HETEROCYCLYL LINKED β-KETOESTERS AS NOVEL ANTIDIABETIC AGENTS: DESIGN SYNTHESIS AND COMPUTATIONAL VALIDATION STUDIES

ABSTRACT

Type 2 diabetes mellitus (T2DM) has emerged as an epidemic in our country as well as globally. Cardiovascular complications have been known to alter the lifestyle and reduce the life expectancy of patients with type 2 diabetes. Renal failure, blindness, limb amputation, obesity etc. are other complications associated with T2DM. PPARs are crucial in regulation of energy homeostasis, with each of the three subtypes of PPAR receptors controlling particular aspects, hence are important therapeutic targets for the treatment of T2DM. Since the cloning of PPAR as an orphan receptor, various ligands and target genes have been identified. Indeed, PPAR agonists have emerged as a promising group of agents for treating type 2 diabetes and associated cardiovascular risk factors represented by the marketed 2,4-thiazolidenediones (TZDs). Natural and synthetic ligands for the three PPAR subtypes have been reported, mainly focusing on PPARγ. The identification of new ligands, added to improved knowledge of their specificity, will enlarge the panel drugs for therapeutic intervention in various energy homeostasis dysfunctions. In particular, PPARα and PPARγ seem to be antagonizing partners in maintenance of lipid homeostasis. The PPARδ/β isotype function has been the least documented thus far and would benefit from further development of pharmacological tools. However, its ubiquitous expression, particularly high during development, suggests that PPARδ/β could be implicated in cell proliferation/differentiation or in more basic cellular functions such as cell membrane synthesis. On the basis of the relatively few compounds marketed until now, PPAR ligands have attracted much unfavorable attention because of their potential side effects. Ongoing pharmaceutical research is continuing to pursue PPAR ligands with enhanced therapeutic efficacy and better safety margins. Thus, compounds with dual PPARγ and PPARα activity have been proposed to combine the benefits of insulin sensitization with lipid lowering in a single drug to reduce hyperglycemia and hyperlipidemia and to simultaneously prevent progression of cardiovascular complications.
Unfortunately, clinical development of PPARα/γ dual agonists such as α-alkoxy propanoic acid derivatives, tyrosine derivatives etc. has been mostly discontinued because of their undesirable pharmacological effects. The side effects of these agents may be due to their unbalanced supratherapeutic activity toward PPARγ and PPARα. Therefore, dual agonists with selective and balanced agonistic activity toward PPARα/γ could constitute an appropriate therapeutic option. In the search for new PPAR agonists, some PPARα/δ and PPARγ/δ dual agonists have also been investigated, followed by pan-agonists having the full spectrum of α/δ/γ activity.

However, despite the diversity of the new ligands for PPARs, only a few compounds are currently under clinical development. Recent studies have reported new PPAR ligands based on the concept of multitargeted drugs, with the development of PPAR-11β-HSD1, PPAR-CB2, PPAR-COX dual functional agents, in order to enhance efficacy and/or improve safety compared to present one-drug-one-target methods.

Cardiovascular safety is the new bottleneck for PPAR agonists, with regulations requesting more stringent and complete drug trials before approval. It should be kept in mind that even drugs deemed successful against their intended target might well display severe adverse effects after marketing because of their widespread use, itself shedding new light on their still not fully understood mechanisms of action.

Design, computational validation, synthesis and characterisation of heterocyclyl linked (benzimidazolyl-, indolyl-) β-ketoester based NCEs as novel partial dual PPARα/γ activators have been reported in the present work after investigating the activity and safety profile of the existing individual and dual PPAR agonists and coming up with the assumption that partial agonism at both PPARα and PPARγ receptors by dual partial activators may provide a solution resulting in the desirable responses and reducing the adverse effects caused by the individual and dual agonists for the treatment of T2DM.

Benzimidazolyl-, indolyl- and acridonyl- linked benzyl and benzylidene β-ketoester based NCEs were designed with the help of Theoretical Structure Activity Relationships (TSAR) and 3D QSAR methods. PPAR activities of the designed molecules were predicted employing the developed significant QSAR models by 3D QSAR –CoMFA method and docking studies were carried out to predict binding affinities and interactions.
at PPARα and PPARγ receptors. After critical comparative analysis of the predicted activities and binding affinities among the designed molecules and with respect to some standard dual ligands, best expected partial agonists were selected (benzimidazolyl-, indolyl- linked benzylidene and benzyl containing β-ketoester based NCEs). The selected designed molecules were successfully synthesised by a common convergent route involving Mitsunobu coupling. The chemical structures of all the synthesised NCEs and intermediates involved were confirmed by spectral analysis.