2 Designing of GPR 119 Agonists

2.1 Novel GPR 119 Agonists

The characteristics of Diabesity (Diabetes and Obesity) and the role of GPR 119 in the pathophysiology of this complex disorder have been described in detail in the previous section. The role of GPR 119 in glucose stimulated insulin secretion (GSIS) from the pancreas and glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP) release from the intestine have been scientifically proven. Additionally GPR 119 agonists have been shown to improve insulin resistance associated with obesity. These facts made GPR 119 a promising target for the treatment of T2DM, and since then many synthetic ligands have been discovered and disclosed (see **Figure 9)**. Some of these compounds have been evaluated in clinic for their safety and efficacy in humans. However, none of these candidates entered in to phase III clinical trials.

The challenges in designing GPR119 agonists with acceptable physicochemical properties, the optimization of the pharmacodynamics parameters such as potency at the receptor and extent of activation (maximal intrinsic activity) have proven to be far from trivial. Medicinal chemistry teams have succeeded in designing and synthesizing highly potent GPR119 agonists with activities in the low nanomolar range. However, optimizing maximal receptor activation has been found to be difficult. Also the extent of receptor activation (partial, full or even super agonism) required to achieve an optimal therapeutic effect is still an unresolved question. Poor translation of therapeutic effects from rodents to humans has been a bigger challenge since rodent GPR119 receptor sequences differ from the human receptor as stated earlier. Furthermore, tachyphylaxis, a well-known phenomenon in activation of GPCRs, needs to be considered as a possible limitation for a chronic treatment. These facts made the development of GPR119 agonists a complicated and challenging for the scientific community. Finally, a thorough understanding of the relative contributions of receptor activation at the two major sites of GPR119 expression, i.e. gut and pancreas, to the overall pharmacological effect might help to guide the design of agonists. Taken all together, this leads to the important question whether improved 2nd generation GPR119 agonists will be able to

provide diabetic patients with additional benefits, besides glucose lowering, that initially attracted the intense interest.

In an attempt to identify potent GPR119 agonists, designing of new chemical entities with *in-silico* docking studies was initiated.

The Arena molecule (**AR231453**) was docked into the homology model using the induced fit docking (IFD) protocol[34] where **AR231453** fits snugly to binding site and adopts an extended conformation as shown in **Figure 10**. Further, the fluoro-phenyl ring forms pi-pi interaction with Phe 249 and 1,2,4-oxadiazole ring forms a pi-pi interaction with side chain of Tyr 271. This is also stabilized by cation-pi interaction between nitro group of AR231453 and Phe 168. These three interactions seem to stabilize the molecule in binding site. In addition to these interactions, **AR231453** also forms van der Waals interactions with Phe 182, Trp 246, Val 84, Leu 274 and Gln 66. Supposing that these interactions and similar binding mode might be contributing well to the potent agonistic activity, a general structural architecture which formed the basis for further designing of novel compounds described in following section of the thesis was derived.

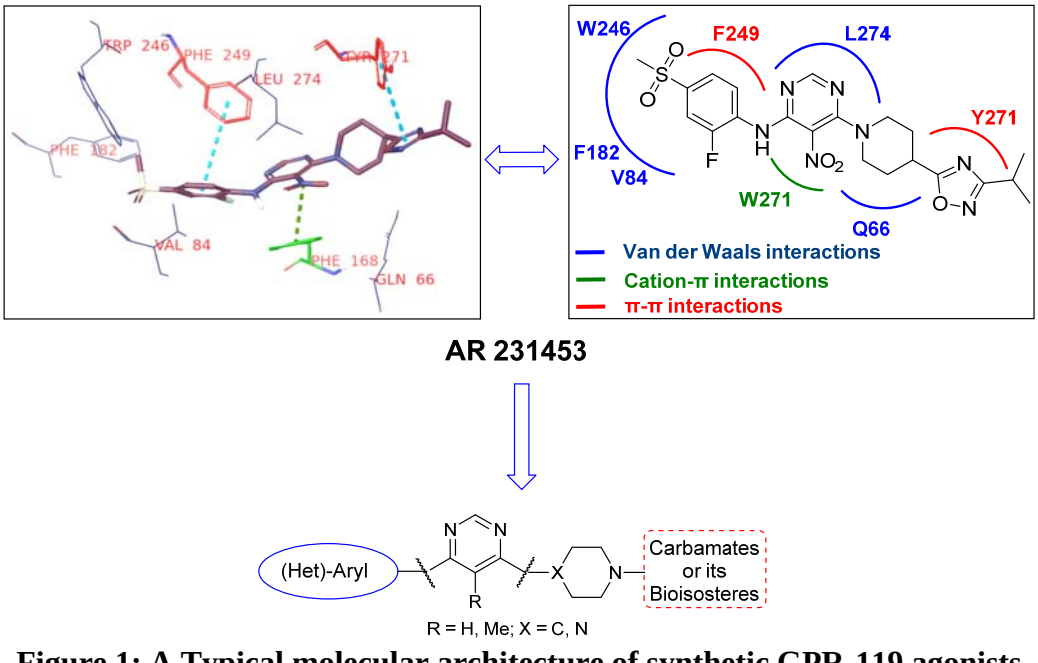

Figure 1: A Typical molecular architecture of synthetic GPR-119 agonists

2.1.1 Rationale for designing *para*-Benzylidene thiazolidinedione's derivatives as GPR 119 agonists

In the foresaid context of high unmet medical needs and the emergence of GPR 119 agonists as a fascinating target for the treatment of diabetes, idea to develop a new class of agonists with distinct biological and safety profile consisting of a novel pharmacophore intrigued us.

A typical structural design of a GPR 119 agonists as shown in **Figure 10** comprises of a (Het-Aryl) as "head group" and "Carbamates or its Bioisosteres" as tail group with a linker (Pyrimidine) in-between. Keeping this scaffold in mind, compound (**II)** was designed (**Figure 11**).

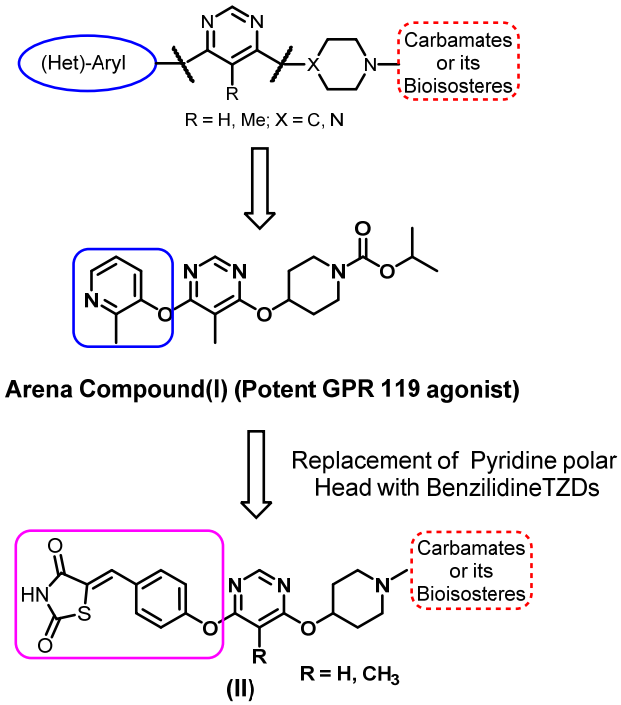

Figure 2: *p*-benzylidene thiazolidinedione containing GPR 119 Agonists.

Arena compound (I) is reported to be a selective and potent agonist of the GPR119 receptor across several species (EC_{50}, melanophore; human: 2 nM; dog: 1 nM; cynomolgus monkey: 35 nM; mouse: 41 nM; rat: 44 nM) and possesses aqueous solubility with no appreciable inhibition of at least five cytochrome P450 enzymes (IC_{50})

(CYP2C9, 15 µM; 1A2 2D6 3A4, > 40 µM; 2C19, 10 µM). **Arena compound (I)** also demonstrated a dose-dependent inhibition of glucose excursion in the oral glucose tolerance test (oGTT) experiment in male SD rats (22%, 0.3 mg/kg p.o.; 24%, 3 mg/kg p.o.; 70%, 30 mg/kg p.o.).[198] However, further development of this compound has been suspended for reasons not disclosed. In the efforts to discover promising and safe GPR119 agonists, 2-methyl pyridine, a polar head of **Arena compound (I)** was replaced with clinically proven pharmacophore benzylidene thiazolidinedione, as a novel heterocyclic head and identified this moiety as a pyridine surrogate (**Figure 11**).[199] Thiazolidinediones (TZDs), also known as glitazones are insulin sensitizers having a pleotropic pharmacology including reduction of insulin resistance, a root cause of diabetes. Importantly these agents also preserve pancreatic *β*-cell function or mass better than insulin secretagogues such as sulfonylureas. The glitazones (rosiglitazone and pioglitazones) are a new class of anti-diabetic drugs that act by improving sensitivity to insulin and are indicated in the treatment of type 2 diabetes. The glitazones have effects on carbohydrate and lipid metabolism and hold the promise of being able to influence many components of the insulin resistance syndrome seen in type 2 diabetes. It is possible that the glitazones are able to prevent or delay the cardiovascular disease, which accompanies type 2 diabetes. In viewed there the properties of TZDs, benzylidene thiazolidinedione as head group was incorporated to identify novel, potent and safe GPR 119 agonists.

2.1.2 Designing of *meta*-Benzylidene thiazolidinedione derivatives as GPR 119 Agonists:

Having studied the SAR of initial compounds, it was decided to optimize the position of thiazolidinedione on phenyl ring. To do so, *meta*-benzylidene thiazolidinedione derivatives (III) were synthesized (**Figure 12**).

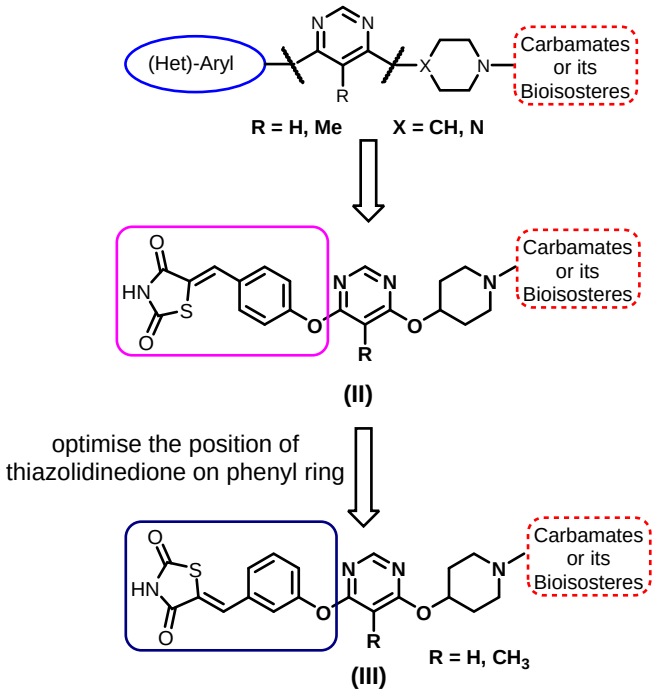

Figure 3: *m*-benzylidene thiazolidinedione containing GPR 119 Agonists

2.1.3 Designing of compounds based on N-substituted *m*-benzylidene thiazolidinedione derivatives as GPR 119 Agonists

The next endeavor in this project was to optimize the lead compound of *meta*-benzylidene thiazolidinedione series. Thus, N-substituted *meta*-benzylidene thiazolidinedione derivatives (IV) were prepared (**Figure 13**).

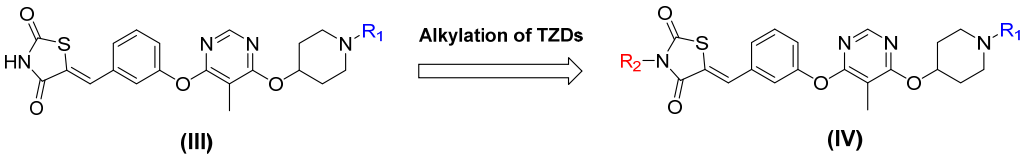

Figure 4: Designing of N-substituted Benzylidene thiazolidinedione as GPR Agonists