic activity

Administration of Triton WR-1339 in rats induced marked hyperlipidemia as evidenced by increase in the plasma level of Tc (3.19-fold) Pl (2.76-fold) and Tg (3.12-fold) as compared to control. Triton treated (induced) rats caused inhibition of plasma PHLA (post-heparin lipolytic activity) (28%) as compared to control. Treatment of hyperlipidemic rats with quinoline derivatives at the dose of 100 mg/kg p.o. reversed the plasma levels of lipid with varying extents. Triton WR-1339 acts as surfactant, suppresses the action of lipase and blocks the uptake of lipoproteins from the circulation by extrahepatic tissues resulting an increase in the levels of circulating lipid [25]. These test samples inhibited cholesterol biosynthesis and potentiated the activity of lipolytic

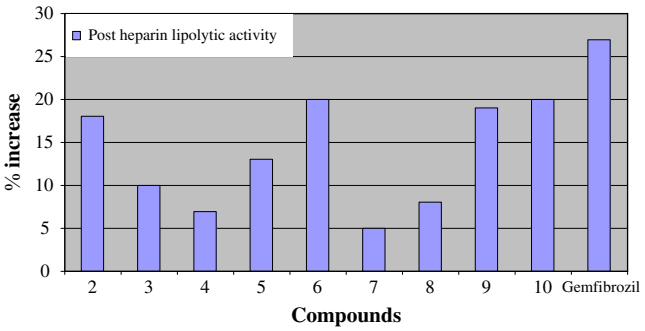


Fig. 2. Showing the post-heparin lipolytic activity of different quinoline Schiffs base derivatives (100 mg/kg) in triton treated hyperlipimedic rats. Triton treated group with control and drug treated group compared with triton group (Unit – nmol free fatty acid formed/h/ml of plasma).

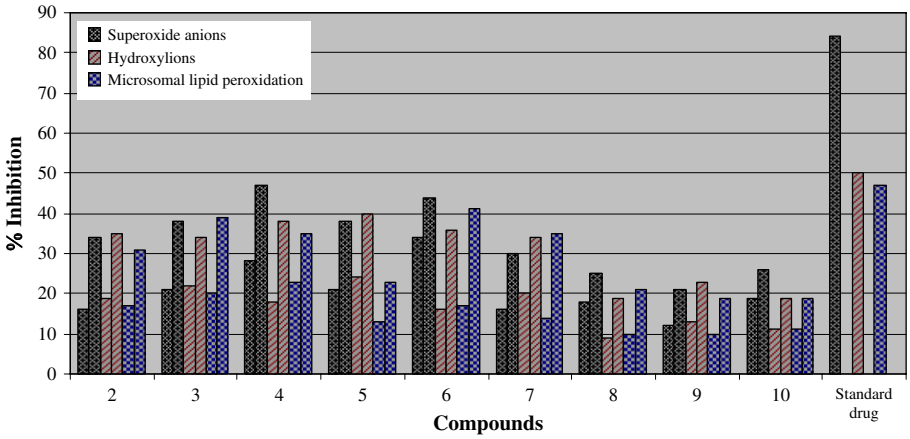


Fig. 3. Showing the effect of quinoline Schiffs base derivatives (100 and 200 μg/ml) on Superoxide ion (*n* mole formazone formed/min), hydroxyl ion (*n* mole MDA formed/h) and lipid peroxidation in microsomes (*n* mole MDA formed/mg protein). (Standard drug for superoxide anions-Alloperinol (20 μg/ml), hydroxyl ions-Manitol and for microsomal lipid peroxidation-α tocopherol (100 μg/ml) was used).

enzymes to early clearance of lipids from circulation in triton-induced hyperlipidemia. Compounds **2** and **6** showed significant decrease in plasma levels of Tc, Pl and Tg by 26, 25, 24%; and 23, 18, 25%, respectively. While compounds **3**–**5**, **8**–**10** showed mild lipid lowering activity. These data compared with standard drug Gemfibrozil at the similar dose of 100 mg/kg showed decrease in plasma levels of Tc, Pl, Tg by 36, 34, 38%, respectively, (Fig. 1). The data in Fig. 2 shows that in triton-induced hyperlipidemica in rats inhibited the post-heparin lipolytic activity (28%) and in case of triton plus drug treated rats suppressed the PHLA activity up to 5–20%, respectively, and in case of standard drug showed 27% activity.

5.2. Effect of quinoline derivatives on oxygen free radical generation in vitro

The scavenging potential of quinoline derivatives at 100 and 200 μg/ml against formation of $O_2^{\bullet}$ and $OH^{\bullet}$ in non-enzymic systems was studied (Fig. 3). Further, the effect of compounds on lipid peroxidation in microsomes was also studied. Compounds **4** and **6** (200 μg/ml) was most potent and showed significant decrease in superoxide anions inhibition by 47 and 44%, hydroxyl radicals inhibition by 38 and 36% and 35 and 41% inhibition in microsomal lipid peroxidation, respectively. The standard drug Alloperinol at 20 μg/ml showed 84% inhibition in superoxide anions. Manitol and α-tocopherol at a dose of 100 μg/ml showed 50 and 47% inhibition of hydroxyl ions and microsomal lipid peroxidation, respectively. While compounds **2**, **3**, **5** and **7** showed moderate activity, compared to **8**–**10**. The properties of these derivatives as antioxidant and scavenger of oxygen free radicals appear to be mediated through radical addition/by electron transfer/or by hydrogen abstraction from compound, like carotenoids wherein by virtue of extended conjugation the compound has the ability to delocalize unpaired electrons.

A closer look at the biological results of the above compounds reveals that compound **6** formed from nucleophilic substitution of **2** with *p*-toluidine was active both in antidyslipidemic and antioxidant assays. The results indicate that Schiff bases formed from substituted primary aromatic amine might act as a lead for further optimization and development showing this dual activity. It will be thus interesting to prepare new analogs of **6** for lead optimization.

In conclusion, a series of novel Schiffs bases derivatives from 8-hydroxyquinoline have been synthesized following an uncommon method of treating compound **2** with various primary amines and evaluated for their antidyslipidemic activity and antioxidative activity. It was found that most of the new analogs were exhibiting significant to moderate activity. Further work, to develop the active compound, as a potential lead is currently underway as these compounds are devoid of cytotoxicity in normal cells, namely vero cell line and primary osteoblast cells. Also, efforts are underway to assess its mode of action and its in vivo efficacy.

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Appendix. Supplementary material

Spectral data of all the compounds associated with this article is available as supplementary data.

Supplementary material associated with this article can also be found in the online version, at doi: 10.1016/j.ejmech.2008.08.004.

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