WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 18, 1206-1214. Review Article ISSN 2277–7105

DESIGN AND SYNTHESIS OF NOVEL PPART AGONISTS: ENHANCING INSULIN SENSITIVITY THROUGH THE INCORPORATION OF ACIDIC AND AROMATIC AMINO ACIDS IN PLACE OF PYRIDINE RING IN ROSIGLITAZONE DERIVATIVES

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Article Received on
03 August 2024,

Revised on 24 August 2024,
Accepted on 13 Sept. 2024

DOI: 10.20959/wjpr202418-33939

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INTRODUCTION

Heterocyclic compounds are organic compounds that contain at least one atom other than carbon within a ring structure. These compounds are incredibly important in medicinal chemistry because they often exhibit a wide range of biological activities, making them useful in the treatment of various diseases. Rosiglitazone is a member of the thiazolidinedione (TZD) class of drugs, which are primarily used to improve insulin sensitivity in the treatment of type 2 diabetes mellitus. The structure-activity relationship (SAR) of Rosiglitazone can be understood by analyzing the key structural components of the molecule and how they contribute to its biological activity, particularly its role as a selective agonist for the peroxisome proliferator- activated receptor gamma (PPARγ).Peroxisome proliferator-activated receptor gamma (PPARγ) is a type of nuclear receptor that functions as a transcription factor, regulating the expression of specific genes involved in various metabolic processes. PPARγ plays a crucial role in the regulation of glucose metabolism, lipid metabolism, and adipogenesis (the formation of fat cells). It is particularly important in the context of insulin sensitivity and the development of type 2 diabetes. Lipophilicity refers to the chemical property of a substance that describes its ability todissolve in fats, oils, and non-polar solvents, such as organic solvents (e.g., hexane or chloroform). In simpler terms, it is the affinity of a molecule for a lipid environment over an aqueous (water) environment. Lipophilic substances are typically non-polar or have significant non-polar regions, which makes them more soluble in lipids than in water.

Structure-Activity Relationship (SAR)

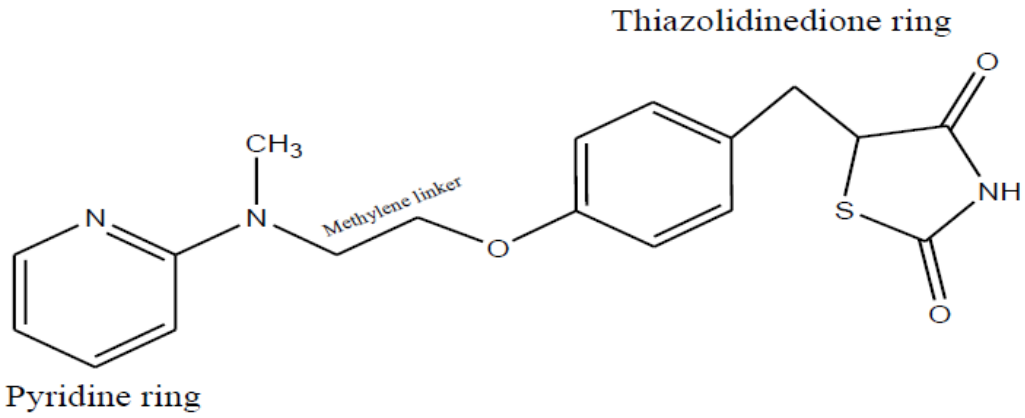


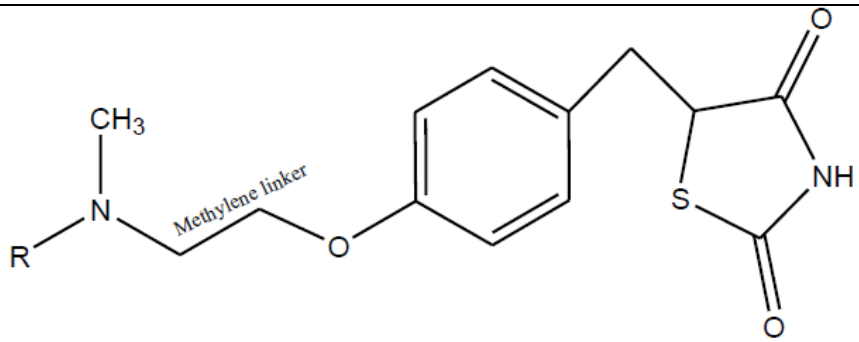
Figure 1: 5-[4-[2-(N-methyl-N-(2-pyridinyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione]

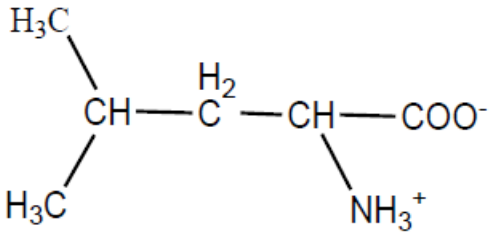
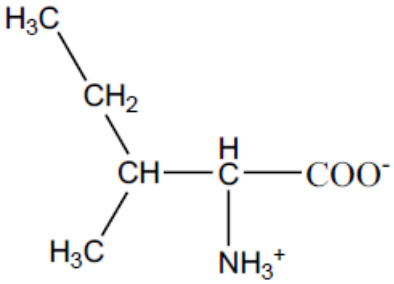
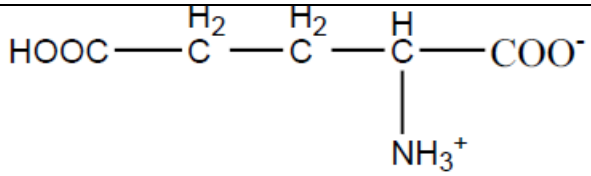
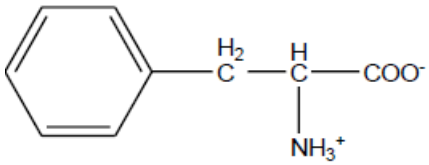
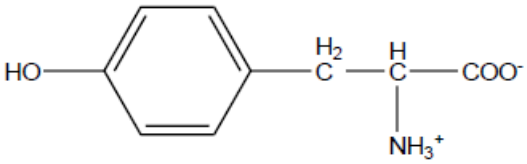
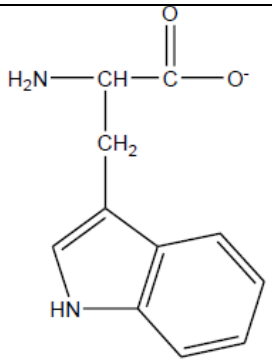
1. **Thiazolidinedione Ring Modifications**
   - The TZD ring is non-negotiable for activity; modifications typically reduce orabolish the drug's ability to activate PPARγ.
   - The acidic nature of the TZD ring is essential for interaction with the receptor, and any alteration that reduces this acidity negatively impacts the activity.

2. **Substitutions on the Phenyl Ring**
   - Substitution patterns on the phenyl ring can affect the potency and selectivity forPPARγ. For example, electron-donating or withdrawing groups can influence thebinding affinity.
   - The optimal position and nature of substituents are critical for maintaining the balance between efficacy and side effects.

3. **Pyridine Ring Substitutions**
   - Modifications to the pyridine ring can improve or reduce the drug's metabolic stability and selectivity for PPARγ over other receptors.
   - Substituents that enhance binding without increasing the molecular weight toomuch can improve the pharmacokinetic profile.

4. **Linker Flexibility**
   - The methylene linker between the TZD ring and the phenyl ring provides the molecule with the necessary flexibility to engage with PPARγ effectively.
   - Altering the length or rigidity of this linker can either improve or diminish the receptor interaction, thus influencing the drug's activity.



Name of Amino Acid	R
Leucine	
Isoleucine	
Glutamic Acid	
Phenylalanine	
Tyrosine	
Tryptophan	

1. **Molecular Design:** Design novel rosiglitazone derivatives by substituting the pyridine ring with various acidic and aromatic amino acids. Utilize computer-aided drug design (CADD) tools, such as molecular docking and structure-activity relationship (SAR) analysis, to predict the binding affinity of the new derivatives to PPARγ.
2. **Synthesis of Novel Rosiglitazone Derivatives;** Choose suitable acidic and aromatic amino acids for substitution.
3. **Synthesis Strategy Development:** Plan the synthesis by identifying key intermediates and reactions required to replace the pyridine ring with the selected amino acids. Utilize established organic synthesis techniques, such as peptide coupling, amidation, and cyclization,to achieve the desired modifications.
4. **Step-by-Step Synthesis:** Protect reactive functional groups in the amino acids to prevent side reactions. Perform reactions such as alkylation, acylation, or condensation to create the necessary intermediates. Purify and characterize intermediates using techniques like column chromatography and mass spectrometry. Couple the amino acid derivatives with the rosiglitazone core structure. Remove protecting groups and perform final cyclization to obtain the target derivatives. Induce cyclization if necessary, to form the final active structure. Purify the final compounds using recrystallization, HPLC, or preparative chromatography.
5. **Characterization of Synthesized Derivatives:** Confirm the chemical structure of the synthesized derivatives. Use NMR (1H and 13C), mass spectrometry (MS), and IR spectroscopy to confirm the chemical structure and purity of the derivatives.
6. **Purity and Yield Analysis:** Determine the purity and yield of the synthesized derivatives by using HPLC or GC.
7. **Preliminary Biological Evaluation:** In Vitro Binding Assays: Test the binding affinity of thesynthesized derivatives to the PPARγ receptor.
8. **Data Analysis and Optimization:** Analyze the data obtained from the synthetic and biological evaluation.

Optimize the chemical structure of the derivatives to enhance their biological activity.

Literature Review

- **From 1983 to 1995**, the TZDs reported were evaluated for hypoglycemic and hypolipidemic activity. It is only after 1995, they were also evaluated for their affinity towards PPARg.

- **Sohda et al. (1990)** reported a series of 5-[4-(pyridylalkoxy) benzyl]-2, 4 thiazolidinediones. They replaced cyclohexylmethyl group of Ciglitazone with heteroaromatic nucleus. These compounds were evaluated for hypoglycemic and hypolipidemic activity in genetically obese and diabetic mice.
- **Hullin et al. (1992)** investigated a novel series of thiazolidinedione analogues design based on the structure of Ciglitazone and Englitazone. Carbonyl group was found to be a better alternative for ether oxygen in the side chain. Analysis of corresponding chalcone revealed no significant improvement in potency.
- **In the year 1994**, scientists at Mitsubishi-Tokyo Pharmaceuticals reported the discovery of a novel thiazolidinedione 2 (MCC-55 later named as Netoglitazone,) by substituting benzene ring with naphthalene ring. They reported that the glucose lowering potency of this compound was greater than that of other TZDs, though it was showing less in vitro binding affinity towards PPARg.
- **Zhang et al. (1996)** reported the in vivo characteristics of the compound (AD-5075), a potent thiazolidinedione which act as antidiabetic as well as hypolipidemic in Zucker diabetic rats & mice.
- **Scientists of Hoffmann-La Roche/Boehringer Mannheim (1998)** reported hypoglycemic and hypolipidemic activities of two compounds (BM13.1258) and (BM15.2054) having the benzothiophene ring in place of the phenyl ring of benzyl group at C5-position on TZD.
- **Furnsinn et al. (1999)** Further the compounds were also reported for their PPARg agonistic activity. They also used soleus muscle strips from lean and genetically obese rats for studying the glucose metabolism in skeletal muscle. From the observation they suggested that the possibility of involvement of other biochemical pathways in glucose metabolism apart from the activation of PPARg.
- **Fukui et al., (2000)** investigated quinoline based TZD as a weak activator of PPARg both in vivo as well as in vitro. Based on the luciferase gene reporter assay studies, it was observed that 3 activated PPARg in a dose dependent manner. It was found to be weaker than Rosiglitazone and Pioglitazone.
- **Madhwan et al., (2002)** A series of pyrimidinone derivatives of thiazolidinediones were reported. All the synthesized analogues were investigated for their hypoglycemic and hypolipidemic properties in insulin-resistant and hyperlipidemic mice.
- **Kim et al., (2004)** investigated and described the synthesis and biological evaluation of

TZD's having substituted pyridines and purines in place of pyridine of Rosiglitazone. The synthesized compounds were evaluated for their effect on triglyceride accumulation in 3T3-L1 cells in vitro and hypoglycemic and hypolipidemic activity in vivo in the genetically diabetic mice.

- **Kim et al., (2007)** designed tetrahydroquinoline-linked thiazolidinediones and the analogues were tested for PPARg agonistic activity.
- **Iqbal et al.,(2012)** reported the design and synthesis of some thiazole, triazole and oxadiazole containing benzylidene TZDs. All the newly synthesized compounds were tested for their hypoglycemic and hypolipidemic activity in vivo. While oxymethyl linker was reported to be less effective with benzyl TZDs.
- **Khazi et al., (2013)** reported the synthesis of thiazolidinedione derivatives having fused imidazo [2,1-b] [1,3,4] thiadiazoles ring coupled with various alkyl/aryl/heterocyclic moieties and tested for in vivo and in vitro PPARg agonist activity. The designed compounds were found to have better in vivo profile when compared with standard drug Pioglitazone.
- **Nazreen et al. (2014)** reported a library of conjugates of chromane and 2,4 thiazolidinedione under one construct through a methylene linkage. The designed derivatives were evaluated for in vivo antidiabetic activity, in vitro PPARg agonistic activity as well as PPARg gene expression.
- **Zhou et al. (2015)** evaluated 2-thioxo-4-thiazolidinone derivatives as PPARg binding studies. Based on the PPARg competitive binding assays it was found that these derivatives have potent PPARg binding activities. Based on the SAR analysis the scaffold of a 2-thioxo-4-thiazolidinone and substitutions of hydrophobic unsaturated linker was found to capable of retaining the PPARg binding activities, while groups to phenyl groups mainly as the ortho- or meta-position lead to decrease in activity.
- **Darwish et al., (2016)** designed some novel thiazolinediones based on the dual receptor approach. Based on the study of crystal structure of PPARg and a homology modeling of free fatty acid receptor 1 (FFAR1), nineteen compounds were synthesized and few of them were found to act as insulin sensitizers.

Future Prospects

The successful completion of such research could pave the way for several significant advancements in the development of antidiabetic therapies:

1. Development of Next-Generation Antidiabetic Drugs.

2. Expansion of Structural Modifications.
3. Broader Applications in Metabolic Disorders.

CONCLUSION

This review article aims to design and synthesize novel PPARγ agonists by replacing the pyridine ring in Rosiglitazone with acidic and aromatic amino acids. The strategic incorporation of these amino acids is expected to enhance insulin sensitivity, offering a promising approach to the development of more effective and safer antidiabetic medications. By exploring the structuraland functional implications of these modifications, the study seeks to provide deeper insights into the interaction of PPARγ agonists with their receptor and their role in glucose homeostasis. The successful execution of this project could significantly contribute to the field of diabetes research, providing a foundation for the development of novel therapies that address the limitations of current treatments and improve the quality of life for individuals with diabetes.

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