Summary AND conclusionS

4 SUMMARY AND CONCLUSION

4.1 Selective PPARα agonist

- As a part of the efforts towards developing selective PPAR*α* agonists, a novel series of 1,3-dioxane-*r*-2-carboxylic acids (**11)** was identified by replacing the lipophilic oxazole group of compound **I** (PPAR*α*/γ dual agonist) by phenyl oxime group. Compound **11c** was found to be a potent PPAR*α* agonist with excellent antihyperglycemic and antihyperlipidemic effects (*in vivo*) due to its superior oral bioavailability.
- In continuation of the efforts towards identifying PPAR*α* selective agonist, a series of indole containing 1,3-dioxane-*r*-2-carboxylic acid derivatives (**17**) were designed and synthesized. Compound **17a** exhibited a potent PPAR*α* agonistic activity. This compound was found to be effective in reducing serum triglycerides and glucose (*in vivo*). The docking studies results of **11c** and **17a** also support the hypothesis, in terms of molecular conformations and hydrogen bond interactions.
- Having identified a potent PPAR*α* agonist, design and synthesize of a partial PPAR*α* selective agonist were undertaken. To achiive this goal three series of 1,3-dioxane-*r*-2-carboxylic acid derivatives containing substituted oximes (**22** and **27**) and olefines (**33**) as lipophilic tails were synthesized and evaluated for their PPAR agonistic activity. Compounds from the series exhibited partial to potent PPAR*α* agonistic activity. Compound **27a** exhibited potent antihyperglycemic and lipid lowering activity in animal model, in spite of partial and weak PPAR*α* agonistic activity, which was subsequently correleated to its high bioavailability. Molecular docking experiment showed critical hydrogen bond interaction of this compound with PPARα receptor and support the *in vitro* activity results.

4.2 PPARα/γ dual agonist

- In order to identify a balanced PPAR*α*/γ dual agonist, four series of compounds were designed and synthesized with different pharmacophores

as potent PPAR*α*/γ dual activators with *ortho* fluoro benzyl group as cyclic tail and naphthalene as central aromaic system. Our investigation led to the identification of compound **70**, as balanced PPAR*α*/γ dual agonist with potent agonistic activity in cell based transactivation assay. Preclinically, compound **70** exhibited a remarkable hypolipidemic and glucose lowering activity in animal models. The results of molecular docking studies conducted on compound **70** also support the hypothesis in terms of molecular conformations and hydrogen bond interactions. Balanced activities (*in vitro*) of compound **70** may render it as a pharmacological tool in elucidating the complex roles of PPAR*α*/γ dual agonists.

- In conclusion, chemical tools useful to modulate subtype selectivity of ligands towards PPARs were investigated. Using this strategy PPAR*α* and PPAR*α*/γ dual agonists were designed, synthesized and evaluated for their *in vitro* and *in vivo* activities.