Summary and conclusions

4 Summary and Conclusions

4.1 Novel GPR 119 Agonists

- In order to achieve the goal of identifying novel GPR 119 agonists, the design and synthesis of three different series of compounds was undertaken. All the final compounds were characterized and were tested for *in-vitro* GPR 119 agonistic activity. The *in-vivo* studies, pharmacokinetic studies as well as molecular modelling studies were carried out for the compounds having promising *in-vitro* activity.

- A novel series of *para*-benzylidene thiazolidinedione derivatives (**16 a-l, 17 a-l)** was prepared by replacing the polar head methyl pyridine group of Arena compound (**I)** (a GPR 119 agonist) in search of NCEs with improved activity. Compounds **16c and 17c** were found to be potent GPR 119 agonists with an excellent glucose lowering effects in *in-vivo* studies and with superior oral bioavailability. The role of pharmacokinetics of a molecule in its therapeutic effects is well demonstrated with the aid of these compounds.

- From the series of *meta*-benzylidene thiazolidinedione derivatives (**23 a-n and 24 a-m**), compound **23c** exhibited exceptional GPR 119 agonistic activity and an excellent exposure in the pharmacokinetic parameters. This compound was found to have an effective serum glucose lowering activity in *in-vivo* experiments (C57 and db/db mice). The results of the docking studies conducted on **23c** also supported the hypothesis in terms of the π-π interactions and the van der Waals interactions.

- Having identified a potent GPR 119 agonist, optimization of *meta*-benzylidene thiazolidinedione derivatives (**23c**, **23i** and **23l**) was undertaken. Thus, N-substituted benzylidene thiazolidinedione analogs were designed, synthesized and evaluated for their GPR 119 agonistic activity. The compounds from this series exhibited partial potent GPR 119 agonistic activity.

- Based on the overall profile, the compound **23c** was subjected to further detailed biological studies.
  - *in-vitro* study of compound **23c** showed a potent GPR119 agonistic activity with EC_{50} = 46.76 nM
  - *in-vivo* studies of compound **23c**, showed a potent anti-diabetic activity with ED_{50} = 8.2 mg/kg in C57 mice single dose oral glucose tolerance test (oGTT) and 1.9 mg/kg after 14 days repeated dose treatment in db/db mice.
  - Incretin-mediated (GLP-1 release) mechanism for antidiabetic effects of compound **23c** was confirmed since it increased active GLP-1 and insulin levels in diabetic mice plasma (db/db mice).
  - It showed a desirable ADME profile.
  - Compound **23c** demonstrated that it has a good preclinical safety profile with no adverse effect level (NOAEL) observed in Rats (>400 mg/kg) and in Dogs (50 mg/kg).

Overall, pre-clinical profile (**Figure 26**) revealed that a novel potent, effective and safe GPR -119 agonist was successfully designed and synthesized for the treatment of type 2 diabetes mellitus (T2DM).

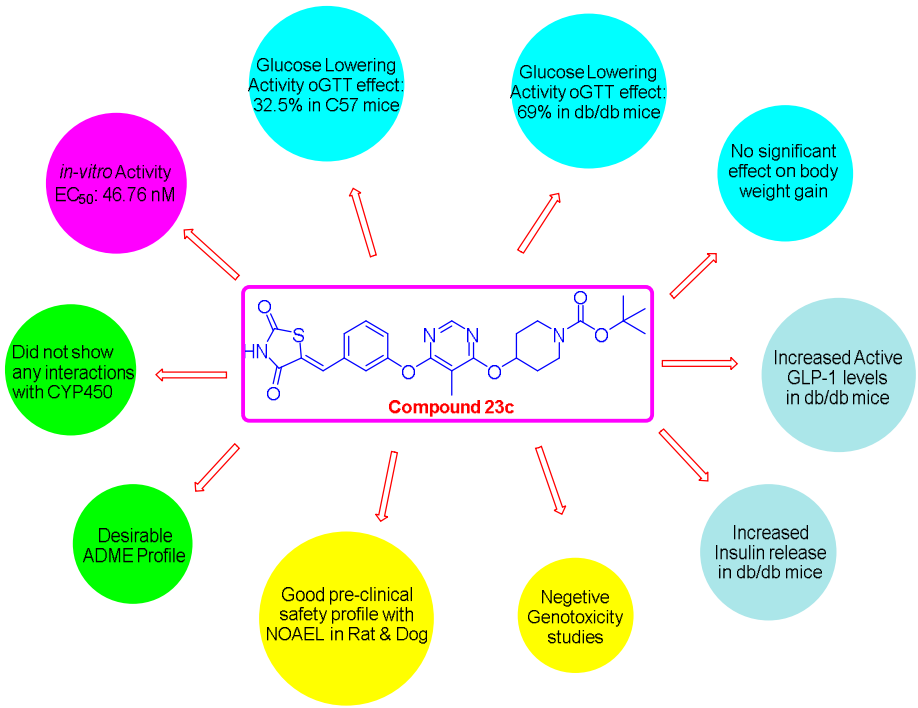

Figure 26: Overall profile of the lead Compound 23c