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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, in vitro anticancer activity and in silico study of new disubstituted thiazolidinedione derivatives

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Abstract Thiazolidinediones are known to have antidiabetic activity, but new activities are being discovered every year; among these, their anticancer activity has received the most attention. In this study, we synthesized three new disubstituted thiazolidinediones and assayed their cytotoxicity against six tumor cell lines, as well as against normal cells. Cytometry studies and molecular modeling were also performed to elucidate the mechanism of cytotoxicity. Of the three new thiazolidinediones synthesized, (5*Z*)-5-(3-bromo-benzylidene)-3-(4-nitrobenzyl)-thiazolidine-2,4-dione (LPSF/SF-13) exhibited the most promising activity; it was selectively cytotoxic against leukemia, lymphoma, glioblastoma, and hepatocarcinoma cell lines without being toxic to normal cells. Apoptosis was the main cell death process induced by this compound, although it also induced necrosis. Furthermore, molecular modeling studies showed that LPSF/SF-13 had good affinity for peroxisome proliferator-activated receptor γ; binding to the receptor involved hydrogen bonds with Arg288 and Ser342 residues (bond distances of 3.1 and 2.8 Å, respectively), as well as a π-bonding interaction with His449. We concluded that LPSF/SF-13 is a promising compound for in vivo and combination therapy studies against cancer.

Keywords Thiazolidinediones · Cytotoxicity · Anticancer · Molecular modeling

This article is dedicated to the memory of Suely Lins Galdino.

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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 (Barros *et al*., 2004). These compounds show significant antidiabetic (Mourão *et al*., 2005), antimicrobial (Gouveia *et al*., 2008), antichagasic (Du *et al*., 2002; Cohen *et al*., 2004), anti-HIV (Rawal *et al*., 2007), anti-inflammatory (Uchôa *et al*., 2009), and anticancer (Chandrappa *et al*., 2008) activities.

Thiazolidine-2,4-diones have been shown to have a broad-spectrum antineoplastic activity, including activity against human leukemia (Liu *et al*., 2006), melanoma (Klopper *et al*., 2009), prostate cancer (Matsuyama and Yoshimura, 2008), and hepatocarcinoma cells (Wu *et al*., 2012). These molecules are agonists of peroxisome proliferator-activated receptor γ (PPARγ), which is expressed in many human tumors, including lung, breast, colon, prostate, and bladder tumors (Han and Roman, 2007). Thiazolidine-2,4-diones act mainly as tumor suppressors

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by inducing the expression of proapoptotic molecules and other molecules that regulate the cell cycle (Han *et al*., 2004), as well as by disabling critical pathways that promote cancer survival, such as the Akt pathway, by inhibiting K-Ras-induced phosphorylation (Shao *et al*., 2002). Furthermore, activation of PPARγ by its ligands induces apoptosis inhibiting nuclear factor kappa B activity, which upregulates various anti-apoptotic genes, and suppressing the expression of pro-apoptotic ones (Chen *et al*., 2002; Tachibana *et al*., 2008).

The thiazolidine-2,4-dione derivatives rosiglitazone, pioglitazone, and troglitazone, which act via PPARγ, have been used for the treatment of type 2 diabetes. They share a common thiazolidine-2,4-dione structure that is responsible for the majority of their pharmacological effects, including their anti-inflammatory effects (Barros *et al*., 2010). Because inflammation is a crucial hallmark of cancer (Hanahan and Weinberg, 2011), it may also be a good target for thiazolidine-2,4-dione derivatives.

The chemical reactivity of the thiazolidine ring allows the introduction of many substituents, which makes the ring a useful framework for the development of novel compounds. Among the many reactions involving the thiazolidine ring, the most frequently reported reactions in the literature include N-alkylation at the 3-position (Graciet *et al*., 1996) and the reactions of carbonyl compounds with the methylene carbon at the 5-position (Vicini *et al*., 2006).

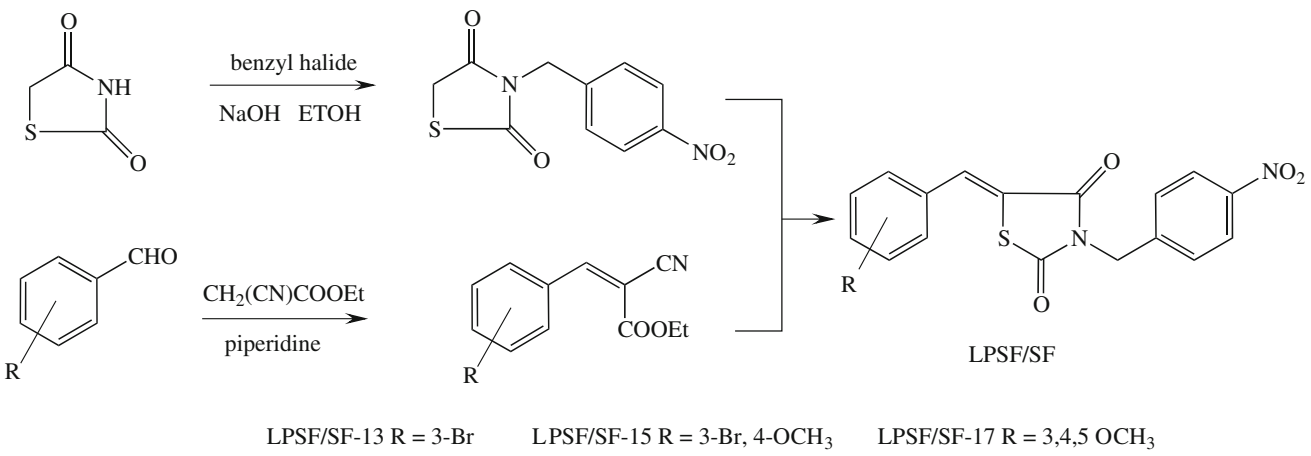
Here, we describe the synthesis and characterization of three new 3,5-disubstituted thiazolidine-2,4-diones. The synthesized compounds were screened for in vitro cytotoxicity against six tumor cell lines, as well as against human peripheral blood mononuclear cells. The molecular mechanism by which the most promising derivative induced cell death was elucidated by flow cytometry, and we also performed molecular modeling of the binding of the derivative to PPARγ.

Materials and methods

Synthesis and characterization of LPSF/SF-13, LPSF/SF-15, and LPSF/SF-17

LPSF/SF-13, LPSF/SF-15, and LPSF/SF-17 were synthesized as shown in Scheme 1. In brief, 3-(4-nitrobenzyl)-thiazolidine-2,4-dione was synthesized by condensation of thiazolidine-2,4-dione with 4-nitrobenzyl bromide in the presence of KOH in ethanol (Silva *et al*., 2001). Then an equimolar mixture of 3-(4-nitrobenzyl)-thiazolidine-2,4-dione and an appropriately substituted ethyl-2-cyano-3-phenylacrylate in ethanol containing 350 μL of piperidine was stirred under reflux for 4 h and cooled to room temperature. The solid that precipitated was filtered under vacuum and washed with water, and absolute ethanol to afford the expected 3,5-disubstituted thiazolidine-2,4-dione products in good yields (>76 %). All the compounds were characterized by infrared (IR) spectroscopy, ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectroscopy, and mass spectrometry. The configurations of the exocyclic C=C double bond of the final products were assigned by means of ^{1}H NMR spectroscopy; the spectra showed only one kind of methine proton, which was characteristic of *Z* geometrical isomers.

All melting points were measured on a Quimis-340.27 apparatus (Quimis, Diadema, SP, Brazil) and are uncorrected. All reactions were monitored by thin-layer chromatography on 0.25-mm silica gel plates (60F254, Merck, Germany). IR spectra were recorded on potassium bromide pellets with a Bruker IFS-66 IR spectrophotometer (Bruker, USA). ^{1}H NMR spectra were recorded on a Unity Plus-300 MHz Varian spectrometer (Varian, USA) with tetramethylsilane as an internal standard and DMSO-d_6 as the solvent. LPSF/SF-15 and LPSF/SF-17 were subjected to electron-impact mass spectrometry (70 eV; Delsi-



Scheme 1 Synthesis of new disubstituted thiazolidinedione derivatives

Nermag R1010C, Delsi-Nermag), and LPSF/SF-13 was subjected to negative-ion-mode electrospray-ionization mass spectrometry (HCTultra, Bruker Daltonics).

Biological evaluation

Human tumor cell lines and MTT assay

The cytotoxicities of LPSF/SF-13, LPSF/SF-15, and LPSF/SF-17 were tested against six human tumor cell lines: NG97 (glioblastoma), HepG2 (hepatocarcinoma), MIA PaCa (pancreatic adenocarcinoma), T47D (human breast cancer), Raji (Burkitt's lymphoma), and Jukart (T cell leukemia). All cell lines were obtained from Rio de Janeiro Tissue Cell Bank except for the NG97 cells, which were kindly provided by Professor Roger Chammas (Universidade de São Paulo). Cells were cultured in RPMI-1640 medium supplemented with 10 % fetal calf serum, 2 mM glutamine, 100 mg/mL streptomycin, and 100 U/mL penicillin at 37 °C with 5 % CO_2.

For the cytotoxicity assay, cells were plated in 96-well plates (10^4 cells/well). After 24 h, a dimethyl sulfoxide solution of the test compound (1–100 μM) was added to each well, and the cells were incubated for 72 h. Control groups were treated with the same amount of dimethyl sulfoxide (0.1 %). Amsacrine was used as a positive control. The growth of tumor cells was quantified by the ability of living cells to reduce the yellow dye 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) to a blue formazan product, as follows. At the end of 72 h of incubation, the medium in each well was replaced with fresh medium (200 μL) containing MTT (0.5 mg/mL). After 3 h, the formazan product of MTT reduction was dissolved in 20 % sodium dodecyl sulfate, and the absorbance of the solution at 570 nm was measured with a multiplate reader (EL808, Biotek, USA). The effect of each test compound was quantified in terms of the absorbance as a percentage of the absorbance of the reduced dye in the 0.1 % DMSO treated group.

Table 1 IC50 values of LPSF/SFs in tumor cells

Compounds	Cell lineages IC50 (μM)						
	T47D	MiaPaca	HepG2	NG97	Raji	Jukart	PBMC
SF-13	>100	>100	58.58	73.73	58.8	62.54	>100
SF-15	>100	>100	>100	>100	>100	80.58	>100
SF-17	>100	>100	>100	>100	>100	96.51	>100
Amsacrine	12.18	13.2	1.51	2.1	4.15	<1	3.73

Selectivity assay

Peripheral blood mononuclear cells were obtained from heparinized blood from healthy, nonsmoking donors who had not taken any drugs for at least 15 days prior to sample collection ($n = 6$), and the cells were isolated via a standard method of density-gradient centrifugation over Ficoll-Hypaque solution (GE Healthcare). Cells were counted in a Neubauer chamber, and viability was determined by the trypan blue exclusion method. Cells were used only when the viability was >98 %. All donors gave informed consent, and the study was approved by the Human Research Ethics Committee of UFPE in the Health Sciences Center (CEP/CCS/UFPE N0 145/09). Cells were plated in 96-well plates (10^6 cells/well). After 24 h, the test compound was added (0.1–100 μM), and the cells were incubated for 48 h and then subjected to the MTT assay as described above.

Flow cytometry

The mechanism by which the test compounds induced cell death was evaluated by Brdu/propidium iodide staining using an APO-Brdu Apoptosis Detection Kit (eBiosciences, San Diego, CA, USA). Tumor cells were seeded at a density of 1×10^5/mL into 6-well plates, and the test compound was added. After 24 h of incubation with the test compound, the cells were washed twice with ice-cold phosphate buffered saline. Each cell sample was transferred to a tube and then centrifuged at $200 \times g$ for 5 min. In accordance with the manufacturer's instructions, cells were resuspended in washing buffer before incubation with DNA-labeling solution (containing TdT enzyme and BrdUTP) for 60 min at 37 °C. After being washed, the cells were resuspended in 100 μL of the antibody solution FITC-anti-BrdU mAb and then incubated in a propidium iodide/RNAse A solution before cytometry acquisition (FACSAria II, Becton, Dickinson and Company, Franklin Lakes, NJ, USA) and data analysis by means of FACSDiva software (Becton, Dickinson and Company).

Statistical analysis

All experiments were performed at least three times. IC50 values and 95 % confidence intervals were obtained by nonlinear regression with the OriginPro program (ver. 8.0, OriginLab, Northampton, MA, USA).

Molecular modeling

The structure of PPARγ used for molecular modeling was obtained from the Protein Data Bank (http://www.pdb.org, PDB code 2HWQ). This protein has been recognized as a possible target for cancer therapy. The structure of the first

monomer of the PPAR-γ protein was chosen as a target for docking calculations, which were carried out by means of GOLD software (ver. 5.1, Cambridge Crystallographic Data Centre). The active site of the protein was defined as all atoms within a radius of 6.0 Å from the cocrystallized ligand [(1-{3-[(6-benzoyl-1-propyl-2-naphthyl)oxy]propyl}-1H-indol-5-yl)oxy]acetic acid (designated as 'DRY'). The BINANA program (Durrant and Mccammon, 2011) was used to conduct a detailed inspection of the molecular interactions obtained from the docking calculations; the default settings were used, except for the hydrogen bond distance, which was changed to 3.5 Å.

Results and discussion

Thiazolidinone derivatives LPSF/SF-13, LPSF/SF-15, and LPSF/SF-17 were prepared as shown in Scheme 1. The presence of the arylidene proton peak in the ^{1}H NMR spectra of the compounds confirmed that the nucleophilic addition reaction was successful. The identity of the compounds was confirmed by mass spectrometry data obtained in positive- or negative-ion mode, and the IR spectra of the compounds showed peaks characteristic of a carbonyl group and an arylidene group (HC=).

With the target thiazolidinone derivatives in hand, we initially performed a selectivity assay because compounds with high toxicity against nontumor cells are not viable for in vivo transposition assays (Chari, 2008). All three thiazolidine derivatives were nontoxic to normal human peripheral blood mononuclear cells (IC50 > 100 μm), whereas the positive control (amsacrine) showed an IC50 of 3.73 μm against the normal cells. Next, we assayed the cytotoxicity of the thiazolidinone derivatives against various tumor cell lines (Table 1). None of the compounds showed activity against the T47D breast cell line, the line for which the IC50 of the positive control was the highest. LPSF/SF-15 and LPSF/SF-17 showed no anticancer activity against most of the tested cell lines; they showed a small cytotoxic effect against the leukemia cell line (Jukart). In contrast, LPSF/SF-13 showed significant anticancer activity in four cells lines (HepG2, NG97, Jukart, and Raji), presenting a typical dose–response curve (Fig. 1).

These results suggest that the bromine substituent on the benzylidene group of LPSF/SF-13 and LPSF/SF-15 contributed substantially to the cytotoxicity against these four cell lines. LPSF/SF-13 contains only one substituent on the benzylidene group (a bromine atom at the 3-position), whereas LPSF/SF-15 and LPSF/SF-17 both have at least one relatively bulky methoxy group, which may have

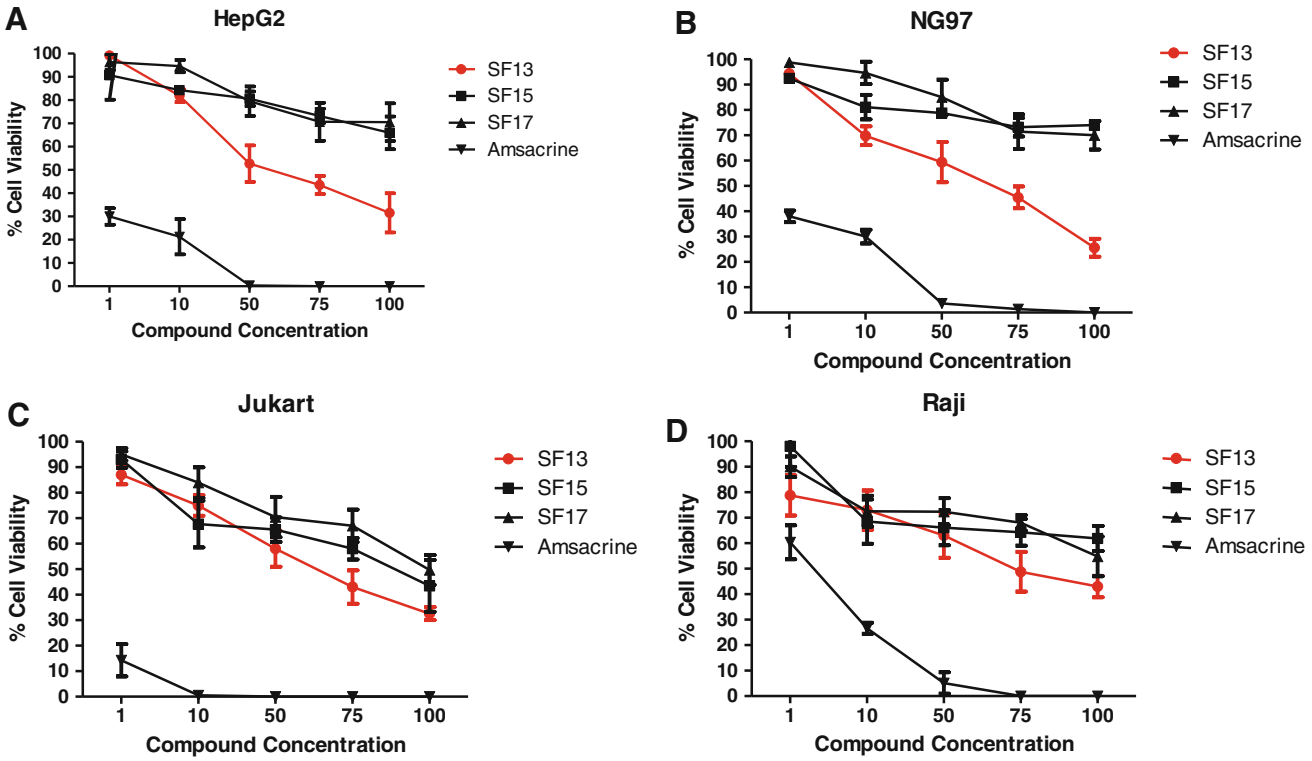


Fig. 1 Dose–response curves for the cytotoxicity of the new thiazolidine-2,4-diones against (**a**) HepG2, (**b**) NG97, (**c**) Jurkat, and (**d**) Raji cancer cell lines. Against all the analyzed cell lines, LPSF/SF-13 showed the best response among all the three synthesized derivatives

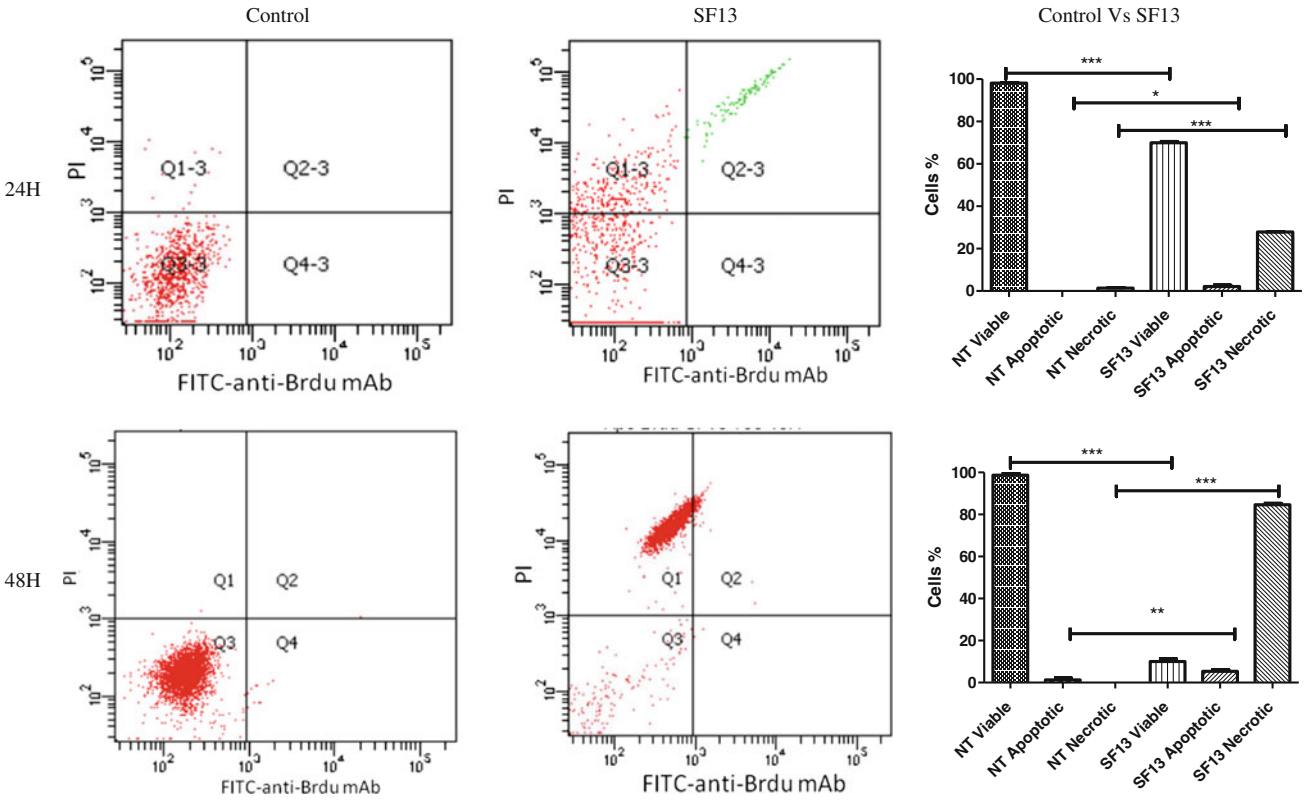


Fig. 2 Flow cytometry analysis of the method of cell death induction by LPSF/SF-13 against Raji cells. The *rows* show the treatment period, the *columns* show the cytometry profiles of the untreated control and LPSF/SF-13, and the *bar graph* shows the untreated control versus the LPSF/SF-13 control

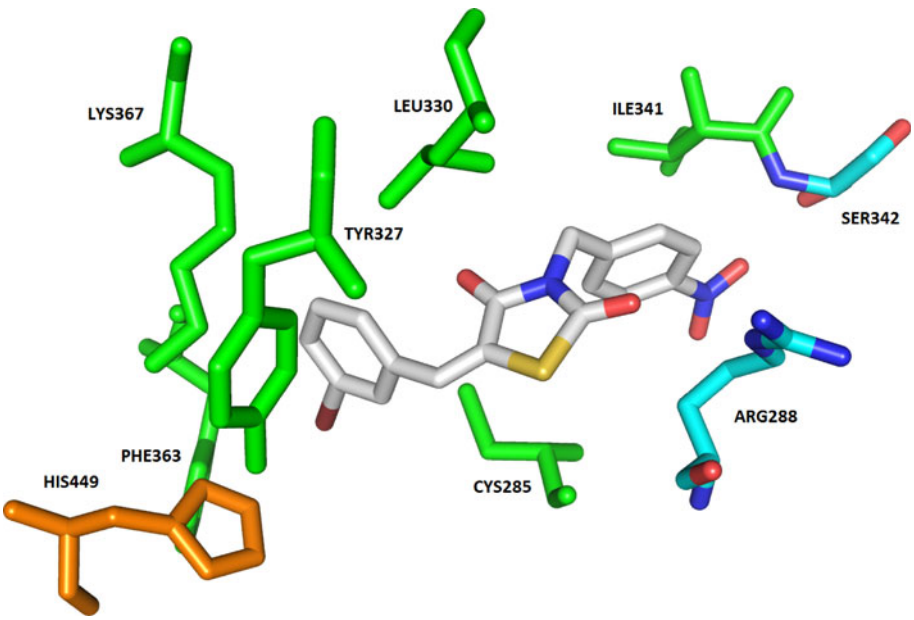


Fig. 3 Calculated solution for docking of LPSF/SF-13 (*gray*) on PPAR-γ. The residues that interact hydrophobically are highlighted in *green*, the residues that form hydrogen bonds are highlighted in *blue*, and the residues that form a π-bonding (T-shaped) interaction with LPSF/SF-13 are highlighted in *orange*. The figure was generated with the PYMOL program (Color figure online)

reduced their cytotoxicity. The steric effect of a methoxy group has already been reported in studies of epidermal growth factor receptor tyrosine kinase inhibitors (Zhou *et al.*, 2009).

To better understand, how the most promising compound (LPSF/SF-13) induced the death of cancer cells, we performed a flow cytometry assay with the Raji cell line which was one of the two cell lines that showed the highest

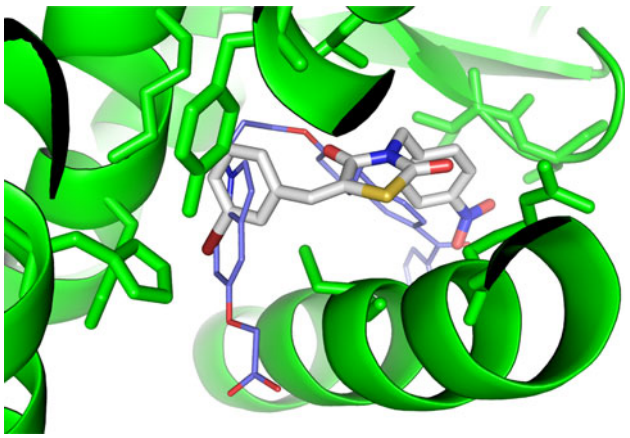


Fig. 4 Calculated solutions for docking of LPSF/SF-13 (*gray sticks*) and the cocrystallized ligand 'DRY' (*blue lines*) on PPAR-γ (*green*). The figure was generated with the PYMOL program (Color figure online)

susceptibility to LPSF/SF-13. Raji cells were incubated with LPSF/SF-13 at the IC50 dose for 24 and 48 h (Fig. 2). At both incubation durations, death by necrosis was observed to a greater extent in relation to the nontreated group ($p < 0.001$). However, there was a small, but significant increase in the induction of apoptosis after 24 h of treatment ($p < 0.05$) and a large increase after 48 h ($p < 0.001$), revealing a time-dependent relationship. The activation of both death mechanisms could be useful for cancer treatment (Amaravadi and Thompson, 2007) because apoptosis involves self-elimination of cells and necrosis could promote recruitment and activation of immune cells that could attack the tumor (Rovere-Querini *et al*., 2004).

To clarify the binding interactions between LPSF/SF-13 and PPARγ, we performed molecular docking calculations. The proposed binding mode for LPSF/SF-13 was chosen as the solution with the highest (most positive) ChemPLP score among all the possible solutions (Korb *et al*., 2009).

LPSF/SF-13 showed good affinity for the PPARγ receptor, with a ChemPLP score of 73.26 (Fig. 3). The complex formed with PPARγ exhibited hydrogen bonds involving the Arg288 and Ser342 residues, with bond distances of 3.1 and 2.8 Å, respectively. A π-bonding interaction (T-shaped) with His449 was also observed, and six additional residues interacted hydrophobically with the ligand. In Fig. 4, superimposition of the docking solution for LPSF/SF-13 with the solution for the cocrystallized ligand ('DRY') reveals that LPSF/SF-13 binds to the active site of PPARγ in the same orientation as the cocrystallized ligand.

Conclusion

The three novel thiazolidine derivatives (*5Z*)-5-(3-bromobenzylidene)-3-(4-nitrobenzyl)-thiazolidine-2,4-dione, (*5Z*)-5-(3-bromo-4-methoxy-benzylidene)-3-(4-nitrobenzyl)-thiazolidine-2,4-dione, and (*5Z*)-5-(3,4,5-trimethoxy-benzylidene)-3-(4-nitrobenzyl)-thiazolidine-2,4-dione were synthesized and characterized. None of the compounds was toxic to normal human cells, but (*5Z*)-5-(3-bromo-benzylidene)-3-(4-nitrobenzyl)-thiazolidine-2,4-dione showed significant antitumor activity. This compound induced cell death primarily by necrosis but also by apoptosis and is a promising compound for in vivo and combination therapy studies against cancer.

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Conflict of interest The authors declare that they have no conflicts of interest.

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