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REVIEW ARTICLE

VIEW ON SOME APPROACHES USED IN SYNTHESIZED NEW PPAR α, PPAR γ AND PPAR δ AGONISTS AND THEIR PHARMACOLOGICAL EVALUATION

Abhishekkashyap[1]* and AbhishekAgarwal[2]

[1]Department of Pharmaceutical Chemistry, Agra Public Pharmacy College, Heeralal Ki Pyau, Village Artoni, Delhi-Agra National Highway (NH-2), Agra - 282007

[2]Department of Pharmaceutical Chemistry, Sanjay College of Pharmacy, 21st Milestone, NH#2, Mathura-Delhi Road, Chaumuhan, Tehsil: Chhata, Dist:-Mathura, Uttar Pradesh, Pin-281406

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ABSTRACT

Peroxisome prolifrated activated receptor (PPAR) belongs to the nuclear hormon receptor (NHR) Super family, three subtypes PPAR α, PPAR γ and PPARδ, for this receptor have been identified and found to be important target for the treatment of type 2 diabetes, dyslipidemia, atherosclerosis,etc[6].
Fibrates are used in the treatment of lipid abnormalities to decrease triglyceride (TG) levels and increase HDL- Cholesterol (HDL-C) level moderately. In many Intervention studies, fibrates showed beneficial effect in preventing the progression of atherosclerotic lesions and cardiovascular events in both non diabetic and diabetic patients. These effects are attributed to PPAR α activation, which enhance lipid catabolism, decreases TG by lowering apoC-III synthesis and increase HDL-C by induction of apoA-I, A-II.[5]
In the present review we are seeing some approaches used to synthesize PPAR α, PPAR γ as well as PPAR δ agonists and evaluation of their pharmacological effects.

INTRODUCTION

Peroxisome proliferated activated receptor (PPARs) are members of the nuclear receptor super family and the PPAR subfamily consist of three members PPAR α, PPAR γ, and PPAR δ. Many studies on PPAR α and PPAR γ have been performed and their roles are well established.[7]Further, these efforts led to the discovery of hypolipidemic agents and insulin sensitizers.

The molecule belonging to fibrate class of drugs, such a clofibrate, fenofibrate are now to act as PPAR α agonist. Thiazolidinediones (TZDs) class of insulin sensitizer, synthesized in early 1980, where later found to mediate hypoglycaemic effect through PPAR γ.[6] Frequently prescribed hypolipidemicgemfibrozil having a 5-phenoxypentanoic acid moiety instead of the fibric acid moiety is also considered a fibrate because of having almost similar pharmacological properties as the other classical fibrates.[4] We postulated that highly potent and selective PPAR α agonist would be useful drugs for dyslipidemia and atherosclerosis without body weight gain, edema or other adverse effects observed with PPAR γ activation.[5]

In Addition to the anti lipidemic effect the fibrates and the related drug gemfibrozil act on plasma concentration of proteins involved in coagulation, fibrinolysis and platelets action, several studies indicated that fibrate decrease the levels of factors promoting coagulation and increase fibrinolysis. This dual anti- lipidemic/ anti platelet effect of fibrate makes them interesting candidate for the prevention and treatment of thrombotic disorders.[1]

The fibrates primary mode of action is to selectively activate the alpha – isotype of the receptors peroxisome proliferated activated receptors (PPARs). Activation PPAR- α modulates the expression of several genes involved in lipoprotein metabolism. The activity of lipoprotein lipase4 is increase and results in an increase in the clearance of circulating triglycerides- rich lipoproteins. It is established that the apolipoprotienC-III (apoC-III) inhibits lipoprotein lipase. The biosynthesis of apoC-III is decreased by fibrates. Hence Low apoC-III levels will further enhanced the clearance of

triglycerides – rich lipoproteins. In addition to the anti hyperlipidemic effect, the fibrates have anti – inflammatory action as evidenced by a reduction acute phase reaction such as C-reactive proteins as well as a number of cytokines, IL-6, TNF – α and interferon – γ.[4]

Moreover, several Studies indicate that fibrate decrease the level of factors promoting coagulation and increase fibrinolysis. The dual hypolipidemic / antiplatelet effect of fibrates render them interesting candidate for redusing the risk of atherosclerotic and its thrombotic complication, which are the major cause of coronary artery disease. Recent studies revalidated the ability of fibrates to inhbit the activity of aldose reductase enzyme makes them reliable agents in preventing the progression of secondary diabetic complications.

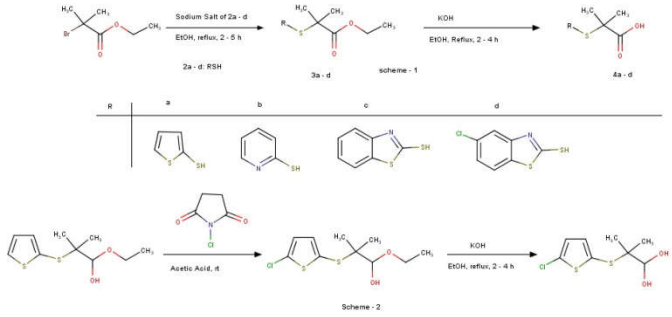
In present review we giving some approaches used in synthesizing PPAR α, PPAR γ and PPAR δ agonists and evaluation of their pharmacological actions.

Approaches used in chemistry and Evaluation

Various approaches have used to synthesize PPARs agonists. Some of approaches we are studying here, as well as their pharmacological evaluation. These approaches are used to develop PPAR α, PPAR γ, PPAR δ, agonists, some approaches are used to develop dual agonist, which can be effective in both the ways as hypolipidemic and anti- diabetic uses.

Alessandra *et al*., (2005) reported synthesis of thioaryloxyacids analogues of clofibric acid, the acids 4a-e were repoted by reaction of ethyl 2- bromoisobutyrate with sodium salt of commercially available thiols 2a-d, in refluxing ethanol in scheme 1.

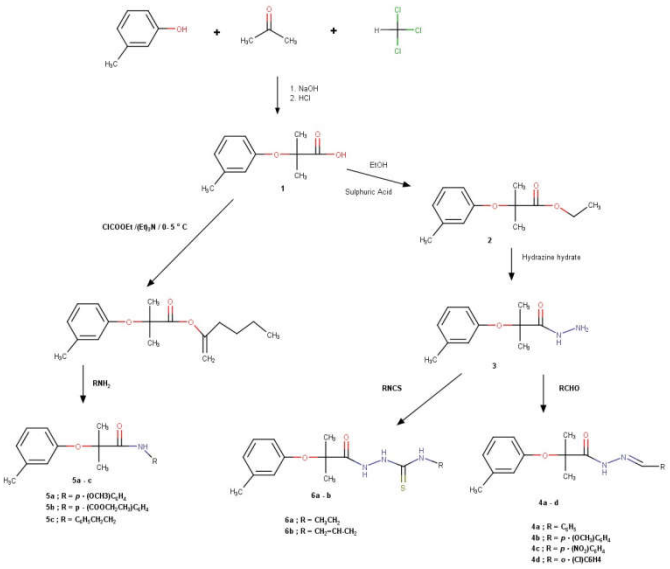
In scheme 2 chlorination was done of compound 3a with N-chlorosuccinimide in glacial acetic acid at room temperature. All the esters 3a-e were hydrolysed in presence of KOH to give the acids 4a-e.[1]



Effect of compounds 4a – e on platelet aggregation were monitored with a PFA – 100 instrument using anticoagulated bull blood. Gemfibrozil and acetylsalicylic acid were used as reference drugs. Compound 4e showed the best activity among all the tested compounds. Compound 4e is only effective at high concentration. The presence of a chlorine atom on the heterocyclic system seems to increase the activity, compound without these substituent showed lower anti aggregate properties. Size of the heterocyclemay also influenced the result, with benzothiazolethioaryloxyacids more active than thiophene and pyrimidine derivative.[1]

G.A. Idrees *et al*. (2009) reported that treating m-cresol with acetone and chloroform in the presence of sodium hydroxide afforded 2-(m-tolyloxy) isobutyric acid **1** that was converted in to hydrazide**3, condensation** of hydrazide with the appropriate carbonyl compounds afforded the arylidenes**4a – d.**

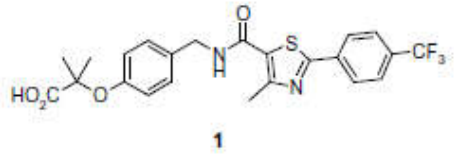
The acid **1** was converted to the corresponding carboxamides**5a – c** by the mixed anhydride method using ethyl chloroformate. The desired 1,4 – di substituted thiosemicarbazide**6a – b** were obtained by treating the hydrazide**3** with the appropriate alkyl isothiocynate.



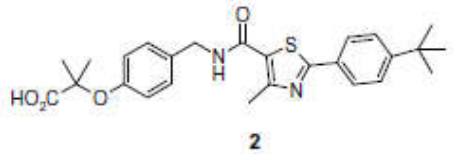
Compound 5a exhibited the maximum hypolipidemicactivity expressed as 23.24% and 25.97% reduction in the level of total cholesterol and TG.

Paul Martres *et al*.(2007) reported the discovery of a new potent selective PPAR αagonist, **1**Starting from the structure of **1**, they have designed a new class of PPAR α/γ dual agonists. SAR studies around **1** have demonstrated that the para substitution of the phenyl ring anchored to the thiazole moiety could modulate potency on the PPAR γ isoform.The p-trifluoromethyl analogue **1** is weakly active on PPAR γ whereas the p-tert-butyl **2** displays significant PPARγ activity while being as potent as **1** on PPARα.[3]

Table 1
In vitro potencies of PPARα agonists.[a]



1



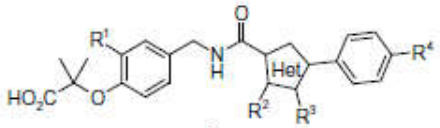
2

Isoform	EC_{50} (μM)	
	1	**2**
h-PPARα	0.004	0.004
h-PPARδ	2.83	10
h-PPARγ	9.71	0.8

[a] Data generated using cell based transient transfection assays[12]; compounds behave as full agonists.

In addition, molecular modeling studies of the alpha and gamma binding modes have been performed on the generic scaffold. The model has raised the hypothesis thataliphatic substitution at R^1 and R^2/R^3 on 3 could lead to an increasein potency on PPARγ. According to the crystal structure of PPARsligand binding domain,two hydrophobic pockets exist on αand γ subunits which could be accommodated by

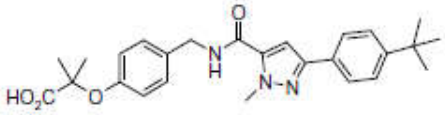
R^1groups for the first pocket and R^3/R^3 groups for the second. The pyrazole corewas selected as a versatile ring which would be synthetically amenableto the rapid variation of substituents at the R^2/R^3positions. p-tert-Butyl derivative **4**, the first example synthesized, maintainedpotency on the gamma isoform with a significant decrease in potencyon the alpha isoform when compared to **2.**[3]



3

Figure 1. Generic scaffold of PPARα/γ agonists.

Table 2
In vitro potencies of compound **4**.[a]



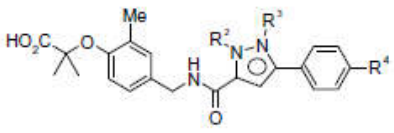
4

Isoform	EC_{50} (μM)
h-PPARα	0.16
h-PPARδ	10
h-PPARγ	1.0

[a] Data generated using cell based transient transfection assays[12]; compounds behave as full agonists.

An SAR study was conducted retaining pyrazoleas the central core heterocycle. Compounds bearing a bulkyaliphatic group at R4 were synthesized with variation at R^1, $R^2$and R^3. The choice of R^1 was driven by our knowledge of the binding mode in the alpha and gamma subunit. Although the PPARαand PPARγ binding pockets are very similar in size and shape, one key determinant for subtype selectivity is the size of the R^1 group. Larger R^1 groups generally give higher PPARαpotencytherefore we hypothesized that smaller groups such as methyl and methoxy should experience diminished steric interactionsand therefore could be more suitable for PPARα/γ dual compounds.[3]

Table 3
In vitro potencies of pyrazoles **5-17**[a] (R^1 = Me).



Compound	R^2	R^3	R^4	EC_{50} (μM) h-PPARα	EC_{50} (μM) h-PPARδ	EC_{50} (μM) h-PPARγ
5		H	t-Bu	0.383	>25	0.270
6	Me		t-Bu	0.050	2.165	0.03
7		Me	t-Bu	0.01	>10	0.006
8	Me		i-Pr	0.020	1.360	0.05
9		Me	i-Pr	0.004	4.850	0.008
10	Me		i-Bu	0.045	2.870	0.05
11		Me	i-Bu	0.002	2.060	0.008
12	Et		t-Bu	0.050	2.700	0.030
13		Et	t-Bu	0.010	>25	0.015
14			t-Bu	0.045	1.150	0.06
15			t-Bu	0.032	>25	0.069
16			t-Bu	0.066	2.05	0.303
17			t-Bu	0.042	>25	0.478

[a] Data generated using cell based transient transfection assays[12]; compounds behave as full agonists.

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