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Activity Anti-Inflammatory and *in silico* Study of New Thiazolidinedione Derivatives

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MCADL, TGS, ALS and IRP designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors LFCCL, MHZ, VS and BRS administered the study's analysis. Authors LRM, IBVA, CNAC and BSIM performed the biological activity. Authors LS and LCLO managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: Evaluation of the anti-inflammatory properties of new thiazolidine-2,4-diones derivatives.
Study Design: Study the effects of new thiazolidine-2,4-diones derivatives on the inflammatory process.

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Place and Duration of Study: Departamento de Antibióticos, Universidade Federal de Pernambuco (UFPE), between June 2011 and July 2012.
Methodology: Compounds thiazolidine-2,4-diones were tested for anti-inflammatory activity by air pouch model. Swiss albino mice were used for the study. Air cavities were produced by subcutaneous injection of 2.5 mL of sterile air into the intrascapular area of the back. An additional 2.5 mL of air was injected into the cavity every 3 days to keep the space open. Seven days after the initial air injection, 1 mL of a 1% solution of carrageenan dissolved in saline was injected directly into the pouch to produce an inflammatory response. The compoundsthiazolidine-2,4-diones and standard piroxicam were tested at doses of 3 mg/kg body weight. The total number of polymorphonuclear leukocytes (PMNL) was countedusing an improved.
Results: The results support the use of these derivatives in inflammatory process. Among the compounds tested the ones that showed a greater effect in inhibiting the migration of neutrophils were the 3a, 3b, 3c, 3d and 3e. The anti-inflammatory effects showed by 3a-j were promising, probably due to the duality of action on PPAR alpha and gamma.
Conclusion: In conclusion, this study has shown that the thiazolidine derivatives do possess significant anti-inflammatory effects in laboratory animals. The exact mechanism and the bioactive principles responsible for these actions remain to be explained.

Keywords: Thiazolidinedione; molecular modeling; anti-inflammatory properties.

1. INTRODUCTION

Thiazolidine-2,4-diones have been extensively studied owing to their involvement in the regulation of various physiological processes such as cell proliferation, angiogenesis, inflammation, and glucose metabolism [1]. These compounds show significant antidiabetic [2], antimicrobial [3], antichagasic [4,5,6], anti-HIV [7], anti-inflammatory [8], antiatherosclerotic [9] and anticancer [10,11,12] activities.

The inflammatory response involves the sequential release of mediators and the recruitment of circulating leukocytes, which become activated at the inflammatory site and release further mediators. This response is self-limiting and resolves through the release of endogenous anti-inflammatory mediators and the clearance of inflammatory cells. The persistent accumulation and activation of leukocytes is a hallmark of chronic inflammation. Current approaches to the treatment of inflammation rely on the inhibition of pro-inflammatory mediator production and of mechanisms that initiate the inflammatory response [1]. However, the mechanisms by which the inflammatory response resolves might provide new targets in the treatment of chronic inflammation. Peroxisome proliferator-activated receptors (PPARs) are members of the intracellular hormone receptors family and act as ligand-activated transcription factors [2]. The three receptors, PPARα, PPARδ e PPARγ, are encoded by different genes but show substantial amino acid similarity, especially within the DNA and ligand binding domains. Synthetic PPARα ligands such fibrates (eg. Fenofibric acid) are used in patients to lower triglyceride-rich lipopotreins [3]. Some Thiazolidine-2,4-dione derivatives (TZDs) such as rosiglitazone, pioglitazone and troglitazone were clinically and commercially available as antidiabetic drugs in the treatment of type 2 diabetes acting via PPARγ. These three thiazolidines share a common thiazolidine-2,4-dione structure that is responsible for the majority of their pharmacological effects, including anti-inflammatory ones [13].

Recently, there has been a great deal of interest in the involvement of PPAR in inflammation [4]. Were the first to report that mice with deficient PPARα presented a increased inflammatory response induced by leukotriene B4 and arachidonic acid. There are evidences from in vitro and in vivo studies demonstrating that PPARα agonists may present anti-inflammatory activity. Fenofibrate e gemfibrozil inhibit the production of interleukin IL-6 e prostaglandins (PG) and the expression of cyclooxygenase (COX)-2 genes induced by IL-1B in the smooth muscle cells [5]. Other PPARα agonists, clorofibrate and WY-14643, also inhibit the expression of genes for IL-6 and IL-8 in human keratinocytes irradiated with ultraviolet light. In vivo studies have given further support to the inhibitory effects of PPARα agonists on cytokines production and also demonstrated that they inhibit the edema and cell influx into to the skin in experimental models of dermatitis. PPARα agonists inhibit the edema and thermal allodynia induced by carrageenan in rats [6]. The variety of the biological activities attributed to the thiazolidine derivatives motivated us to use them as prototypes on the synthesis of the 5-arylidene-3-(4-phenyl-benzyl)-thiazolidine-2,4- dione series. According to previous knowledge of the distinct pharmacophoric subunits of the series 5-arylidene-3-(4-phenyl-benzyl)-thiazolidine-2,4-dione employing methodological strategies of medical chemistry, the purpose of this work was to evaluate ten new bioactive thiazolidinic derivatives substituted on the position 3 and 5 by the 4-phenyl-benzyl and arylidene, respectively [7]. In particular, we investigated the anti-inflammatory and activities by using the air pouch model and peritonitis induced by carrageenan.

2. MATERIALS AND METHODS

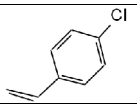
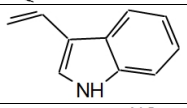
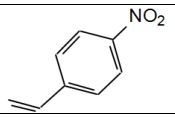
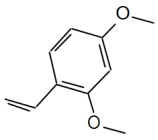
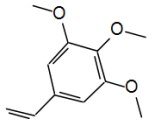
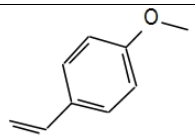
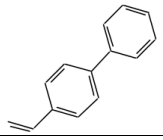
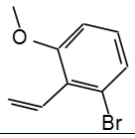
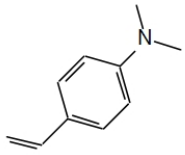
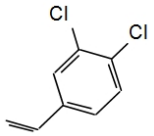
2.1 Chemical

The derivatives 5-arylidene-3-(4-phenyl-benzyl)-thiazolidine-2,4-dione (3a-3j) were synthesized and provided by the Research Center on Therapeutic Innovation of the Federal University of Pernambuco, Brazil (Table 1). The carrageenan and piroxicam were purchased from Sigma. The compounds tested and the standard drugs were dissolved in saline solution containing tween 80 (9:1; v/v).

2.2 Biological Activity

Compounds 3a-j were tested for anti-inflammatory activity by air pouch model, as previously described [11,12]. All experimental procedures described below were approved by the Animal Care Committee of the Universidade de Federal de Pernambuco (processo nº 001046/207-42). Swiss albino mice of either sex weighing between (25-30 g) were used for the present study. They were housed in plastic cages (6 per cage) and maintained in a light and humidity controlled environment. Food and water were allowed ad libitum. For 8 h prior to an experiment, the mice were deprived of food but not water. Air cavities were produced by subcutaneous injection of 2.5 mL of sterile air into the intrascapular area of the back. An additional 2.5 mL of air was injected into the cavity every 3 days to keep the space open.

Table 1. Structure of new thiazolidine-2,4-diones derivatives used in this study

Compound	Radicals	Yield (%)
3-(4-phenyl-benzyl)-thiazolidine-2,4-dione	-	85
5-(4-chloro-benzylidene)-3-(4-phenyl-benzyl)-thiazolidine-2,4- dione (3a, R= 4-Chloro)		89
3-(4-phenyl-benzyl)-5-(indol-3-yl-methylene)-thiazolidine-2,4-dione (3b, R= 5-indole		75
5-(4-nitro-benzylidene)-3-(4-phenyl-benzyl)-thiazolidine-2,4- dione (3c, R= 4-nitro)		56
5-(2,4-dimethoxy-benzylidene)-3-(4-phenyl-benzyl)-thiazolidine-2,4-dione (3d, R= 2,4-dimethoxy)		46
5-(3,4,5-trimethoxy-benzylidene)-3-(4-phenyl-benzyl)-thiazolidine-2,4-dione (3e, R= 3,4,5-trimethoxy)		74
5-(4-methoxy-benzylidene)-3-(4- phenyl-benzyl)-thiazolidine-2,4-dione (3f, R= 4-methoxy)		84
5-(4-phenyl-benzylidene)-3-(4-phenyl-benzyl)-thiazolidine-2,4- dione (3g, R= 4-phenyl)		63,5
5-(2-methoxy-5-bromo-benzylidene)-3-(4-phenyl-benzyl)- thiazolidine-2,4-dione (3h, R= 2- methoxy-5-bromo)		79
5-(4-N,N-dimethylamine- benzylidene)-3-(4-phenyl-benzyl)- thiazolidine-2,4-dione (3i, R= 4-N-dimethyl-amine)		56
5-(3,4-dichloro-benzylidene)-3-(4-phenyl-benzyl)-thiazolidine-2,4- dione (3j, R= 3,4-dichloro)		39

Seven days after the initial air injection, 1mL of a 1% solution of carrageenan (Sigma) dissolved in saline was injected directly into the pouch to produce an inflammatory response.

The doses were chosen according to previously published data by our group using similar compounds [13]. The compounds 3a-3j and standard piroxicam in the doses 3 mg/kg or vehicle (water/Tween 80, 95:5 v/v) ware administered orally 1h before injection of carrageenan (1 mL; 1% w/v in saline) into the air pouch. After 6h of injection of carrageenan, mice were killed and pouches washed thoroughly with 3 mL of phosphate buffer solution (PBS) containing 50mUI/mL heparine. The total number of polymorphonuclear leukocytes (PMNL) was counted using an improved.

2.3 Docking

The structural optimization of the 5-arylidene-3-(4-phenyl-benzyl)-thiazolidine-2,4-dione (3a-3j), and piroxicam were initially obtained using the AM1 method [14] implemented at the BioMedCache program BioMedCAChe version 6.1, [Copyright ©2000-2003 Fujitsu Limited, Copyright©1989-2000, Oxford Molecular Ltd. [10] using default values for the convergence criteria. The target structures used in the docking studies were taken from the RCSB Protein Data Bank (13) under the PDB code 1K7L for the peroxisome proliferator activated receptor - alpha (PPARα) protein co-crystallized with 2-(1-methyl-3-oxo-3-phenyl-propylamino)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (544) and the PDB code 2HWQ for the peroxisome proliferator activated receptor - gamma (PPARγ) protein co-crystallized with the [(1-{3-[(6-benzoyl-1-propyl-2-naphthyl)oxy]propyl}-1h-indol-5-yl)oxy]acetic acid (DRY). It should be remarked that the certification of these proteins as possible targets for the anti-inflammatory activity was based in the literature [15]. The structure of only one monomer per protein was chosen as target for docking studies. The Gold 4.0 Software was used for these computations, taking the ligand flexibility (main torsions) into account during the calculations [16]. The protein active site, in each case, was defined as all residues within a radius of 5 Å from any atom of the co-crystallized ligand, respectively. The theoretical binding profile proposed for these ligands with PPARα and PPARγ was determined as the highest (most positive) scored among 10 possible solutions for each ligand generated according to the GOLD Docking Score function. Additionally, each one of the co-crystallized ligands was submitted to a re-docking procedure in order to certify the quality of the docking protocol.

3. RESULTS AND DISCUSSION

The results are expressed as mean ± S.E.M. The statistical analysis was performed by analysis of variance (one-way ANOVA) followed by Tukey's Multiple Comparison Test. Results obtained are described in Tables 2 and 2.1.

The number of animal was 6 in each group. The probability values were calculated using one way ANOVA followed by Tukey's Multiple Comparison Test: *P < 0.05 vs. control; #P < 0.05 vs. piroxican; piroxican vs. 3j = NS.

The most stable docking score for the 5-arylidene-3-(4-phenyl-benzyl)-thiazolidine-2,4-dione (**3a-3j**) besides co-crystallized ligands 544 and DRY, and Piroxicam, (standard drug with anti-inflammatory activities) were shown in Table 3 for the two investigated targets. The docking values are in agreement with experimental ones. The structure of the 3d ligand showed a high affinity value with the target PPARα in accordance with the *in vivo* activity (Table 3). The ligand 3d, also, shows high affinity for the PPARγ target by silico approach, i.e., with high docking scores. The docking scores for Piroxicam is smaller than all compounds 3a-j studied for PPARα and PPARγ.

Table 2. Number of polymorphonuclear leukocytes (average ± standard error) found in the air pouch six hours after the induction of the inflammation

Compounds – dose (3mg/Kg)	Molar concentration	Nº of PMNL/mL (x106)	Percentage (%) of cellular migration inhibition
3a	7,398 mMols/kg	3.60±0.06*#	91.3
3b	7,31 mMols/kg	13.0±1.17*#	68.5
3c	7,211 mMols/kg	11.1±0.17*#	73.1
3d	6,96 mMols/kg	5.1±0.10*#	87.6
3e	6,68mMols/kg	10.0±1.33*#	75.8
3f	7,481 mMols/kg	31.2±0.35*#	24.4
3g	6,711 mMols/kg	36.0±0.31*#	12.8
3h	6,251 mMols/kg	21.0±1.67*#	49.1
3i	7,246 mMols/kg	27.6±0.13*#	33.2
3j	7,41 mMols/kg	19.2±0.12*NS	53.5
Piroxicam	9,40 mMols/kg	17.4±0.07*NS	57,9
Control		41.3±0.57	

Table 2.1 *In vivo* characterization of 3a-e derivatives

Compounds – dose (3mg/Kg)	ED50 (mg)	pED50
3a	0.2095	6.6790
3b	0.1498	6.8245
3c	0.1366	6.8645
3d	0.0811	7.0910
3e	0.0870	7.0604

Table 3. The most stable docking score for the 5-arylidene-3-(4-phenyl-benzyl)-thiazolidine-2,4- dione (3a-3j), piroxicam, DRY and 544 ligands

Compounds	Docking score PPARα (1K7L)	Docking score PPARγ 2HWQ)
3a	67.60	63.98
3b	69.02	67.96
3c	60.11	62.10
3d	69.99	64.74
3e	68.03	67.06
3f	67.35	59.89
3g	70.15	63.82
3h	69.78	64.37
3i	62.75	61.83
3j	69.29	67.13
Piroxicam	48.34	45.00
DRY	-	75.00
544	80.46	

In order to investigate the molecular reasons of the docking scores observed through the *in silico* studies, a detailed analysis of the polar interactions (hydrogen bonds) for the docking ligands with its respective targets could be seen in Table 4, where are shown the distances between the donor and acceptor atoms involved in polar interaction between the compounds and the targets, after docking.

One can see in Figs. 1 and 2 the interesting results found between the docking scores for PPARs target and the PPARs *in vivo* inhibition (at 1μM concentration), revealing that the compounds that presented higher *in vivo* inhibition also presented higher affinities (higher docking scores) with the PPARs target, observed through the *in silico* studies. Fig. 3 provides the relationship between the Gold docking score and the pED50 values to the compounds 3a-e in the PPAR and PPARγ targets. The values of anti-inflammatory activity to all compounds and ED50 of 3a-e are shown in Table 2.

To compare the binding pattern of the compounds 3a-j and Piroxicam with the crystallographic ligand (544), in PPARα, the Fig. 4 shows the conformations of the docking solutions presented in Table 2 alongside the co-crystallized ligand 544. The compound that produced the best result (higher docking score) in docking analysis, the compound 3d, was analyzed in detail along the crystallographic structure of ligand 544 in PPARα, and the results of this comparison are illustrated in Fig. 5 (Figs. 4, 5 and 6, were generated using PYMOL v0.99 – DELANO [17]).

Fig. 6 shows that compound 3d forms hydrogen bonds with THR279, SER280, TYR314 and TYR464 in the PPARα binding site with measured distances 2.85, 3.41, 2.98 and 3.20 Aº, respectively. Notably, "544", co-crystallized with PPARα, also forms important hydrogen bonds with SER280, TYR314, HIS440 and TYR464, whereas the Piroxicam forms hydrogen bonds with THR279, LEU331 and ALA333 (Table 4).

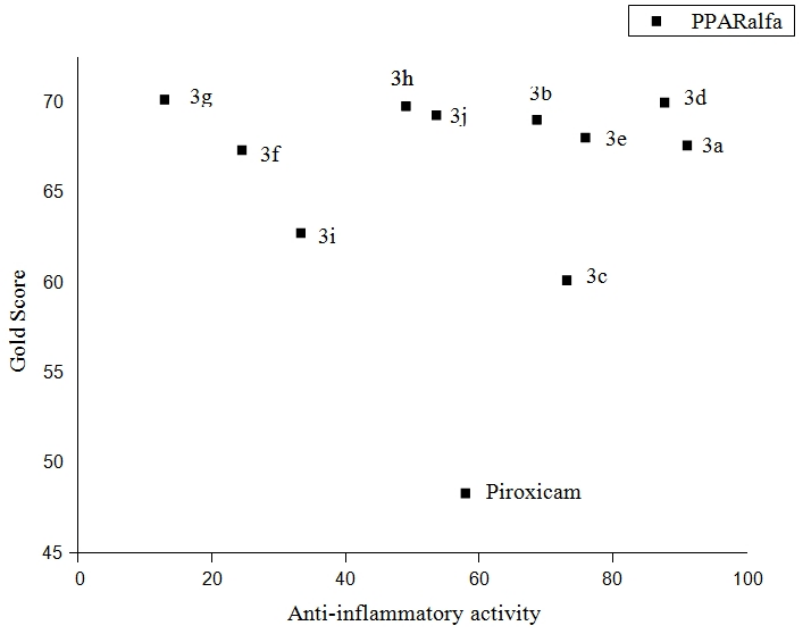


Fig. 1. Docking results and the *in vitro* inhibition for the PPARα target

Table 4. Comparison of the polar interactions obtained after the docking calculations using PPARα and PPARγ as targets. Each value represents the distance, in Å, between the donor and the acceptor atoms involved in the polar interaction. The program used for this analysis was the Pymol, under internal default condition for setup

Compound	Residue of 1K7L target							Residue of 2HWQ target				
	HR279	HIS440	ALA333	SER280	TYR314	TYR464	LEU331	SER289	ARG288	TYR327	HIS449	TYR473	GLN286
3a	3.12			-	-	-		2.61					
3b	-			-	-	-		-	-				
3c	2.93			3.42	3.15	3.30		-	-				2.86 and 2.74
3d	2.85			3.41	2.98	3.20		2.43	-	3.21	3.36		
3e	-			-	3.28	3.06		-	3.45 and 3.49				
3f	2.93			-	-	-		-	-				
3g	-		2.52	-	-	-		-	-				
3h	-			-	-	-		-	-	3.21			
3i	-			-	-	-		-	-				
3j	-			-	-	-		2.74	-				
Piroxicam	2.57		3.04	-	-	-	1.89	1.96 and 3.27	2.23				
DRY	-			-	-	-							
544		2.82		2.72	2.69	2.60		-	-				

The co-crystallized ligand DRY did not show polar interactions, in active site of 2HWQ, when used the Pymol software or hidrofobic b ind with the Ligant Explorer.

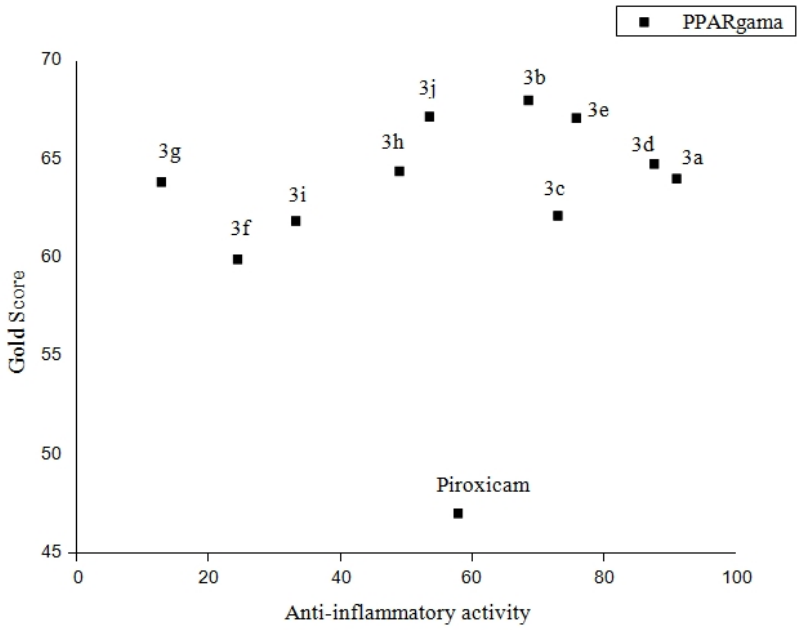


Fig. 2. Docking results and the in vivo inhibition for the PPARγ target.

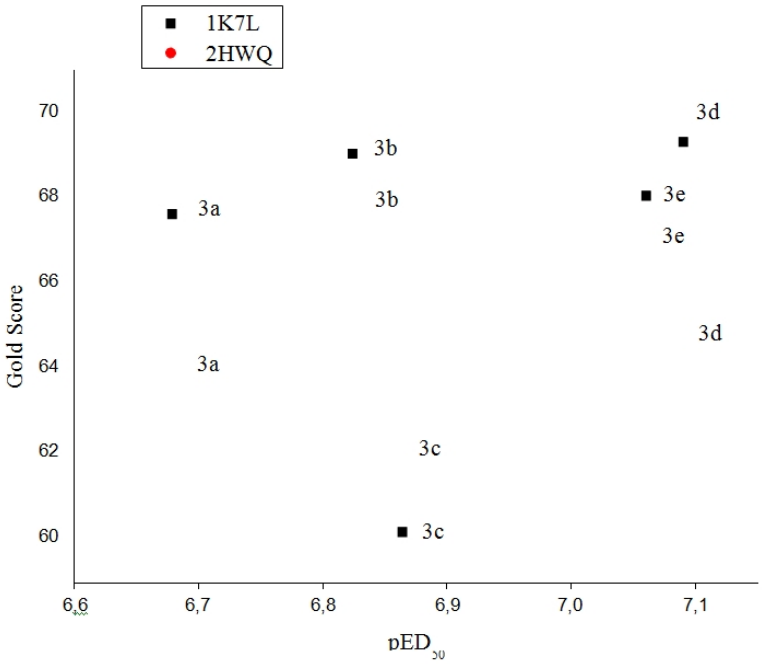


Fig. 3. Relationship between the Gold docking score and the pED_{50} values to the compounds GQ-24 (3a), GQ-28 (3b), GQ-32 (3c), GQ-36 (3d) and GQ-38 (3e) for the PPARα and PPARγ targets

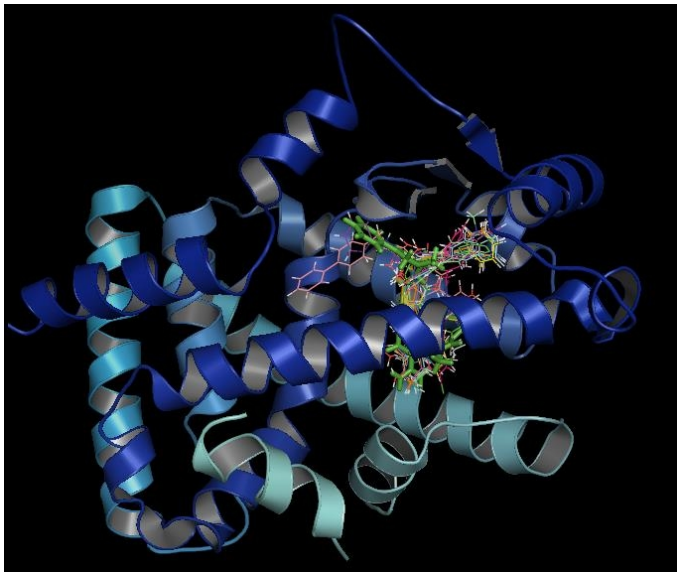


Fig. 4. Superimposed docking conformations of compounds 3a-j (lines) and Piroxicam (sticks), alongside the co-crystallized ligand 544 (green sticks) in active site of PPARα

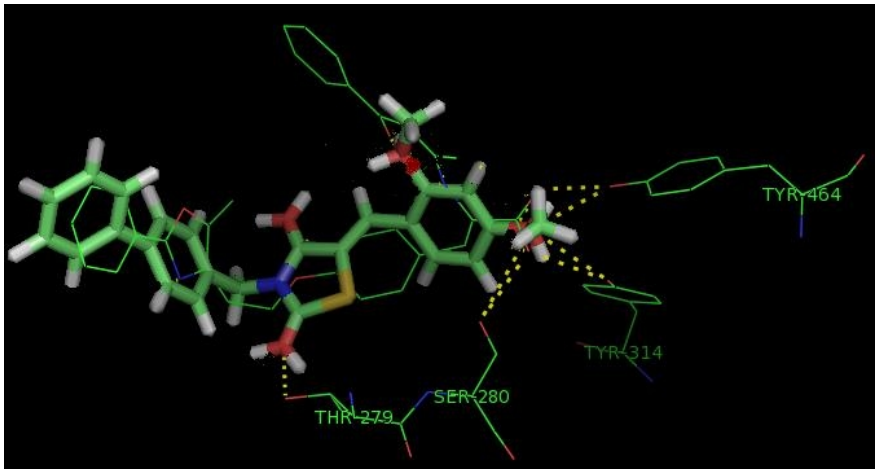


Fig. 5. Docking solution for compound GQ36 (3d) (sticks) alongside the co-crystallized ligand "544" (lines) in active site of PPARα

To compare the binding pattern of the compounds 3a-j and Piroxicam with the crystallographic ligand (DRY), in PPARγ, the Fig. 6 shows the conformations of the docking solutions presented in Table 1 alongside the co-crystallized ligand DRY. After the optimization of the arylidene thiazolidinadiones using the AM1 method, there was a relationship with the results obtained by Leite [18], confirming that the Z isomer as the most stable one, for all the compounds. An in silico study using GOLD program was performed to dock the compounds 3a-j into the active site of the enzyme in order to investigate the molecular characteristic of the heterocyclic derivatives that could be possibly

associated with the inhibition of the PPARα and PPARγ target. As PPARs α and γ were involved in inflammation resolution, and earlier docking studies in PPARα and PPARγ and reduction on plasmatic levels of glucose and triglycerides were observed to similar thiazolidine compounds [19], we could infer that results of inhibition on thiazolidine compounds, could be related to PPAR activation. The compounds 3a-j of the class thiazolidine-2,4-dione-3,5-dissubstitued, were assayed for evaluation of anti- inflammatory activity in the air pouch model induced by carrageenan in mice. Piroxicam were standard drug used. The results obtained in air-pouch model are illustrated in Table 3. Between the most active derivatives in the dose of 3 mg, there are the following compounds: 3d (2,4-dimetoxy, 87,6% of inhibition, pED50 0,0811), and 3e (3,4,5-trimetoxy, 66% of inhibition, pED50 0,087). It should be remarked that the compounds 3d and 3e contain methoxy in the position 2,4 and 6 of group benzyl ring. The compound 3a and 3c contains a chlorine atom in position 4 and a nitro group in position 4 of the benzyl ring, respectively, while the compound 3b contains indole-3-il- methylene group in a position 5 of heterocyclic ring showed higher values for the pED50, therefore lower activity. Among the compounds tested the ones that showed a greater effect in inhibiting the migration of neutrophils were the 3a, 3b, 3c, 3d and 3e. These results are in accordance with Napimoga [20] which showed that the endogenous agonist of PPARγ, 15d-PGJ2, reduces the migration of neutrophils mediating the suppression of expression of ICAM-1 in endothelial cells, but that is not linked to decreased production of cytokines and chemokines or CD11a in neutrophils. However, this action is dependent on the signaling pathways of NO by reducing the polymerization of F-actin in neutrophils. In humans, treatment with PPARγ agonists reduces the circulating level of proteins that serve as markers of inflammation [21]. The ATDZs are described in the literature as PPARγ agonists. The fibrates are PPARα agonist and the glitazone have gamma action. The anti-inflammatory effects showed by 3a-j were promising, probably due to the duality of action on PPAR alpha and gamma.

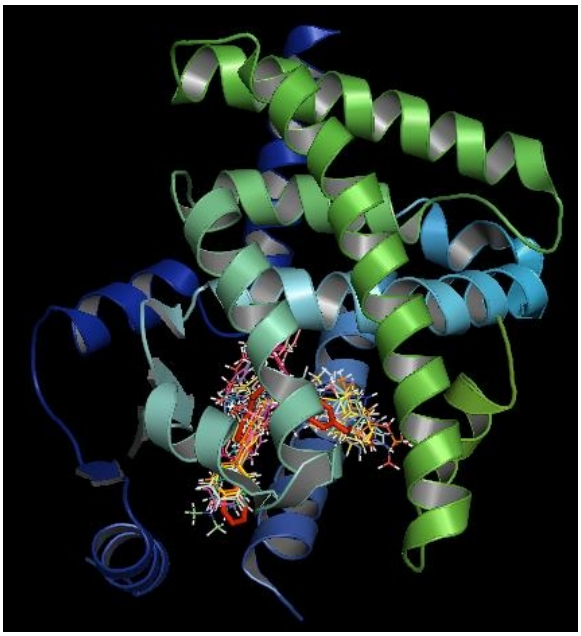


Fig. 6. Superimposed docking conformations of compounds 3a-j (lines) and Piroxicam (lines), alongside the co-crystallized ligand DRY (red sticks) in active site of PPARγ

4. CONCLUSION

Molecular docking calculations followed by a number of in vivo biological assays were used to identify novel anti-inflammatory agents among the class of 2,5-dissubstitued thiazolidine and acting through a PPAR inhibition mechanism. The results strongly suggest that the mechanism of action of the derivatives may be linked partly to PPARs. In conclusion, this study has shown that the thiazolidine derivatives do possess significant anti-inflammatory effects in laboratory animals at the doses of 3 mg/kg for inflammation assays. The results support the use of these derivatives in inflammatory process. The exact mechanism and the bioactive principles responsible for these actions remain to be explained.

CONSENT

The present study did not involve patients.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as the ethical principles of the Brazilian Society of Laboratory Animal Science (SBCAL). All experiments have been examined and approved by the committee for ethics in Animal Research of the UFPE (process number 001046/207-42).

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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