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α-Lipoic acid-based PPARγ agonists for treating inflammatory skin diseases

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Abstract Novel thiazolidinedione derivatives of the potent antioxidant, α-lipoic (thioctic, 1,2-dithiolane) acid, were prepared. The prototype *N*-(2-{4-[2,4-dioxo(1,3-thiazolidin-5-yl)methyl]phenoxy}ethyl)-5-(1,2-dithiolan-3-yl)-*N*-methylpentanamide (designated BP-1003), and dithioester derivatives thereof were shown to be potent activators of peroxisome proliferator-activated receptor gamma (PPARγ) (EC_{50} range 15–101 n*M*) and modest activators of PPARα (EC_{50} 5 μM). Both the relatively hydrophobic dithiolane prototype, BP-1003, and its water-soluble dithioglycinate derivative, BP-1017, were shown to inhibit the proliferation of human keratinocytes and suppress the production of interleukin-2 by human peripheral lymphocytes to a greater extent than the antidiabetic thiazolidinedione, rosiglitazone. Both oral and topical administration of BP-1017 showed significant antiinflammatory effects in the oxazolone-sensitized mouse model of allergic contact dermatitis (ACD). These findings suggest that water-soluble lipoic acid-based thiazolidinediones may be efficacious as oral and topical agents for treating inflammatory skin conditions such as contact dermatitis, atopic dermatitis, and psoriasis.

Keywords Thiazolidinedione · Peroxisome proliferator-activated receptor-γ · α-Lipoic acid · Inflammation · Dermatitis · Psoriasis

Abbreviations *ACD:* Allergic contact dermatitis · *ATCC:* American Type Culture Collection · *FRET:* Fluorescence resonance transactivation · *LBD:* Ligand binding domain · *LDH:* Lactate dehydrogenase · *PBMC:* Peripheral blood mononuclear cells · *PHA:* Phytohemagglutinin · *PPARγ:* Peroxisome proliferator-activated receptor-gamma · *TZD:* Thiazolidinedione

Introduction

The thiazolidinediones (TZDs) are under continuing development as insulin-sensitizing pharmacological agents for the treatment of type 2 (non-insulin-dependent) diabetes mellitus [1]. TZDs are high-affinity ligands for the nuclear receptor, peroxisome proliferator-activated receptor-gamma (PPARγ), a transcription factor that regulates genetic programs involved in glucose and lipid homeostasis, energy metabolism, and adipocyte growth and differentiation [2]. In addition to regulating lipid and glucose metabolism, PPARγ ligands exert antiinflammatory and antiproliferative effects through their ability to influence an array of important signaling pathways [3, 4]. Although TZDs have actions unrelated to PPARγ, such as their ability to block voltage-sensitive [5] and receptor-operated calcium channels [6], their cellular effects appear to be largely mediated through PPARγ activation [1, 2]. Thus, PPARγ appears to be an important molecular target in the development of drugs for the treatment of diverse endocrine, proliferative and inflammatory diseases [3, 4, 7].

We have previously shown that the antidiabetic TZD troglitazone improves psoriasis and normalizes models of inflammatory, proliferative skin disease [8, 9]. Troglitazone has the interesting feature of including an antioxidant α-tocopherol headgroup attached to the TZD backbone. We designed and synthesized a unique class of TZDs by linking the antioxidant vitamin, α-lipoic acid (thioctic, 1,2-dithiolane pentanoic acid) to benzoxy-TZD. Herein, we report that the prototype, *N*-(2-{4-[2,4-dioxo(1,3-thiazolidin-5-yl)methyl]phenoxy}ethyl)-5-(1,2-dithiolan-3-yl)-*N*-methylpentanamide (known as BP-1003) and its water-soluble dithioglycinate analog (BP-1017) strongly activate PPARγ, and moderately activate PPARα, and that these drugs can inhibit both the proliferation of cultured human keratinocytes and the production of interleukin-2 (IL-2) by activated peripheral lymphocytes. The water-soluble derivative BP-1017 showed significant antiinflammatory properties in a mouse model of allergic contact dermatitis (ACD). These findings suggest that lipoic acid-based TZD ligands for PPAR may be useful in the treatment of diseases involving inappropriate keratinocyte proliferation and T lymphocyte activation such as psoriasis and atopic dermatitis.

Materials and methods

Experimental compounds

The dithiolane thiazolidinedione prototype derivative *N*-(2-{4-[2,4-dioxo(1,3-thiazolidin-5-yl)methyl]phenoxy}ethyl)-5-(1,2-dithiolan-3-yl)-*N*-methylpentanamide (designated BP-1003) and other dithioester analogs are shown in Fig. 1.

Cell Culture

Murine 3T3-L1 preadipocytes (CCL-173) and CV-1 monkey epithelial cells (CCL-70) were from ATCC (Bethesda, Md.), and human neonatal keratinocytes were obtained from Clonetics (Walkersville, Md.).

PPAR activation assays

PPAR activity was determined by either cell-based transactivation assays (PPARγ) or by fluorescence resonance energy transfer (FRET) assays (PPARγ, PPARα and PPARδ). For the cell-based transactivation assay, CV-1 cells were maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 5% (v/v) Cosmic calf serum (Hyclone, Logan, Utah) and antibiotics. The cells were plated at 2×10^5 cells/well in 24-well dishes. The medium was replaced 24 h after plating with DMEM containing 0.5% (v/v) charcoal-dextran-treated fetal bovine serum (Hyclone), and 24 h later the cells were transfected with 200 ng PPARγ receptor expression plasmid pGAL4-mPPARγ LBD, 1 μg luciferase reporter plasmid pUAS-tk-luc and 400 ng pCMVSport β-gal (Gibco, Grand Island, N.Y.) as an internal control. Transfections were performed using the GenePorter reagent (Gene Therapy Systems, San Diego, Calif.) according to the manufacturer's instructions. Cells were treated 24 h after transfection with the ligand and incubated for an additional 24 h. Cell extracts were prepared and assayed for luciferase and beta-galactosidase activity using the Promega (Madison, Wis.) luciferase and beta-galactosidase assay systems according to the manufacturer's instructions. All treatments were performed in triplicate, and normalized for β-galactosidase activity. FRET assays were performed using human constructs for PPARα, PPARδ and PPARγ. Ligand concentrations yielding half-maximal activation (EC_{50} values) were calculated using GraphPad Prism version 3.03 (GraphPad Software, San Diego, Calif.).

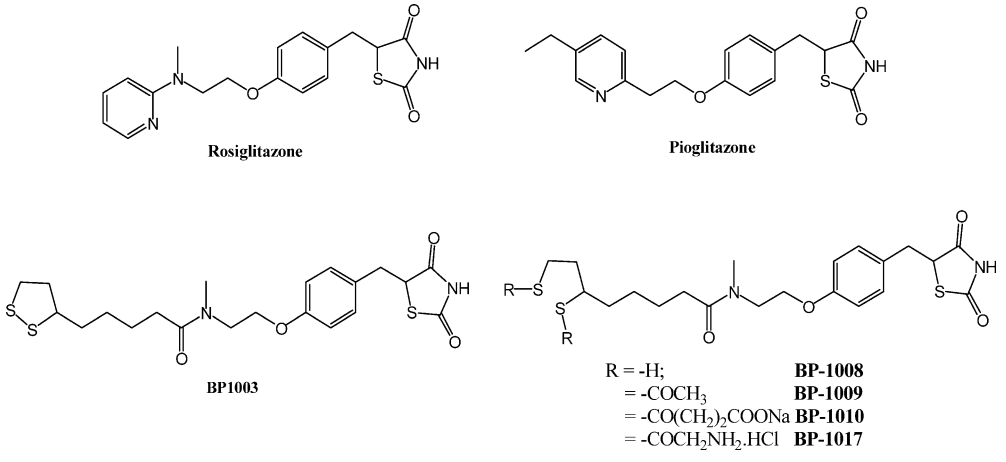

Fig. 1 Structural formulae of the pioglitazone, rosiglitazone, and lipoic acid-based thiazolidinedione derivatives shown in Table 1

Adipocyte differentiation assay

Differentiation assays on preadipocytes were performed by a modification of the technique described by Smith et al. [10]. In brief, murine 3T3-L1 cells were plated in DMEM with 5% calf serum and grown to confluence. After reaching confluence, cells were incubated in DMEM containing 1.0 μmol/l dexamethasone, 5 μg/ml insulin and 0.5 mmol/l 1-methyl-3-isobutylxanthine with 5% calf serum for 32 h, after which the cells were washed with PBS and incubated in medium containing the test compound or vehicle, DMSO (dimethyl sulfoxide). Five days after treatment, cells were fixed with 10% formalin in PBS and stained with Oil Red O.

Keratinocyte proliferation assay

For proliferation studies, keratinocytes were maintained in keratinocyte growth medium (BioWhittaker, Walkersville, Md.), a low-calcium (0.15 m*M*) modification of MCDB-153 medium, supplemented with several growth factors, including human recombinant epidermal growth factor (0.1 ng/ml), insulin (2.5 μg/ml), and 2% (v/v) pituitary extract. Cells were plated in 24-well dishes at 2×10^4 cells/well, and 24 h after attachment, the test compound or DMSO vehicle was added. Control and treated keratinocytes were incubated for 6 days, with one medium change at day 3. Relative cell numbers were determined in four replicates of each concentration using the MTS assay as described in the CellTiter 96 Aqueous Non-Radioactive Cell Proliferation Assay (Promega).

Lymphocyte activation and IL-2 production

T lymphocyte activity was determined as IL-2 production by human peripheral blood mononuclear cells (PBMCs). Cells were isolated from the blood of healthy volunteers by Ficoll density gradient centrifugation, cultured for 24 h in 1 ml RPMI-1640 medium supplemented with glutamine (2 m*M*), penicillin G (100 U/ml), streptomycin (100 mg/ml) and 10% (v/v) FBS at 3×10^6 cells per well in the presence or absence of test compounds. The cells were activated 16 h later by exposure to phytohemagglutinin (PHA, 10 μg/ml) and phorbol myristate acetate (PMA, 10 ng/ml) and cultured for an additional 16 h. The medium was collected and assayed for IL-2 concentration using a commercial ELISA kit (R&D Systems).

Effects on ACD

The antiinflammatory effects of topical and oral administration of BP-1003 and BP-1017 were tested in a mouse model of ACD [11]. ACD was elicited in oxazolone-sensitized NMRI mice with 10 μl of oxazolone applied to the right ears of 8 to 16 mice per group; the left ears remained unchallenged. In studies of the antiinflammatory effects of topically administered BP-1003 or BP-1017, 2% (w/v) oxazolone was applied; in studies of the antiinflammatory effects of orally administered compounds, 0.5% (w/v) oxazolone was applied. ACD was assessed by determining the extent of inflammatory pinnal swelling by comparison of the weights of both ears in animals treated with either the test compounds or in negative controls treated with vehicle only. Positive controls were also included by treating additional animals with pimecrolimus (SDZ ASM 981), an ascomycin macrolactam derivative with well-established anti-inflammatory properties [11]. Oral treatments were administered twice (2 h before and concomitant with oxazolone challenge). The oral doses tested were 30, 10, and 3 mg/kg body weight. In the topical studies, the treatments were performed once to the right ear, 30 min after oxazolone challenge, using a drug concentration of 1 m*M*. Compounds were dissolved in a mixture of acetone, ethanol, and dimethylacetamide 1:1:1 and applied in minimal (10 μl) volumes. In all animal experiments, the guidelines in NIH publication no. 85-23, revised 1985, were followed.

Cytotoxicity assay

Keratinocyte and lymphocyte viability were assessed by LDH release following 24- and 48-h exposures to PPARγ ligands. The amount of LDH released was determined using a CytoTox 96 non-radioactive cytotoxicity assay kit (Promega).

Statistical analysis

The results were analyzed using Student's *t*-test or ANOVA followed by Student-Newman-Keuls testing with statistical significance defined as $P<0.05$.

Results

Structure and relative solubility of lipoic acid-based TZD derivatives

The structures of rosiglitazone, pioglitazone, and novel dithiolane-TZD, dithiol-TZD and dithioester-TZD derivatives are shown in Fig. 1. The relative solubilities of the TZDs were estimated by calculating the oil-water partition function, C logP. BP-1003 was more hydrophobic than either rosiglitazone or pioglitazone. The dithiolane ring was esterified to form various dithioester-TZD derivatives to increase water solubility. The dithiol- and dithioacetate-TZD derivatives (BP-1008 and BP-1009) had water solubilities similar to those of pioglitazone and rosiglitazone, whereas the dithiosuccinate- and dithioglycinate-TZD derivatives (BP-1010 and BP-1017) had water solubilities greater than those of pioglitazone and rosiglitazone (Table 1). BP-1017 (dithioglycinate) was most water soluble, giving it the potential for improved bioavailability, whereas BP-1009 (dithioacetate) and BP-1010 (dithiosuccinate) had intermediate solubilities, making them potential candidates for topical application.

PPAR transactivation by α-lipoic acid-based TZD derivatives and induction of adipocyte differentiation

We first tested the ability of α-lipoic acid-based TZD derivatives to activate PPARγ in a heterologous transactivation assay that eliminates interference from endogenous nuclear receptors. Figure 2 illustrates a typical dose-response result for BP-1003 and BP-1017 compared to

Table 1 Solubility values (C logP) and potency values for activating PPARγ (EC_{50}) of lipoic acid-based TZD derivatives compared to pioglitazone and rosiglitazone

Compound	C logP	EC_{50} (n*M*)
Pioglitazone	3.53	906
Rosiglitazone	3.02	302
BP-1003 (dithiolane)	4.00	16
BP-1008 (dithiol)	3.30	30
BP-1009 (dithioacetate)	3.25	101
BP-1010 (dithiosuccinate)	2.30	50
BP-1017 (dithioglycinate)	1.23	66

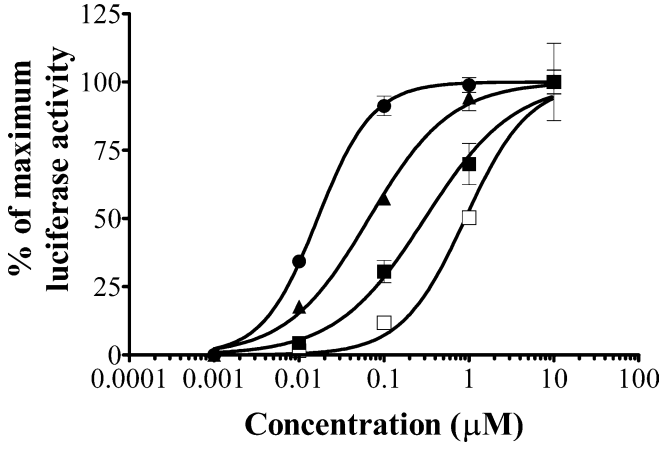

Fig. 2 BP-1003 and BP-1017 are potent PPARγ agonists. Transactivation of the GAL4-PPARγ chimeric receptor by BP-1003, BP-1017, rosiglitazone and pioglitazone in transiently transfected CV-1 cells. Cells were treated with the indicated concentrations of ligand for 24 h and normalized total luciferase activity determined (■ rosiglitazone, ❑ pioglitazone, ● BP-1003, ▲ BP-1017)

pioglitazone and rosiglitazone. An identical analysis was conducted for the other BP compounds. All BP compounds tested were full agonists of PPARγ and were more potent than pioglitazone and rosiglitazone (Table 1). BP-1003 was 18 times more potent (EC_{50} 16 n*M*) than rosiglitazone (EC_{50} 302 n*M*; Table 1). PPAR activation data obtained in the cell-free FRET assay yielded results similar to those obtained in the cell-based transactivation assay. FRET proximity analyses for activation of PPARγ by BP-1003 and BP-1017 yielded EC_{50} values of 1 n*M* for both compounds. The EC_{50} for PPARα by FRET analysis was 5 μM also for both compounds, more than three orders of magnitude higher than the EC_{50} values for PPARγ. The EC_{50} for PPARδ by FRET analysis was determined to be greater than 10 μM for both BP-1003 and BP-1017. Thus both BP-1003 and BP-1017 appear to be strongly selective for PPARγ

Ligand-activated PPARγ is required for differentiation of adipose tissue in vivo and in vitro [12]. Murine 3T3 L1 preadipocytes expressing PPARγ were treated with 2 μM BP-1003, BP-1017, or rosiglitazone, and were observed to undergo differentiation to Oil Red O-positive adipocytes (Fig. 3). This demonstrates that these two novel TZDs are capable of causing functional activation of the endogenous PPARγ receptor.

Effect of lipoic acid-based TZD derivatives on keratinocyte growth

Proliferating cultures of normal human keratinocytes were treated with rosiglitazone, BP-1003 or BP-1017 as described in Materials and methods. After 6 days exposure to drug, the relative cell numbers were determined by the MTS assay. Rosiglitazone, BP-1003 and BP-1017 all inhibited keratinocyte growth in a dose-dependent manner (Fig. 4). The rank-order for the inhibitory effect of these compounds on keratinocyte proliferation was BP-1003>BP-1017>rosiglitazone. At all concentrations tested, the BP compounds were more effective at inhibiting

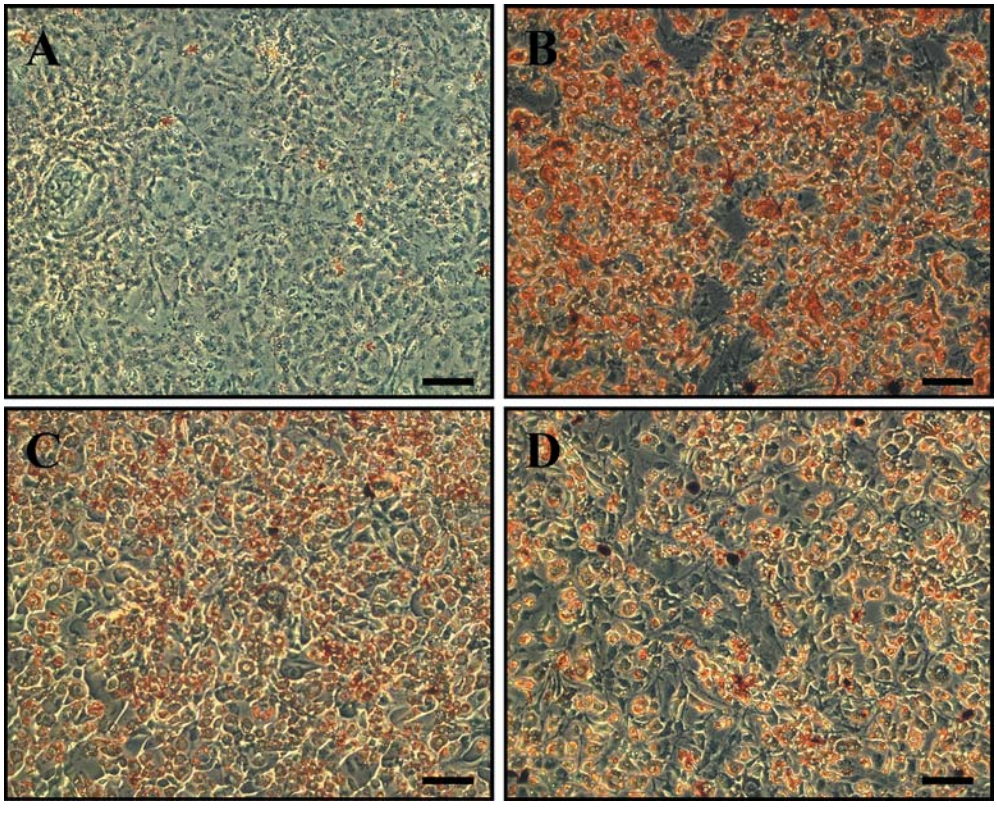

Fig. 3A–D BP-1003 and BP-1017 induce adipogenesis in 3T3-L1 murine preadipocytes. Confluent cultures were treated with insulin, dexamethasone and IBMX for 32 h. The cells were then treated with vehicle (DMSO) or 2 μM of the indicated compound for 5 days. Following fixation with 10% formalin in PBS, the cells were stained with Oil Red O (**A** vehicle, 0.004% v/v DMSO; **B** rosiglitazone; **C** BP-1003; **D** BP-1017)

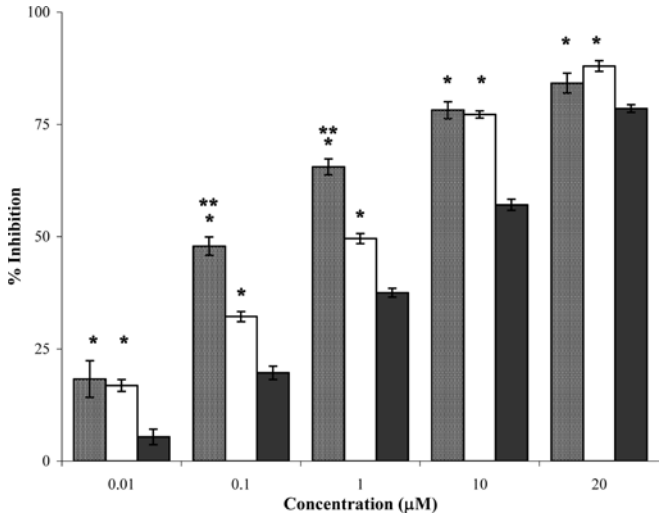

Fig. 4 Inhibitory effect of BP-1003 (*shaded bars*), BP-1017 (*open bars*) and rosiglitazone (*filled bars*) on keratinocyte proliferation. Proliferating cultures of normal human keratinocytes in serum-free growth medium were treated with vehicle, rosiglitazone, BP-1003, or BP-1017, as described in Materials and methods. After 6 days exposure to drug, the relative cell numbers were determined spectrophotometrically using the MTS assay. Rosiglitazone, BP-1003 and BP-1017 all inhibited keratinocyte growth in a dose-dependent manner. Data points are means±SEM of quadruplicate replicate determinations. **P*<0.05 vs rosiglitazone, ***P*<0.05 BP-1017 vs BP-1003, by ANOVA and Student-Newman-Keuls test

keratinocyte proliferation than rosiglitazone. At lower concentrations (0.01–1 μM), BP-1003 was significantly more effective than BP-1017 while the two compounds showed similar efficacy at higher concentrations. At the concentrations tested, none of the compounds appeared cytotoxic as determined by LDH release into the medium (data not shown). Removal of medium containing BP-1003 and BP-1017 resulted in resumption of proliferation, further confirming the non-injurious nature of these compounds at the concentrations used.

Effects of BP-1003 and BP-1017 on IL-2 production by lymphocytes

Human PBMCs are enriched in T lymphocytes. The inhibitory effects of BP-1003, BP-1017 and rosiglitazone on T lymphocyte activation were measured as their ability to inhibit IL-2 production in PMA/PHA-activated PBMCs (Table 2). All three compounds significantly inhibited IL-2 production in a dose-dependent manner. At 10 μM the inhibitory effects of BP-1003 and BP-1017 (about 90%) significantly exceeded that of rosiglitazone (75%).

Effects of BP-1003 and BP-1017 on ACD

BP-1003 did not show a significant antiinflammatory effect when administered either orally or topically in the ACD mouse model. In contrast, the more water-soluble molecule, BP-1017, showed significant antiinflammatory effects with both topical and oral administration (Fig. 5). Topically applied BP-1017 at 1 mM was associated with significant inhibition of pinnal swelling (22±4%) although the effect was less than that observed (37±5%) with topically applied pimecrolimus (SDZ ASM 981), an ascomycin macrolactam derivative that has been clinically approved for the topical treatment of atopic dermatitis. Oral administration of BP-1017 also caused significant inhibition of pinnal swelling, even at the lowest dose tested (3 mg/kg, Fig. 5). In contrast, the pimecrolimus compound approved only for topical use showed no anti-inflammatory effects at this same oral dose (Fig. 5).

Discussion

The PPARs (α, γ and δ isoforms) have been under intensive investigation ever since PPARγ was identified as the intracellular high-affinity receptor for the antidiabetic TZDs [13]. Troglitazone, the first TZD approved in the USA for the treatment of type 2 diabetes, was later withdrawn from the market because of liver toxicity. Two other TZDs, rosiglitazone (Avandia) and pioglitazone (Actos), marketed since 1999, appear to be free from hepatotoxicity.

Although originally developed as insulin-sensitizing agents, TZDs were later shown to have antiinflammatory [3, 4, 9] and immunomodulatory effects [14, 15, 16]. These compounds also exert antiproliferative effects by inducing cell cycle withdrawal through G_1 arrest [17] and by transforming cells from their proliferative (synthetic) phenotype to their terminally differentiated, mature (metabolic) phenotype [18].

Ligand activation of PPARγ has been shown to inhibit the production of inflammatory molecules, including IL-

Table 2 Inhibitory effect of lipoic acid-based TZD derivatives on IL-2 release by human lymphocytes. Values are means±SEM of four determinations in one experiment

Drug and concentration (μM)		IL-2 released (pg/ml)	Inhibition (%)
Control (no drug)		459±20	–
Rosiglitazone	1	406±12	12
	10	114±5*	75
BP-1003	1	362±17*	22
	10	39±5**	92
BP-1017	1	339±21*	26
	10	45±7**	90

**P*<0.05 vs control, ***P*<0.05 vs control and vs rosiglitazone, by ANOVA and Student-Newman-Keuls test

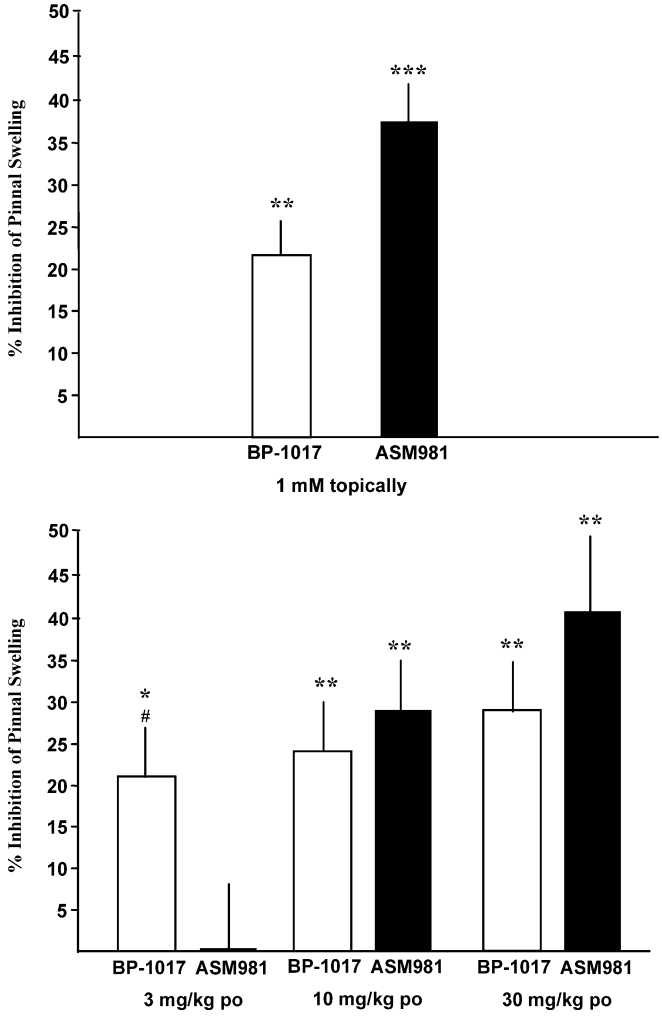

Fig. 5 Antiinflammatory effects determined in the mouse model of ACD. The antiinflammatory effects of topical and oral administration of BP-1003 and BP-1017 were tested in a mouse model of ACD. ACD was elicited in oxazolone-sensitized NMRI mice with 10 μl oxazolone applied to the right ears; left ears remained unchallenged. In studies of the antiinflammatory effects of topically administered BP-1003 or BP-1017, 2% (w/v) oxazolone was applied; in studies of the antiinflammatory effects of orally administered compounds, 0.5% (w/v) oxazolone was applied. ACD was assessed by determining the extent of inflammatory pinnal swelling by comparison of the weights of both ears in animals treated with either the test compounds or vehicle only. Positive controls were animals treated with pimecrolimus. Oral treatments were administered twice (2 h before and concomitant with oxazolone challenge). *Top* effect of topical administration, *bottom* effect of oral administration. $^{**}P<0.01$, $^{*}P<0.05$, vs vehicle-treated controls by *t*-test; $^{***}P<0.01$, vs vehicle-treated controls and BP-1017; $^{\#}P<0.05$, vs pimecrolimus

1β, IL-2, IL-6, tumor necrosis factor-α, interferon-γ, nuclear factor-κB, inducible nitric oxide synthase, and proteases such as matrix metalloproteinase-9 (gelatinase B) [3, 4, 14, 15, 16, 19]. Yang et al. [20] have demonstrated that troglitazone inhibits the activity of NFAT (nuclear factor of activated T cells) which regulates the IL-2 promoter and downstream IL-2 production by T lymphocytes. IL-2 is a key inflammatory component of disorders such as psoriasis, multiple sclerosis and Alzheimer's disease, in which TZDs have been shown to have potential therapeutic effects [7, 8, 9, 14, 15, 20, 21, 22].

α-Lipoic acid is a potent antioxidant found endogenously as lipoamide in eukaryotic dehydrogenases where it is covalently bound to a lysyl residue [23]. Exogenously supplied lipoic acid is taken up readily by a variety of cells and tissues where it is reduced rapidly to dihydrolipoic acid [24]. Unmodified α-lipoic acid has been reported to have antiinflammatory and cytoprotective effects [24]. In the study reported here, we demonstrated the feasibility of linking the methoxybenzyl-2,4-thiazolidinedione moiety of existing TZDs to lipoic acid via an amide bridge. This structure provides a flexible scaffold for synthesizing dithioester prodrugs or other thiol-based derivatives with a wide constellation of pharmacokinetic properties including variable water solubility as illustrated in Table 1.

The pathogenesis of inflammatory skin diseases is known to be associated with altered signal transduction pathways involved in keratinocyte proliferation and cutaneous T cell-mediated inflammation [25]. We have previously reported that troglitazone normalizes models of proliferative skin disease, inhibits keratinocyte proliferation, and improves psoriasis in nondiabetic patients [8, 9]. Similar findings have been observed in pilot studies of nondiabetic psoriatic patients treated with rosiglitazone (Pershadsingh et al., unpublished observations) or pioglitazone [22].

In the current studies, we found that both BP-1003 and BP-1017 are potent activators of PPARγ (Table 1). Both compounds inhibited keratinocyte proliferation (Fig. 3) and IL-2 production by T lymphocytes (Table 2) to a greater extent than rosiglitazone. It is important to note that these results do not conclusively demonstrate that the effects of these compounds on inflammation and proliferation are due to the activation of PPARγ. This observation is particularly relevant since thiazolidinediones have been shown to have PPARγ-dependent and -independent effects on inflammatory responses in macrophages [26]. However, these findings do indicate that BP-1003 and BP-1017 may be efficacious as antiinflammatory and antiproliferative agents. The water-soluble prodrug, BP-1017, was also found to exert significant antiinflammatory effects when administered either orally or topically in the mouse model of ACD.

Taken together, these findings suggest that BP-1017 may be effective as a topical or oral agent for treating contact dermatitis, atopic dermatitis and psoriasis. The current findings should also motivate future studies of the extent to which the antiproliferative and antiinflammatory effects of these compounds can be attributed to their antioxidant lipoic acid moieties versus their ability to activate PPARγ. Preliminary studies suggest that at least in the mouse model of ACD, the lipoic acid moiety may be an important determinant of the antiinflammatory effects of these compounds (unpublished observations). If so, the inclusion of the antioxidant moiety in these molecules may extend their clinical utility beyond that of conventional PPARγ ligands.

The finding that the hydrophobic BP-1003 was ineffective in the ACD model, whereas the hydrophilic BP-1017 compound was effective whether administered orally or topically, suggests that administering α-lipoic acid-based thiazolidinedione derivatives as the water soluble pro-drugs such as BP-1017 may be important for enhanced bioavailability. This finding underscores the flexibility and convenience of synthesizing compounds by thioesterification of the dithiolane/dithiol scaffold to produce the desired pro-drug. The glycinate residues would be cleaved away during metabolism to yield the lipoic acid/dihydrolipoic acid couple as a functional antioxidant adduct.

Water solubility is but one of the characteristics that can be explored, as in the case of BP-1017. In addition it should be possible to exploit the dithiolane/dithiol scaffold to produce "caged" compounds or hybrid (bifunctional) compounds designed for controlled delivery to specific tissue targets. In this regard, it is of interest to note that others have shown that the 1,2-dithiolane-3-pentyl moiety of lipoic acid can function as the "targetor moiety" for drug targeting to lung tissue [27]. Given that regulation of PPARγ expression in the airway has been proposed as a therapeutic target in the treatment of asthma [28] and that PPARγ agonists are reported to be associated with improvement of asthma via downregulation of allergic inflammation and eosinophil activation [29, 30], these dithioester-TZD compounds may be useful for treatment of lower airway diseases by topical delivery (i.e., by inhalation).

The clinical potential of TZDs has been demonstrated in nondermatological inflammatory, proliferative diseases with related immunopathophysiological mechanisms. Examples include atherosclerosis [31], prevention of vascular restenosis [32], ulcerative colitis [33], chorioretinal neovascularization [34, 35], Alzheimer's disease [21] and multiple sclerosis [36]. The current results suggest the potential utility of lipoic acid-based TZD derivatives for the treatment of inflammatory, proliferative skin diseases such as psoriasis, contact dermatitis and atopic dermatitis, and perhaps other inflammatory diseases as well.

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