Summary & Conclusions

"We must not forget that when radium was discovered no one knew that it would prove useful in hospitals. The work was one of pure science. And this is a proof that scientific work must not be considered from the point of view of the direct usefulness of it. It must be done for itself, for the beauty of science, and then there is always the chance that a scientific discovery may become like the radium a benefit for humanity"

Marie Curie

4. SUMMARY & CONCLUSIONS

4.1. PPARα/γ dual agonists

- While starting the present journey, it was envisioned to design a pharmacophore by incorporating structural features of fibric acid and glitazones in a single chemotype. The said journey was started with designing 1,3-dioxane-2-carboxylic acid that resembles glitazones structurally and possesses free carboxylic function resembling fibric acid pattern followed by synthesis of the compounds containing this pharmacophore and oxazole moiety as lipophilic tail. These compounds were evaluated for their *in vitro* PPAR agonistic potential and *in vivo* hypoglycemic and hypolipidemic efficacy in animal models. Compounds of this series exhibited PPARα/γ dual agonism, thus establishing the evidence for our hypothesis of combining the structural features of fibric acid and glitazone in a single chemotype in order to develop novel pharmacophore of PPARα/γ dual agonists. Compound **15b** is one such PPARα/γ dual agonist that could demonstrate the viability of this approach. Compound **15b** exhibited potent hypoglycemic, hypolipidemic and insulin sensitizing effects in *db/db* mice and Zucker *fa/fa* rats. Thus we discovered a series of novel 1,3-dioxane carboxylic acid derivatives to aid in the characterization of PPARα/γ dual agonists
- Having our hypothesis validated, we then designed and synthesized compounds **18** by modifying the lipophilic tail portion to explore this novel 1,3-dioxane carboxylic acid pharmacophore further. The objective of studying this series is to replace the oxazole group of previous series (compounds **15**) in order to develop novel PPARα/γ dual agonists with distinct biological and safety profiles. Compound **18a** was found to be a weak PPAR activator but exhibited potent hypolipidemic and hypoglycemic activities *in vivo* due to superior

bioavailability whereas **18f** exhibited potent *in vitro* and *in vivo* effects. The results of molecular docking studies conducted on **15b**, **18a** and **18f** also support our hypothesis in terms of molecular conformations and hydrogen bond interactions. It is hoped that the PPARα/γ dual activation strategy will provide a comprehensive treatment for type 2 diabetes and dyslipidemia.

4.2. Selective PPARα agonists

- Once we had PPARα/γ dual agonists in hand, we then initiated our efforts to design and synthesize selective PPARα agonists. To achieve this goal a series of 1,3-dioxane-2-carboxylic acid derivatives containing alkyl chain tether and substituted phenyl group as a lipophilic tail have been synthesized and evaluated for their PPAR agonistic activity. Although these compounds were found to be weak activators of PPARα *in vitro*, **32b** exhibited potent *anti*-hyperglycemic and lipid lowering activity in animal models. It was a surprise for us initially when the compound **32b** exerted high *in vivo* efficacy in spite of its poor *in vitro* potency, which was subsequently correlated to its high bioavailability. The role of pharmacokinetics of a molecule in its therapeutic effects is well demonstrated with the aid of this compound.
- In an effort to develop chemical tools for the modulation of subtype selectivity of PPAR agonits, we designed and synthesized few compounds with chemical variations in the spacer region of Imiglitazar and Muraglitazar. To execute this, the phenylene group in these compounds was replaced with a polymethylene group. From this series, compound **42a** was found to be highly potent and selective PPARα agonist. A novel hydrogen-bonding interaction was observed in molecular docking study of this compound in PPARα active site, which may be responsible for the potency and selectivity of this compound. Though the high potency of this compound did not translate into *in vivo*

efficacy, we could establish the role of spacer (or tether) portion of ligands in modulating the sub type selectivity towards PPARs.

- A series of bis oximinoalkanoic acid derivatives were designed and synthesized as selective PPARα agonists by replacing the oxazole ring in **42b** with flexible oximino group in the lipophilic tail part. Selected compounds **48d** and **48m** showed excellent potency and high selectivity towards PPARα *in vitro*. These compounds are found effective in reducing serum triglycerides (TG) *in vivo*.
- In conclusion, we have designed a novel pharmacophore and synthesized compounds comprising this pharmacophore as potent and efficacious dual PPARα/γ agonists. We have also investigated chemical tools useful in modulating sub type selectivity of ligands towards PPARs. Using this strategy we have designed selective PPARα agonists and evaluated their *in vitro* and *in vivo* activites.