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Design, synthesis and in vivo screening of some novel quinazoline analogs as anti-hyperlipidemic and hypoglycemic agents

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ABSTRACT

A novel series of substituted quinazoline derivatives were designed, synthesized and evaluated for their hypolipidemic activity in cholesterol induced hyperlipidemic rats. In vivo screening concluded that compounds **A-4**, **C-5** and **C-6** have shown potent antihyperlipidemic activity by decreasing the plasma level of triglycerides (TG), very low density lipoprotein (VLDL), low density lipoprotein (LDL), followed by increase in level of high density lipoprotein (HDL).

In industrialized world the rate of morbidity and mortality is increased due to coronary heart diseases. Triglycerides and cholesterol are major component of lipids circulating in the blood stream.[1,2] In human digestive system the hydrolyzed form of triglycerides are produced, that is, free fatty acid and monoglycerides which reabsorbed by intestine leading to different type of cardiovascular and obesity diseases.[3,4]

The currently prescribed fibrates, such as clofibrate and fenofibrate have been effective ligands of PPARα receptor; specifically involved in the regulation and expression of target genes responsible for lipid and lipoprotein metabolism.[1]The hypolipidemic effects of fibrates are obtained through activation of PPRAα receptor, by lowering the level of TG, LDL and increasing the level of HDL by increasing the transcription of apolipoprotein.[5,6]

The general structure of fibrate analogs comprised of lipophilic tail, acidic pharmacophore and spacer in between.[7] The phenoxy acetic/propanoic acid pharmacophore is frequently coupled with heterocycles for hyperlipidemic activity (Fig. 1). Instigated with all the above facts and in continuation with our efforts towards to form a rational design the heterocycle quinazoline is coupled with phenoxy acetic acid and 2-methyl propanoic acid to form active ligands of fibrates.[8,9]

In the present investigation, designed quinazoline derivatives (Fig. 1) were prepared by the methods that have been outlined in Schemes 1–4. The synthesized derivatives were evaluated for their anti-hyperlipidemic and hypoglycemic activity.

The Scheme 1 consist of synthesis of 2-methyl-2-(4-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)phenoxy)propanoic acid (**A-4**) and 2-(4-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)phenoxy)acetic acid (**A-5**). The first step consist of cyclization of 2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**A-2**) by addition of acetic anhydride to the 2-amino benzoic acid. Then resultant compound was refluxed with 4-amino phenol to give 3-(4-hydroxyphenyl)-2-methylquinazolin-4(3*H*)-one (**A-3**).[10] Finally compounds **A-4** and **A-5** were synthesized by etherification of compound **A-3** by 2-bromo-2-methyl propanoic acid and 2-chloro acetic acid respectively.

Similarly, compounds **B-6**, **B-7**, **C-5**, **C-6**, **D-4** and **D-5** were synthesized as per stated in Schemes 2–4 and their structures have been verified by IR, ^{1}H NMR, ^{13}C NMR and LC–MS spectroscopy. The purity of these compounds was ascertained by TLC and spectral analysis. The spectral data are provided in Experimental section.

The hypoglycemic and hypolipidemic activity of the synthesized compounds was studied in the high fat diet induced hyperlipidemic Sprague–Dawley rats for 30 days by oral administration of the drug and compounds.[3,6] The in vivo profile of the synthesized compounds was compared with reference drug fenofibrate at 250 mg/kg dose.

The body weight as well as hypoglycemic activity of synthesized compounds was summarized Table 1. The compounds **C5** (83.0 mg/dl) and **C6** (85.3 mg/dl) showed most potent hypoglycemic effect as compare to standard (86.41 mg/dl) whereas compounds **A4** and **A5** showed moderate activity.

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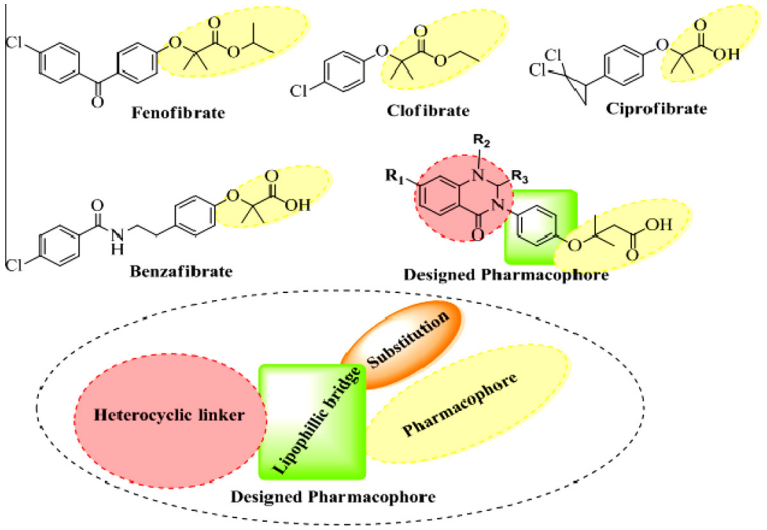
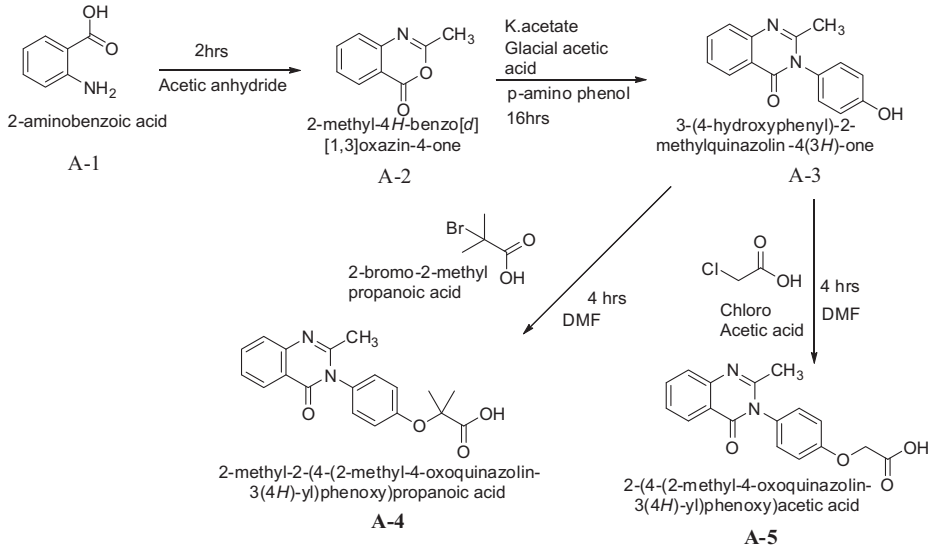


Figure 1. Designed pharmacophore for quinazoline fibrates.



Scheme 1. Synthesis of designed compounds **A4** and **A5**.

The hypolipidemic activity of compounds were tabulated in Table 2. The total lipid profile, that is, cholesterol, TG, VLDL, LDL, HDL, CHO/HDL were shown that all the compounds possess good to moderate hypolipidemic activity. Experimental values of blood lipids reduction of compounds **A5**, **C5** and **C6** were more potent as compare to fenofibrate.

The structure activity relationship showed that the compounds containing 7-hydroxy 2-methyl quinazolinone moiety (compounds **C5** and **C6**) were shown better activity than other synthesized compounds whereas 2-methyl quinazolinone derivatives (compounds **A4** and **A5**) showed moderate to potent hypolipidemic activity. The compounds containing 1-phenyl 2-methyl quinazolinone and 2-phenyl quinazolinone nucleus was shown lesser hypoglycemic and hypolipidemic activity. Compound **B6** demonstrated more emphasis on hypocholesterolemic rather than hypotriglyceridemic activity in assessing the hypolipidemic activity of test compounds.

In this study we synthesized the novel quinazoline derivatives containing acetic acid and 2-methyl propanoic acid as pharmacophore for their hypoglycemic and hypolipidemic activity. Hence the present series could be developed as a novel class of hypolipidemic and hypoglycemic agents.