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DIFFERENTIAL ACTIVITY OF ROSIGLITAZONE ENANTIOMERS AT PPARγ

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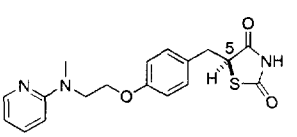
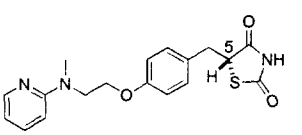
Abstract: Analysis of the enantiomers of rosiglitazone in a PPARγ binding assay suggests that the (*S*)-(–)-isomer is responsible for the antidiabetic activity.

(±)-Rosiglitazone (**1**) is an insulin sensitizer in clinical development for treatment of type 2 diabetes. In common with other thiazolidinediones (glitazones), **1** was discovered through screening in rodent models of diabetes for antihyperglycemic activity.[1] Glitazones contain a stereogenic center at C-5 of the thiazolidine ring that is prone to racemization at physiological pH (Figure 1). Consequently, in animal models the individual enantiomers and racemates of glitazones show equivalent activity as antidiabetic agents.[2] Recently, the biochemical target for the glitazones was discovered to be the nuclear receptor PPARγ.[3] Binding and activation of this nuclear receptor was shown to correlate with in vivo antidiabetic activity for a series of glitazones including **1**.[4] Analytical methods for the separation of the rosiglitazone (**1**) enantiomers have been described,[5] as has an asymmetric synthesis of (*R*)-(+)-rosiglitazone (**1b**).[6] Since no information was available on the relative activity of **1a** and **1b** at PPARγ, we decided to study the differential binding of these enantiomers to their target receptor.

Figure 1. Rosiglitazone enantiomers.



(*S*)-(–)-rosiglitazone (**1a**)



(*R*)-(+)-rosiglitazone (**1b**)

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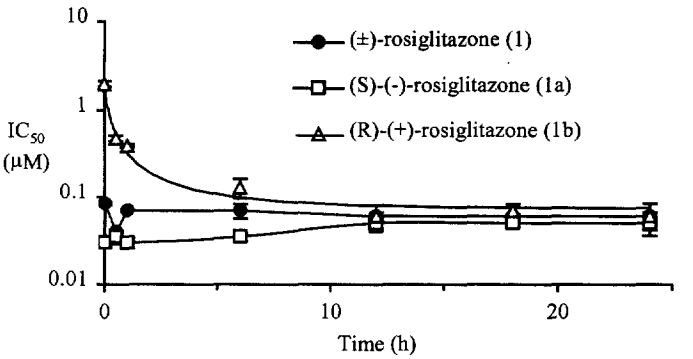
(*S*)-(−)-Rosiglitazone (**1a**) and (*R*)-(+)-rosiglitazone (**1b**) were separated by preparative chiral HPLC.[7] Analysis of their binding affinity to PPARγ was determined using a standard competition binding assay.[8,9]

Figure 2. PPARγ binding data

	IC_{50} (μM)	
	Initial	Final
1a	0.030 ± 0.004	0.060 ± 0.006
1b	2.00 ± 0.16	0.050 ± 0.008



Under the assay conditions we observed that (*S*)-(−)-rosiglitazone (**1a**) showed high affinity binding to PPARγ with an initial IC_{50} = 30 nM, but that (*R*)-(+)-rosiglitazone (**1b**) showed relatively weak binding (Figure 2). By monitoring the change in IC_{50} over the time course of the assay we were able to estimate the rate of racemization. At pH 7.2, the $t_{1/2}$ for racemization was determined to be 3 h.[10]

In conclusion, the enantiomers of rosiglitazone (**1**) show differential activity at PPARγ with binding affinity residing primarily in the (*S*)-(−)-enantiomer (**1a**). Our data predicts that the antidiabetic activity of rosiglitazone in humans will be due to the (*S*)-(−)-enantiomer (**1a**),[4] and suggests that the development chiral nonracemic PPARγ ligands may lead to improved antidiabetic drugs (e.g. references 11 and 12).

References and Notes:

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7. Chiralpak AD (2 x 25 cm), 100% EtOH, 4.5 mL/min. **1a**•HCl; rt = 43 min; $[\alpha]_D$ −106 (c, 0.6; MeOH); 99% ee. **1b**•HCl; rt = 84 min, $[\alpha]_D$ +106 (c, 0.53; MeOH); 99% ee. Stereochemical assignments were made by comparison with references 5 and 6. The authors acknowledge the assistance of Nicole Doria with this separation.
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9. The assay was run as previously described (reference 8) with the pH of the buffer adjusted to 7.2. The binding reaction was initiated by dilution of a DMSO solution of **1**, **1a** or **1b** into the assay buffer containing the receptor and radioligand. The wells were counted at the indicated times after assay initiation and IC_{50}s were calculated ± SE, n=3.
10. Consistent with this observation, both **1a** and **1b** show equivalent activity in cell-based reporter gene assays that require >12 h incubation with the test compound.
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