# *Designing PPAR agonists*

*"Science may set limits to knowledge, but should not set limits to imagination"*

*Bertrand Russell*

# 2. DESIGNING PPAR AGONISTS

## 2.1. PPAR$\alpha/\gamma$ dual 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 section. The roles of PPAR$\gamma$ in adipogenesis at a cellular level and insulin sensitization have been demonstrated. PPAR$\gamma$ agonists, Rosiglitazone and Pioglitazone are proven to be efficacious as insulin sensitizing agents for the treatment of type 2 diabetes and are currently available in the market [**161,198**]. Similarly, the role of PPAR$\alpha$ in fatty acids oxidation and lipoprotein metabolism is supported by clinical effects such as lowering of triglycerides and elevating HDL levels exerted by fibrates (Fenofibrate, Clofibrate and Bezafibrate) [**199-203**]. The majority of metabolic syndrome patients suffer from atherogenic lipid abnormalities in addition to insulin resistance [**10**]. The importance of controlling both glucose and lipid levels in metabolic syndrome, gave rise to the concept of identifying dual agonists, which can activate both PPAR$\alpha$ and PPAR$\gamma$. As stated earlier, in addition to their hypolipidemic effects, fibrates reduce body weight gain without affecting food intake [**56, 204**]. This finding led to a hypothesis that probably activation of PPAR$\alpha$ may mitigate the weight gain induced by PPAR$\gamma$ activation and PPAR$\alpha/\gamma$ dual agonism would provide synergistic pharmacological effects. This further led to the discovery and development of several PPAR$\alpha/\gamma$ dual agonists (**Figure 9**). However none of these dual agonists has been marketed. Thus the development of PPAR$\alpha/\gamma$ dual agonists with distinct biological and safety profiles has been an attractive target among the several research groups working in the area of metabolic syndrome all over the globe.

### 2.1.1. Rationale for designing 1,3-dioxane-2-carboxylic acids as PPAR$\alpha/\gamma$ dual agonists

In the fore said context of high unmet medical need and the emergence of PPAR$\alpha/\gamma$ dual agonists as a fascinating target for the treatment of metabolic

disorders, idea to develop a new class of dual agonists with distinct biological and safety profile consisting of a novel pharmacophore intrigued us.

Fibric acid is the key pharmacophore of PPAR$\alpha$ ligands like Fenofibrate, Clofibrate and Bezafibrate. While all the glitazone class of compounds possess 2,4-thiazolodinedione as key pharmacophore as in Rosiglitazone and Pioglitazone. We wished to design compounds with a novel pharmacophore possessing the features of both fibric acid and glitazone so that these compounds can be developed as PPAR$\alpha/\gamma$ dual agonists. We started the structural design by introducing an oxygen atom on the alpha carbon of carboxylic acid of fibric acid chemotype and cyclising with the aryl oxygen forming a 1,3-dioxane ring connected to phenyl ring either directly or with a spacer like methylene or ethylene group forming the key pharmacophore of the novel compounds. The newly designed pharmacophore resembles glitazones structurally and possesses a free carboxylic function resembling fibric acid pattern and provides rationale to study the compounds with this pharmacophore as dual PPAR$\alpha/\gamma$agonists (**Figure 10**).

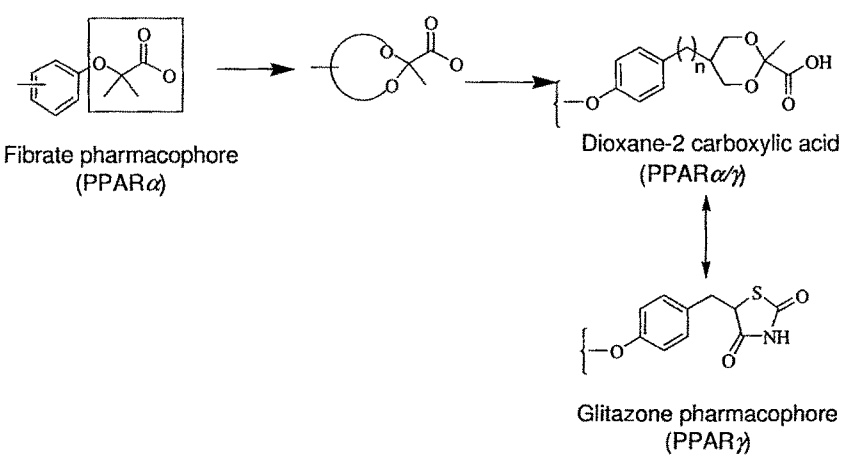


**Figure 10.** Design of dioxane carboxylic acids.

A typical structural design of a PPAR agonist as shown in **Figure 11** comprises of a lipophilic heterocyclic tail and an acidic pharmacophore with a spacer in-between. In most of PPARα/γ dual agonist the middle spacer

comprises of a phenyl ring connected to the lipophilic tail by an alkoxy group. Keeping this motive in mind, we have designed compounds **I** and **II** (**Figure 11**).

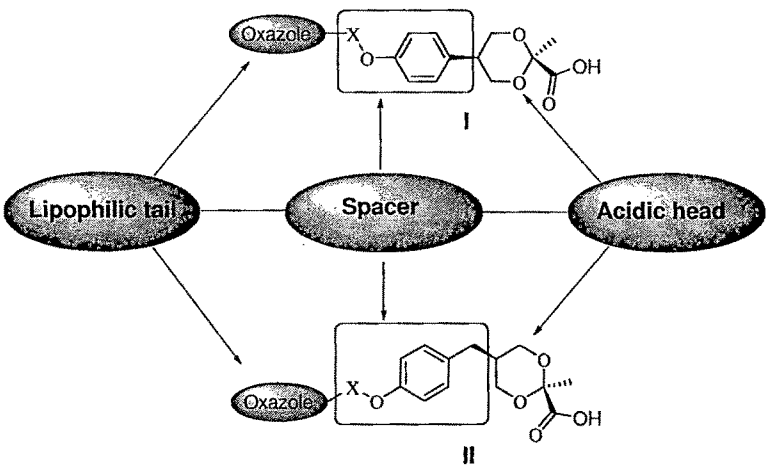


**Figure 11.** Oxazole containing 1,3-Dioxane-2-carboxylic acid

To synthesize the compounds based on this novel pharmacophore, we chose phenyl and benzyl dioxane carboxylic acids mimicking a typical chemotype of PPAR agonist. Then we selected substituted oxazole group as lipophilic tail.

We initiated synthesis of these proposed compounds **I** and **II** containing differentially substituted oxazoles as lipophilic tail. Subsequently, oxazole moiety was replaced with the other heterocycles (**Figure 12**) based on the structures of PPAR ligands that have been advanced to clinical development.

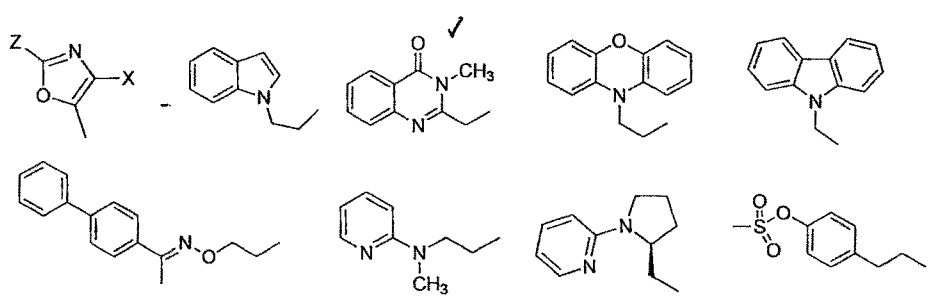


**Figure 12.** stuctures of lipophilic tails

## 2.2. Selective PPAR$\alpha$ agonists

Recent literature disclosed that selective PPARα agonists lower triglycerides, increase HDL and exert insulin-sensitizing effects [**202,203**]. Thus, the discovery of potent and selective activators of PPAR$\alpha$ may serve as a better remedy for disorders mediated by lipid and carbohydrate metabolism. Obviously, we were also interested in design and synthesis of selective PPAR$\alpha$ agonists. To attain this objective, we intended to design the compounds by retaining 1,3-dioxane carboxylic acid intact as acidic head and centering the modifications on both the lipophilic tail and the central tether portion. A potent and selective PPAR$\alpha$ agonist NS-220 [**150**] is reported to exert hypoglycemic and lipid modulating effects in animal models. Further development of this compound is discontinued for unknown reasons. Another compound K-111 [**149**], a relatively weak PPAR$\alpha$ agonist is presently undergoing clinical trials for the treatment of type2 diabetes. Based on these reports we then intended to design novel 1,3-dioxane carboxylic acid derivatives **III** by the hybridization of the compounds NS-220 and K-111 (**Figure 13**).

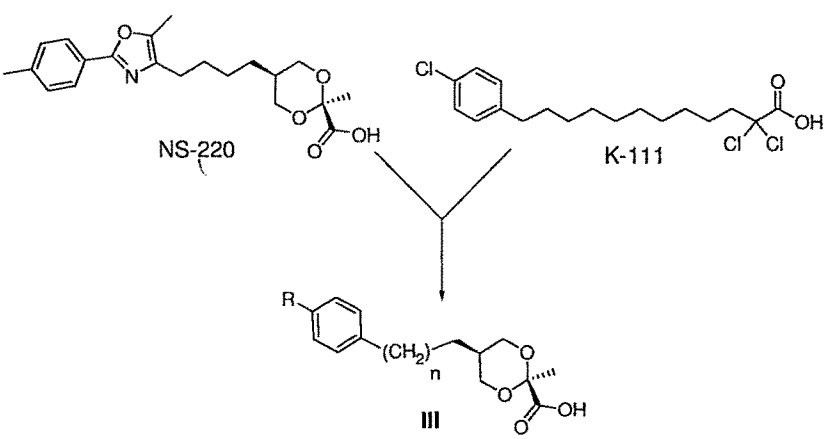


**Figure 13.** Designing selective PPAR$\alpha$ agonists

A close look at the structures of PPAR agonists reveals that, most of the dual PPAR$\alpha/\gamma$ agonists (e.g. Imiglitazar, Muraglitazar) possess a phenylene group at the centre commonly referred to as tether or spacer. We anticipate

compound **II** to activate both PPAR$\alpha$ and $\gamma$. Compound **II** differs from NS-220 only in the spacer region *i.e.* in compound **II** the spacer is a phenylene ring whereas in NS-220 it is a tetramethylene chain. Based on these observations we envisioned that PPAR subtype selectivity of ligands may be sensitive to chemical variations in the spacer region of the structure and intended to study the effect of changing the phenylene spacer of Imiglitazar and Muraglitazar to a polymethylene spacer in order to develop selective PPAR$\alpha$ agonists. We initailly intend to synthesize the compounds of general structure **IV** and **V** with varied length of spacer chain as shown in **Figure 14.**

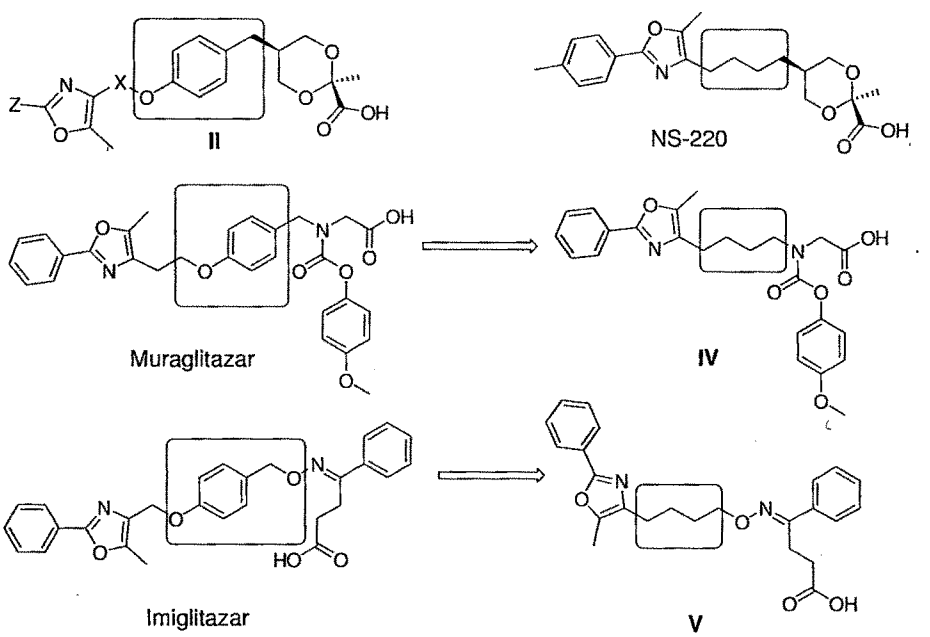


**Figure 14.** Imiglitazar, Muraglitazar and **II** possess aromatic phenylene spacer between acidic head and lipophilic tail and are PPAR$\alpha/\gamma$ dual agonists whereas NS-220 contains polymethylene spacer and is PPAR$\alpha$ selective agonists.

Based on the *in vitro* results of derivatives of **IV** and **V** we have modified compound **V** to compounds **VI** centering the modifications in heterocyclic tail portion as depicted in **Figure 15.**

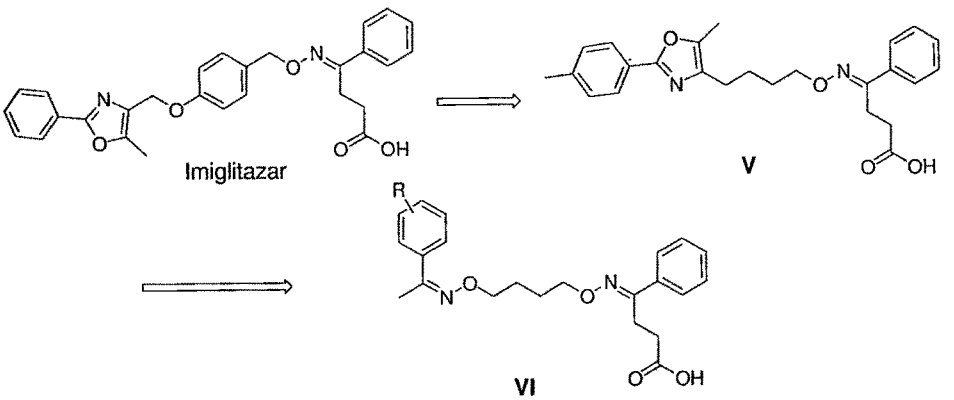


**Figure 15.** Designing selective PPAR$\alpha$ agonist.