Designing

of

PPAR AGONISTS

2 DESIGNING PPAR AGONISTS

2.1 Selective PPARα agonists

The aspects of metabolic syndrome and the role of PPARs in pathophysiology of this complex disorder have been described in detail in the previous chapter. Activation of PPAR*α* leads to elevated expression of apolipoproteins and cellular glucose transporters, resulting in an enhanced clearance of lipids and glucose from the blood. PPAR*α* also improves insulin resistance associated with obesity. Therefore PPAR*α* is thought to be a potential molecular target for the treatment of metabolic disorders.[222,223]

Fibrates are weak agonists of PPAR*α* with poor subtype selectivity and are effective at high doses which lead to unwanted side effects.[224] Thus, the discovery of potent and selective activators of PPAR*α* may serve as a better remedy for disorders mediated by lipid and carbohydrate metabolisim. Obviously it was of interest to design and synthesis selective PPAR*α* agonists.

2.1.1 Modulation of PPAR subtype selectivity. Part 1: Transforming PPAR*α*/γ dual agonist into a selective PPAR*α* agonist

In the fore said context of high unmet medical need and the emergence of selective PPAR*α* agonist as a fascinating target for the treatement of metabolic syndrome, the idea to develop a new class of PPAR*α* agonist with distnict biological and safety profile constiting of novel pharmacophore was intriguing.

As a part of the research in the field of PPARs to develop novel therapeutic agents to treat metabolic disorder, a novel pharmacophore was conceptualized by combining the structural features of glitazone and fibric acid.[225] (**Figure 15**)

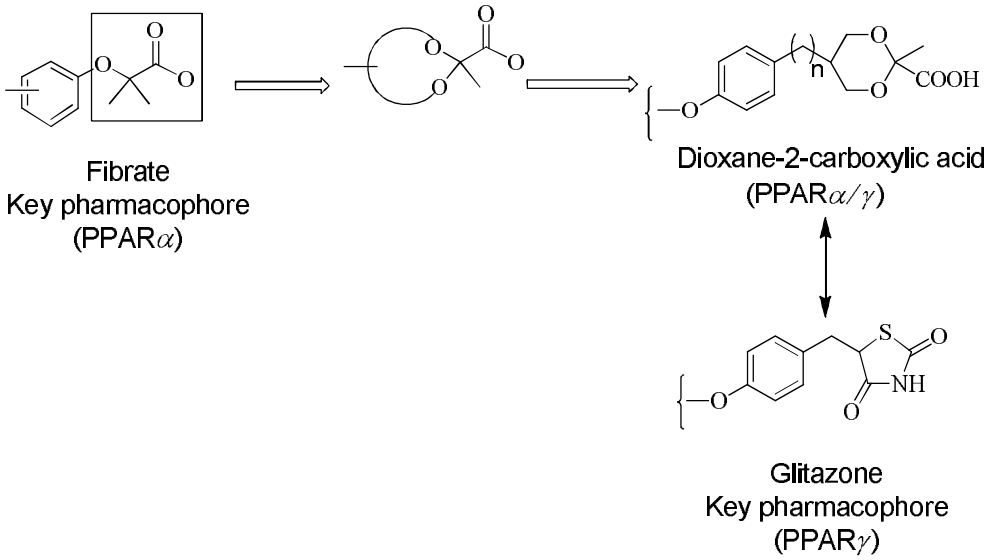

Figure 15: Design of dioxane carboxylic acids

A series of the compounds constituted by 1,3-dioxane-*r*-2-carboxylic acid, as a pharmacophore and substituted oxazole moiety, as a lipophilic tail, were found to be PPAR*α*/*γ* dual agonists and the lead compound **I** (**Figure 16**) exhibited potent hypoglycemic, hypolipidemic and insulin sensitizing effects in rodent models.

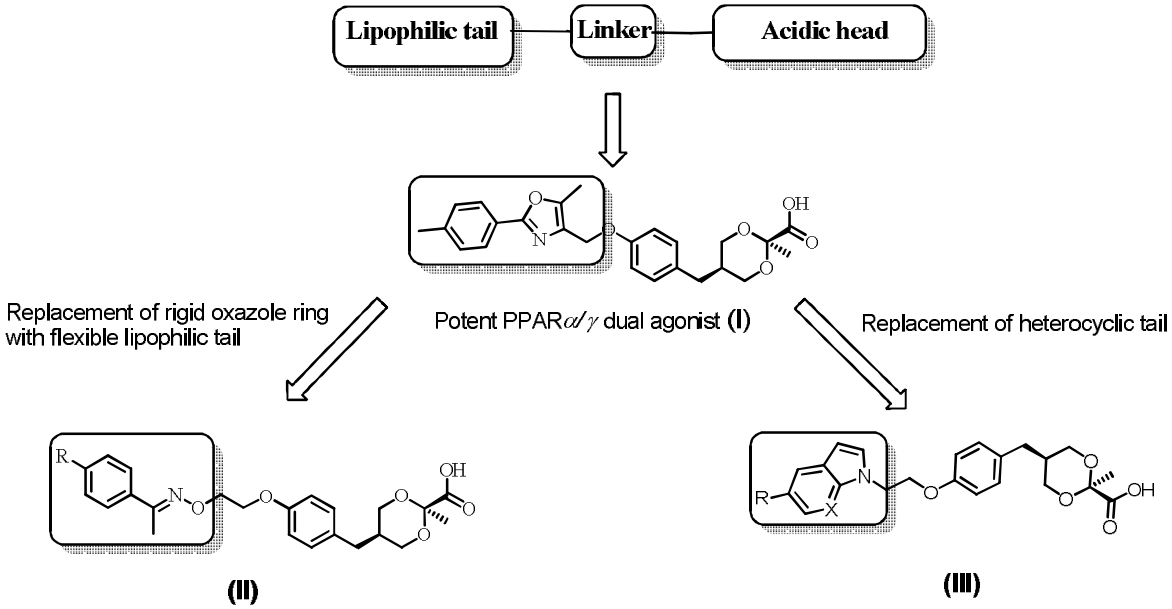

Figure 16: Identification of lipophilic part for selective PPAR*α* agonistic activity

Conceptually, modification of the lipophilic tail and the linker could change the conformation of the molecule substantially and therefore, alter its PPAR

binding, selectivity and functional activity, as well as its *in vitro* profile. Therefore it was intended to design the compounds by retaining 1,3-dioxane-*r*-2-carboxylic acid as the acidic head and centering the modifications on both the lipophilic tail and the central tether portion of **I**. So the 1,3-dioxane-*r*-2-carboxylic acid pharmacophore was explored further.

A typical structural design of a PPAR agonist as shown in **Figure 16** comprises of a lipophilic/ heterocylic tail and an acidic phramacophore with a linker in-between. To synthesize the compounds (**II** and **III**) based on benzyl 1,3-dioxane-*r*-2-carboxylic acid derivatives, the rigid oxazole ring of the previously reported PPARα/γ dual agonist (**I**), was replaced with flexible lipophilic groups (phenyl oxime and indole) based on the structures of PPAR ligands that have been advanced to clinical development.

2.1.2 Modulation of PPAR subtype selectivity. Part 2: Transforming PPAR α/γ dual agonist into weak and partial PPARα selective agonist

Most of the potent and selective PPARα agonists are reported to exert hypoglycemic and lipid modulating effects in animal models.[150,151,153,154,163,226,227] However none of the potent and selective PPAR*α* agonists has entered the market, mainly due to safety concerns.[210] Thus there is an unmet need to develop a new generation PPAR*α* agonists for the treatment metabolic disorders.

Recently very potent PPAR*α*/γ dual agonist (**IV**) was designed by replacement of oxazole group of compound **I**, with 1-biphenyl-4-yl-ethanone. When the terminal phenyl group of **IV** was removed and substituted with methyl group the resulting compound **V** showed a moderate PPAR*α* and PPARγ *a*ctivity with a good *in vivo* efficacy. Though compound **V** is a moderate PPAR*α*/γ dual activator, it showed the highest PPAR*α* agonistic efficacy (αEC_{50} = 0.14 µM, maximal efficacy (E_{max}) = 181% compared to the full agonist WY14643) with weak PPARγ efficacy (γEC_{50} = 0.75 µM, E_{max} = 49% compared to the full agonist Rosiglitazone) *in vitro*. The results of the molecular modelling experiment of **V**, also supports its high potency towards PPAR*α*.[228] But its high hPPAR*α* potency *in vitro* raised the safety concerns. Having insight from these results, it was

envisaged that the structural modification of **V** could provide with a safe, efficacious and selective PPAR*α* compound. Therefore, it was decided to optimize the lipophilic portion of compound **V** as illustrated in **Figure 17**.

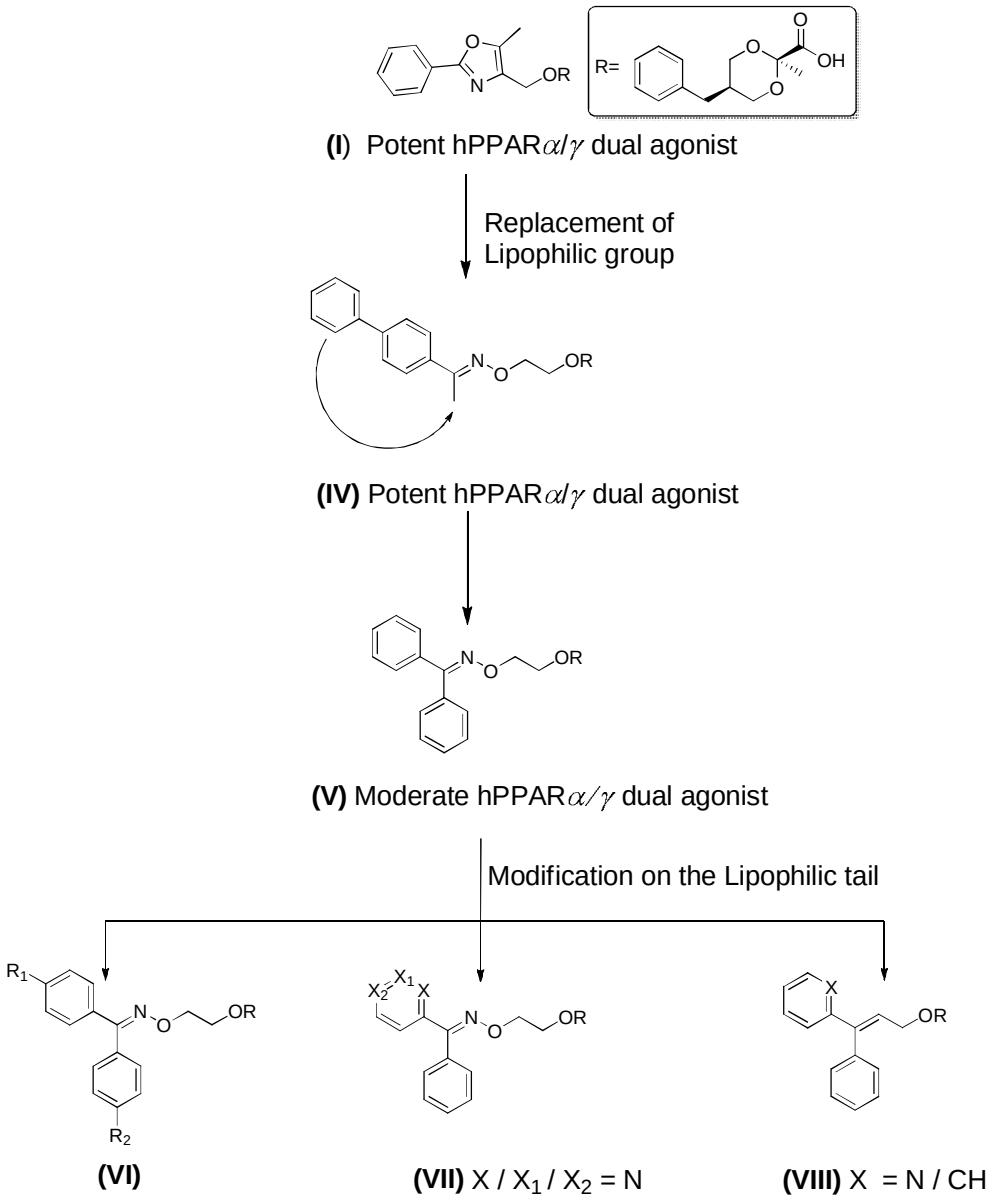

Figure 17: Structural development of potent hPPAR*α*/γ dual agonist (**I**) for weak and partial hPPAR*α* agonists

The effect of substitutions on *para*-positions of the phenyl groups of lipophilic part with groups having different electronic and steric properties was planned to be investigated. Initially it was intended to synthesize the compounds of general structure **VI**. Based on the *in vitro* and *in vivo* results of derivatives **VI**,

compound **VI** were modified to **VII** with ring equivalent bioisosteric replacement on lipophilic tail by replacing phenyl with pyridyl group and finally the compound **VIII** were synthesized by replacing the oximino group with the olefin functionality.

2.2 PPARα/γ dual agonists

The PPARα agonists (Fibrates) can improve lipid control and PPARγ agonist (Glitazones) can improve glucose homeostasis. The importance of controling both lipid and glucose levels in metabolic syndrome, gave rise to the concept of identifying dual agonists, which activate both PPARα and PPARγ. The dual PPARα/γ agonists can be used to treat cardiometabolic imbalances at the same time. These molecules can be designed so that to diminish each others adverse effects.[229] These finding led to the hypothesis that weight increase due to the adipogenic effects of PPARγ agonist can potentially negated by PPARα mediated increase in lipid catabolisim. Although many of the dual PPARα/γ agnoists have undergone clinical trials, most of them failed to enter the market due to unresolved safety concerns.[229] More recently, it was reported that 7 to 10 fold PPARα preferental PPARα/γ dual agonists showed the preserved antidiabetic activity and diminshed adverse effect profile.[230] However, optimal α to γ ratio at each receptor and whether the desired therapeutic effects are additive, complementary or synergistic have not been established. Thus the development of selective and balanced PPARα/γ dual agonist may be sensible option for the treatment of metabolic syndrome.

2.2.1 Modulation of PPAR subtype selectivity. Part 3: Transforming PPAR α/γ dual agonist into balanced PPARα/γ dual agonist

A close look at the structures of PPAR agonists revealed that, most of the dual PPARα/γ agonists possess a phenyl group at the centre commonly referred to as tether or spacer. Regarding the aromatic center, close inspection of several X-ray structures revealed that a simple phenyl ring does not optimally fit the cavity of the receptor. In both PPARα and PPARγ, enough space seems to be

available to accommodate a larger ring system and the reports suggested bicyclic annulated ring system as planar replacements but relatively few bicyclic annulated ring systems in the central aromatic region are found to be present in PPAR agonists, such as in Netoglitazone[231], NC-2100[217], Englitazone[174], Edaglitazone and Aleglitazar[206] Therefore it was decided to explore the potential of bicyclic core as tether or spacer (**Figure 18**).

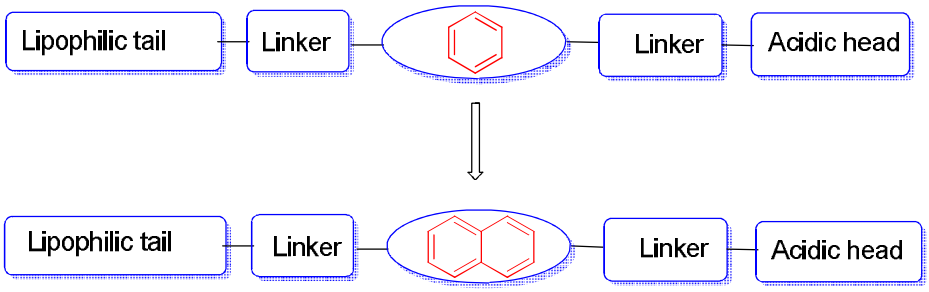

Figure 18: Designing of novel PPAR agonist

Different acidic war heads which form up to four essential bonds with serine, tyrosine and histidine of the protein, the strong hydrogen acceptors are crucial for obtaining potent agonists. It was intended to synthesize the compounds (**IX-XII**), retaining the, 1,3-dioxane-*r*-2-carboxylic acid, glycine, oximino acid and α-alkoxy-substiuted propanoic acid head groups are binding motifs for the AF2-helix interface present in clinically advanced PPARα/γ dual agonists such as **I**[225], Muraglitazar[158], Imiglitazar[232] and Tesaglitazar[233] respectively. For the partially solvent exposed cyclic tail, the benzyloxy moiety which in general is quite tolerant with respect to structural variations was focused upon. It was also decided to explore the potential of bicylic core specifically naphthalene, present in PPAR ligand like Netoglitazone. (**Figure 19)**

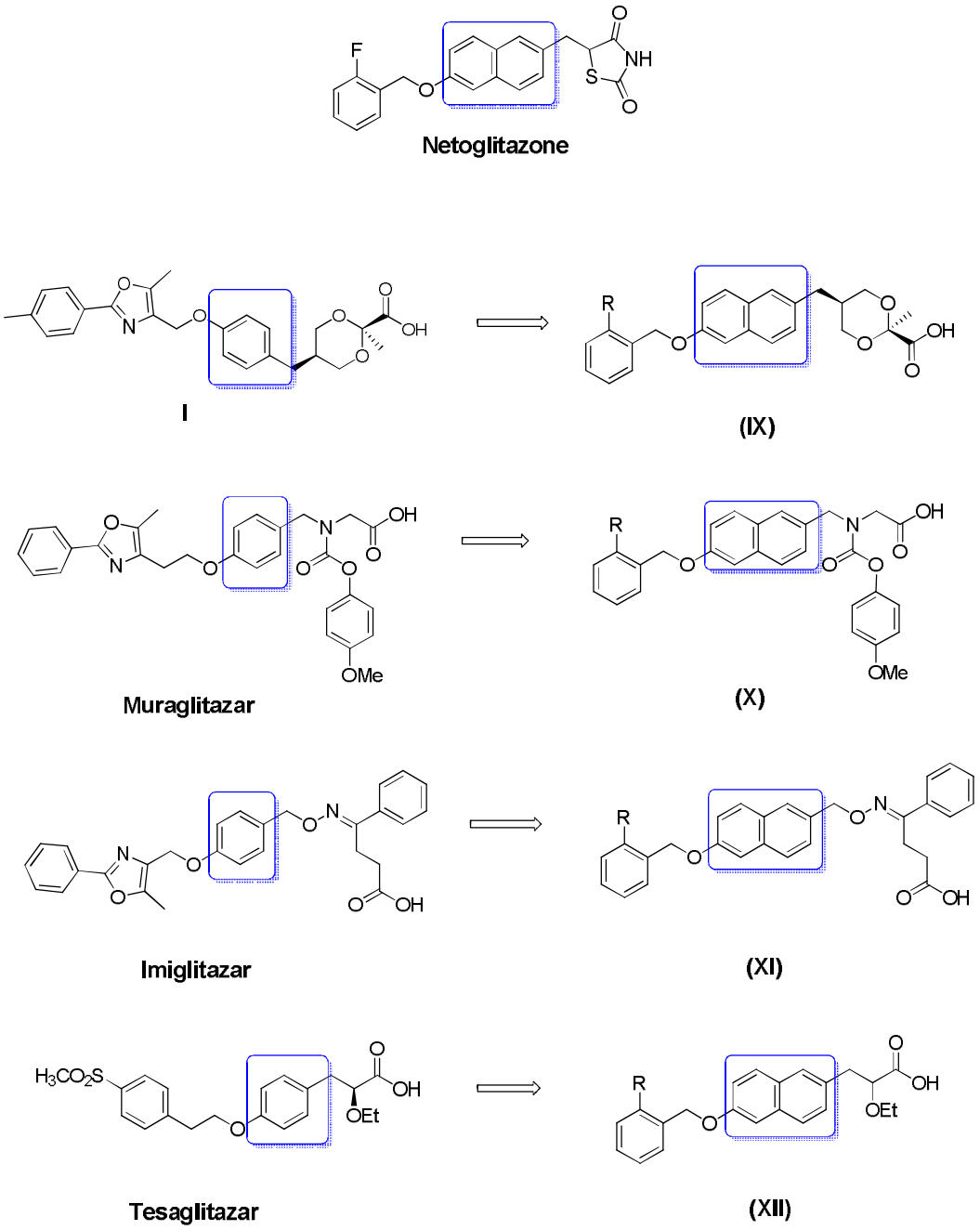

Figure 19: Replacement of phenyl ring with naphthalene as central aromatic spacer.