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NOVEL PHENOXAZINONES AS POTENT AGONIST OF PPAR-α: DESIGN, SYNTHESIS, MOLECULAR DOCKING AND IN VIVO STUDIES

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Background: Treatment of dyslipidemia impacts directly on the cardiovascular health. The use of statin, a 3-hydroxy-3-methylglutaryl coenzyme, a reductase inhibitor for the treatment of dyslipidemia has been associated with dose limiting hepatoxicity, myototoxicity and tolerability due to myalgias thereby necessitating the synthesis of new drug candidates for the treatment of lipid disorder.

Methods: The reaction of appropriate benzenesulphonamide with substituted phenoxazinone in the presence of phenylboronic acid gave the targeted compounds. The molecular docking study were carried out using autodock tool against peroxisome proliferator activated receptor alpha. The *in vivo* lipid profiles were assayed using conventional methods. The kidney and liver function test were carried out to assess the effect of the derivatives on the organs. The LD50 of the most active derivatives were determined using mice.

Results: The targeted compounds were successfully synthesized in excellent yields and characterized using spectroscopic techniques. The results of the molecular docking experiment showed that they were good stimulant of peroxisome proliferator activated receptor alpha. Compound 9f showed activity at K_i of 2.8 nM and 12.6 kcal/mol of binding energy. All the compounds tested reduced triglyceride, total cholesterol, low density lipoprotein cholesterol and very low density lipoprotein cholesterol level in the mice model. Some of the reported compounds also increased high density lipoprotein cholesterol level in the mice. The compounds did not have appreciable effect on the kidney and liver of the mice used. The LD_{50} showed that the novel compounds have improved toxicity profile.

Conclusion: The synthesis of 15 new derivatives of carboxamides bearing phenoxazinone and sulphonamide were successful. The compounds possessed comparable activity to gemfibrozil. The reported compounds had better toxicity profile than gemfibrozil and could serve as a replacement for the statins and fibrate class of lipid agents.

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