ELSEVIER

Interaction between peroxisome proliferator-activated receptor γ and its agonists: Docking study of oximes having 5-benzyl-2,4-thiazolidinedione

Yoriko Iwata,* Shuichi Miyamoto,* Makoto Takamura,† Hiroaki Yanagisawa† and Atsushi Kasuya*

**Exploratory Chemistry Research Laboratories, and †Medicinal Chemistry Research Laboratories, Sankyo Co., Ltd., Tokyo, Japan*

The molecular modelling of oximes having 5-benzyl-2,4-thiazolidinedione moieties, agonists of the peroxisome proliferator-activated receptor γ (PPARγ), was performed with respect to their structures complexed with the ligand binding domain of PPARγ. For each ligand molecule, the 5-benzyl-2,4-thiazolidinedione head group was used as an anchor and the conformation of the rest of the molecule was searched for the most energetically favorable interaction with the receptor by systematic conformation search and manual modelling. Although both tail-up and tail-down configurations, which have been observed in the crystal structure of eicosapentaenoic acid when complexed with PPARδ, appeared among the lowest energy structures for most of the compounds, potent agonists were found to adopt a configuration similar to that of rosiglitazone when bound to PPARγ, according to the crystal structure. The structure–activity relationships were analyzed based on the receptor–ligand interaction. The alkyl group and the aromatic ring of the tail group of the ligands had hydrophobic interactions with the receptor, and these interactions were found to be essential for the strong activity. © 2001 by Elsevier Science Inc.

Keywords: docking study, structure–activity relationship, PPARγ, thiazolidinedione, rosiglitazone

Color Plates for this article are on pages 598–600.

*Corresponding author: A. Kasuya, Exploratory Chemistry Research Laboratories, Sankyo Co., Ltd., 2-58, Hiromachi 1-chome, Shinagawa-ku, Tokyo 140-8710, Japan. Tel.: +81-3-3492-3131; Fax: +81-3-5436-8570.

E-mail address: kasuya@shina.sankyo.co.jp

INTRODUCTION

Thiazolidinediones (TZDs), which are known to sensitize tissues to insulin, have been developed and clinically used as antidiabetic agents. They have been shown to reduce plasma glucose, lipid, and insulin levels, and used for the treatment of type 2 diabetes.[1,2] The target of the TZDs has been identified as the peroxisome proliferator-activated receptor γ (PPARγ),[3] and the glucose-lowering activities of the TZDs were shown to be closely related to their PPARγ agonistic activity.[4] PPARγ plays important roles in regulating the storage and catabolism of dietary fats,[5,6] and it is generally recognized that by activating the PPARγ, TZDs enhance adipocyte differentiation and increase the insulin-sensitivity of tissues.[7]

Several structures of the PPARγ ligand-binding domain (LBD) determined by X-ray crystallography have been reported. These include the structures of the apo-PPARγ LBD,[8,9] a ternary complex of the LBD with the TZD of rosiglitazone and an 88 amino acid fragment of the coactivator SRC1,[8] and the LBD complexed with a partial agonist, GW0072.[10] The structure of the PPARγ LBD has an overall folding pattern quite similar to other nuclear receptor structures.[11] The structure consists of 13 α-helices and a small four-stranded β-sheet. Helices 3, 7, and 10 form the scaffold of the Y-shaped ligand-binding cavity. In the ternary complex of the PPARγ LBD with rosiglitazone and SRC1,[8] the S-isomer of rosiglitazone binds in a U-shaped conformation, wrapping around helix 3. The thiazolidinedione head group of rosiglitazone interacts specifically with amino acid residues in helices 3, 4, and 10 and the activating function-2 (AF-2) motif (Figure 1). The nitrogen atom in the TZD ring forms a hydrogen bond with the sidechain hydroxyl group of Y473 of the AF-2 helix. It is proposed that the ligand–receptor interactions including this hydrogen bond cause the conformational change of the AF-2, and enable the binding of coactivator SRC1, followed by the

Journal of Molecular Graphics and Modelling 19, 536–542, 2001

655 Avenue of the Americas, New York, NY 10010

1093-3263/01/$–see front matter
PII S1093-3263(00)00086-9

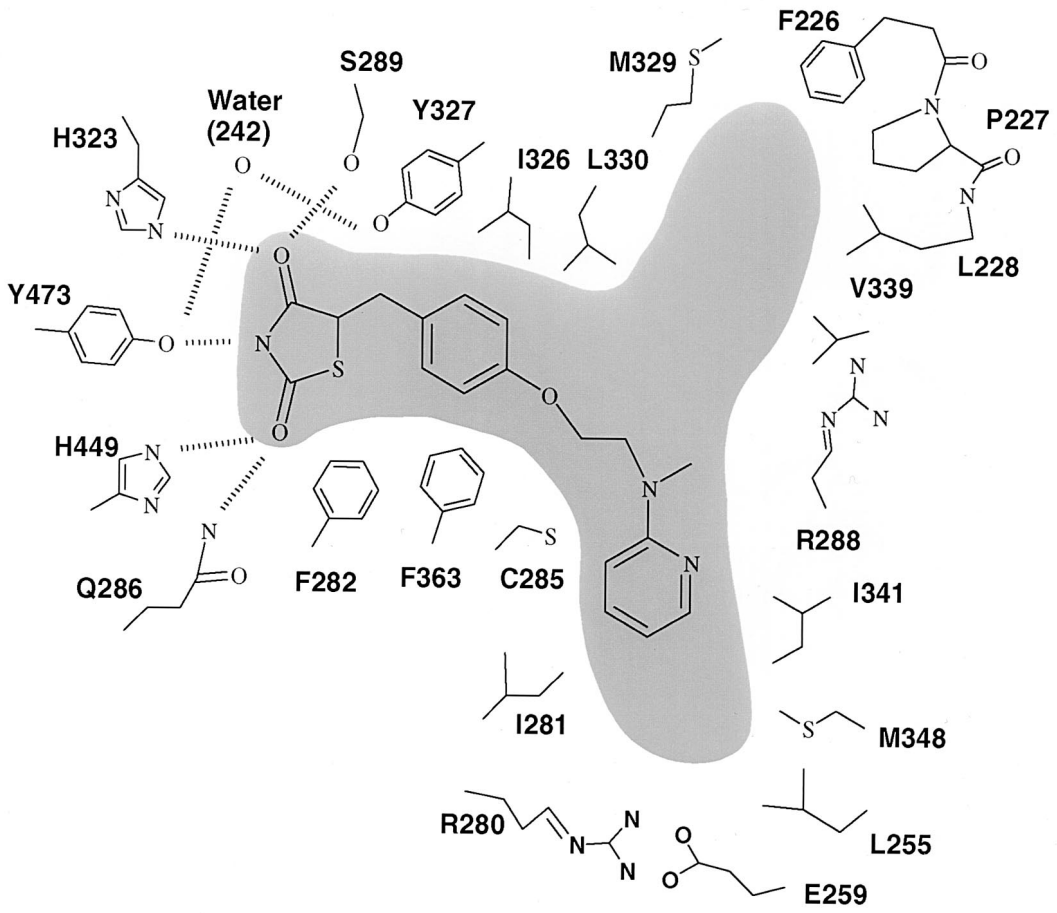


Figure 1. Schematic representation of the interaction of rosiglitazone with PPARγ LBD in the ternary complex crystal structure.[8] The shaded area indicates the Y-shaped cavity of the LBD.

activation of the receptor.[8,10] The pyridine ring of the tail group of rosiglitazone was in the downward arm of the Y-shaped cavity, interacting with amino acids including M348, I341, and I281.

Recently, Gampe et al. reported two crystal structures of the PPARγ/RXRα heterodimer,[12] in which the PPARγ is complexed with SRC1 and with either rosiglitazone or GI262570. The conformation of rosiglitazone in the heterodimer complex was different from that in the homodimer structure although the overall structure of the LBD of PPARγ was similar. In the heterodimer structure, the pyridyl tail of rosiglitazone adopts a different gauche conformation with its N-methyl group forming hydrophobic interactions with C285, M364, and L353.[12]

We have reported that the oximes having 5-benzyl-2,4-thiazolidinedione moieties were antihyperglycemic agents.[13] As shown in Table 1, compounds **1** and **2** showed strong PPARγ agonistic activities, while a loss of the activity was seen for compounds **3**–**6** of which the R_1 and R_2 groups were modified except for **5**, which had moderate activity. Loss of the activity was also observed for compound **7** having an elongated carbon chain. We presumed that these changes in the activity were the results of different binding affinities of these compounds to PPARγ.

In this study, the structures of these compounds complexed with the PPARγ LBD were modelled and their interactions were analyzed. Three-dimensional structure–activity relationships were investigated, and the interactions crucial for the activity of these compounds were elucidated.

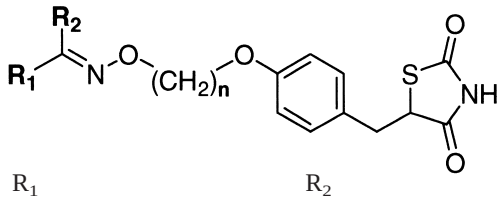
METHODS

The structure of the ternary complex of the PPARγ LBD, rosiglitazone, and SRC1 (PDB[14] ID: 2PRG[8]) was used as the initial structure. In the crystal structure, the LBD forms a homodimer in which both monomers have nearly identical Cα conformations. We used the structure of the A-monomer of the LBD homodimer. The docking study of the ligands was carried out with the QUANTA/CHARMm system.[15] An all-atom force field with a distance-dependent dielectric constant ($\epsilon = 4r$) was used.

To explore the possible binding modes of the ligands in the large cavity, we employed the systematic search method. The common part of the molecules, the 5-benzyl-2,4-thiazolidinedione head group, was used as an anchor. This anchor part of each of the compounds was placed in the receptor pocket using the crystal structure of rosiglitazone bound to the PPARγ LBD homodimer as the reference structure. For the chiral atom of the head group, the S-isomer, which was the binding isomer of rosiglitazone, was used.

The stable conformations of molecules **1**–**5** and **7** in the

Table 1. Structure and PPARγ agonistic activity of oxime derivatives



Compound	R_1	R_2	n	EC_{50} (μM)[13]
1	4-Ph-Ph	Me	2	0.40
2	3-Ph-Ph	Me	2	0.33
3	2-Ph-Ph	Me	2	>100
4	4-Ph-Ph	H	2	>100
5	4-Ph-Ph	Et	2	1.6
6	4-Ph-Ph	Pr	2	>100
7	4-Ph-Ph	Me	3	>100
rosiglitazone				0.73

binding site of the receptor were searched by a systematic rotation of torsion angles. During the search, the structure of the anchor was fixed in the initial conformation while the conformation of the rest of the molecule was changed systematically in the cavity of the receptor. The molecular mechanics energy was calculated for each conformer. Figure 2 shows the rotated bonds and torsion angle values used to generate conformers for compounds **5** and **7**. For compounds **1**–**4**, the same bonds and angle values as **5** except for τ_8 were used.

Among the systematically generated conformers, only those with the lowest energies were selected for further geometry optimization, and the bumped structures were discarded to

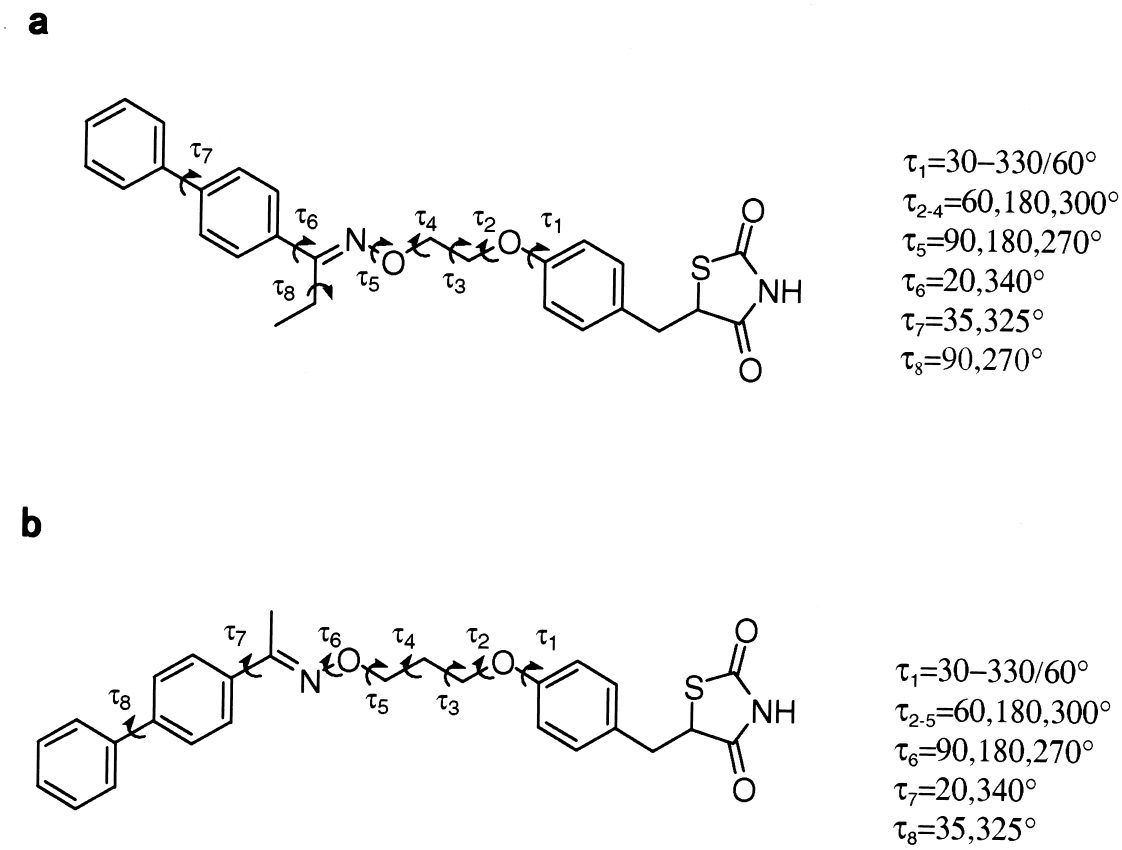


Figure 2. Chemical structures and torsional angle definitions of oxime derivatives, together with values assigned in the systematic search.

limit the amount of calculations to a feasible level. Thus, from the 2,916 conformers initially generated for compound **1**, 60 conformers were selected. For each of the 60 conformers, the geometry of the ligand was optimized by energy-minimization, first by fixing the LBD atoms, and then including the sidechain atoms of the LBD residues within 8 Å of the ligand. The optimized structures were clustered into groups by a 0.1 Å cutoff of the root mean square differences of all the nonhydrogen atoms used in the geometry optimization, and the lowest energy clusters were investigated.

The number of conformers for optimization was set to 120 for compounds **2** and **3** taking their asymmetry around bond τ_6 into account. For compounds **4** and **5**, conformers modelled using the lowest energy conformations of **1** as reference were also included. For compound **6**, which has too many rotatable bonds to perform a similar systematic search, the conformations were built directly from stable conformations of **1**, and only the conformation of the propyl group was systematically analyzed. For comparison, a docking similar to compounds **1**–**5** was also performed for rosiglitazone. The number of conformers generated and optimized for rosiglitazone was 324 and 30, respectively.

RESULTS AND DISCUSSION

As shown in Table 1, the activities of compounds **1**–**7** are greatly dependent on the structures of the R_1 and R_2 groups. With respect to the R_1 group, the 4-biphenylyl and the 3-biphenylyl compound (**1** and **2**) retained their activity, while the activity declined for compound **3**, which has a 2-biphenylyl group. For the R_2 substituent, although the active compounds have a methyl or an ethyl group (**1** and **5**), the activity was diminished for the compounds having n-propyl (**6**) or having no substituent (**4**). Furthermore, from the comparison of **1** with **7**, the length of the linking alkylene group also appears to be significant for the activity.

The Overall Structures of the Complex

In the crystal structures of the rosiglitazone-LBD complex,[8,12] the thiazolidinedione head group of rosiglitazone makes several specific interactions with amino acids of the LBD. The interactions, including hydrogen bonding with H323, H449, and Y473, are considered to be essential for the activity. Therefore, in this study, the 5-benzyl-2,4-thiazolidinedione head group of compounds **1**–**7** was used as an anchor in the systematic conformer generation. Although the entire ligand molecule and the sidechain atoms of the surrounding amino acids of the LBD were included in the geometry optimization, the conformation of the thiazolidinedione part of molecules **1**–**7** as well as the receptor sidechains in the final model did not change significantly from the initial structure.

Among the stable structures of the complex generated in the modelling study, structures in which the biphenylyl group of the ligand occupies the upward arm of the Y-shaped cavity were found. Such a configuration has been seen in the crystal structure of the eicosapentaenoic acid (EPA)-PPARδ complex, in which the hydrophobic tail of EPA was found to adopt two configurations, namely tail-up and tail-down.[16] In the complex structure of PPARγ with GW0072, one of the benzyl groups of the dibenzylamide of GW0072 similarly occupied the tail-up region of the receptor pocket, interacting with amino acids including M329, I326, and A292.[10] Although the tail-down configuration would seem to be more favorable than the tail-up configuration for compounds **1**–**7** (see below and Color Plate 4), the structures with the lowest energies, either in the tail-up or tail-down configuration, will be considered and discussed in the later sections.

The optimized structures were clustered by the root mean square differences of all the nonhydrogen atoms used in the geometry optimization. A cutoff value of 0.1 Å was used to remove those with practically the same conformations. For compound **1**, the number of clusters within 5 kcal/mol of the lowest energy structure was 18, with 5 structures grouped into the lowest energy cluster. Many of the structures of the low energy clusters shared the same binding mode, although different conformations of the linker group and/or slightly changed tail group positions of the ligand made them grouped into separate clusters. When a larger cutoff value of 0.3 Å was used, the number of clusters decreased to 6 and the two lowest energy clusters represented the tail-up and tail-down configurations. A similar number of clusters was obtained for the other compounds except for **4**, for which 6 and 4 clusters were obtained by the 0.1 Å and 0.3 Å cutoff, respectively.

The Docking of Rosiglitazone

In this study, we presumed that the interaction of the thiazolidinedione head group seen in the crystal structures of the complex is essential for the agonistic activity of the TZDs. Therefore, a rather conventional systematic search method in which the head group was treated as an anchor was used. To confirm the adequacy of this conformer generation method, a docking of rosiglitazone was also performed. From the docking, a conformation similar to that of bound rosiglitazone in the PPARγ homodimer crystal structure was obtained as one of the energetically stable structures, although it was not the lowest energy structure ($\Delta E = 0.9$ kcal/mol). Three such rosiglitazone conformations appeared in the 60 optimized structures and were grouped into the same cluster of the 0.1-Å threshold. The root mean square difference calculated for the atoms of rosiglitazone between the model and the crystal structure was 0.6 Å. In the lowest energy model, rosiglitazone had a different conformation with its N-methyl group directed toward a hydrophobic pocket formed by C285, M364, and L353, while the position of the pyridyl group was almost unchanged. Such conformation of rosiglitazone has been found in the crystal structure of the PPARγ/RXRα heterodimer.[12] Thus, the conformation of rosiglitazone bound to the LBD (the active conformations) have been reproduced by the docking. In addition, the lowest energy structures having a similar binding mode to the active conformations of rosiglitazone have been obtained from the separate docking calculations for each of the active compounds **1**, **2**, and **5**. These results ensure the validity of the conformation search used in this docking study.

The Effect of Different R_1 Groups

In the lowest energy structure of compounds **1**, **2**, and **3** complexed with the PPARγ LBD, the biphenylyl part of the molecule adopted the tail-down configuration, although for **1** there was one structure in the tail-up configuration having an energy of only 0.4 kcal/mol above the minimum tail-down structure. The structures of **1** and **3** are shown in Color Plate 1

together with the rosiglitazone conformation in the LBD homodimer. The biphenylyl group of **1** was positioned in the hydrophobic cavity formed by the amino acids including I341, I281, M348, and L255. The benzene ring adjacent to the oxime group located in a similar position as the pyridine ring of rosiglitazone in the crystal structures of the complex, interacted with the sidechains of I341 and I281. The terminal phenyl group had additional interactions with M348 and L255. The biphenylyl group was similarly positioned in the most stable complex structure of **2**. In contrast, the most stable structure of compound **3** had the biphenylyl group protruding between helix **3** and the β3 chain toward the outside of the receptor, indicating that the 2-biphenylyl group of **3** cannot be situated in the same position as **1** and **2**. This biphenylyl group of **3** was in close contact with the sidechain alkyl group of R288 and the mainchain of S342, separated by a relatively short distance (1.9 Å between the two hydrogen atoms) from the main chain amide NH group of S342. The guanidino group of the sidechain of R288 formed a salt bridge with the sidechain carboxy group of E295 in the models as well as in the crystal structures. The salt bridge fixed the conformation of the sidechains of R288, which have otherwise been flexible and might not have formed a close contact. The methyl group (R_2) of compounds **1** and **3** interacted with the sidechains of I341, R288, and C285, and the corresponding methyl group of **2** pointed toward the inside of the receptor, interacting with L353 and M348. They were in a similar position as the N-methyl group of rosiglitazone in the PPARγ homodimer and the PPARγ/RXRα heterodimer, respectively, and in either position, the methyl group formed good hydrophobic interactions with the receptor.

The Interaction of Different R_2 Substituents

Compounds **4**, **5**, and **6** differ from **1** in their R_2 substituent. Both the tail-up and the tail-down configurations were found in the stable structures of these three molecules, and the most stable conformation was the tail-up configuration for **4** and **6**. By analyzing the results of the systematic search and the manual modelling, we found that these three compounds adopted similar conformations as **1** in their most stable tail-up and tail-down structures, respectively. The only exception was the tail-up configuration of **4**. The conformation of the ethylene linker of **4** was different from the other tail-up structures and had similar τ_1-τ_3 angles to those of the tail-down structures of all the compounds. The R_2 ethyl group of **5**, similarly to the methyl group of **1**, interacts with the sidechains of I341 and C285, and the alkyl chain of R288. Compound **4**, which has no substituent, lacks this interaction. The n-propyl R_2 group of **6** also had a similar conformation to **1** and **5**, although the terminal methyl group of the propyl substituent of **6** was in close contact with the main chain NH group of S342 and the sidechain of R288 in its tail-down and tail-up configuration, respectively. Moreover, the environment around this methyl group is hydrophilic, since, in the crystal structure of the rosiglitazone-LBD complex, a solvent water molecule (W227) was found near this position within hydrogen-bonding distance with the backbone amide nitrogen of S342.[8] The propyl group of **6** in the tail-down configuration would displace the water molecule, forming a less favorable interaction (Color Plate 2).

The Linker Group

The structure of **7** is similar to **1**, but has a trimethylene group instead of the ethylene group of **1**. For compound **7**, only tail-down structures were obtained from the systematic conformation search. It is considered that the longer tail of this compound would hit against the pocket of the receptor when adopting the tail-up configuration. In the lowest energy conformation of **7**, the biphenylyl group was situated in the same position as that of **1** and **2**. The torsion angle values τ_1-τ_3 of the most stable structure of **7** were similar to those of the tail-up configuration of **1**, while the adjacent part (τ_3-τ_5) adopted an unstable $g^+g^+g^+$ conformation to make a sharp downward turn. Compound **7** had two structures almost equally stable as its lowest energy structure and had similar torsion angle values to those of the tail-down configuration of **1**. One of the structures with τ_1-τ_5 angles similar to **1** had the biphenylyl group projecting out of the pocket between H3 and β3. The other structure had the angle values of τ_1-τ_3 and τ_5-τ_6 similar to those of τ_1-τ_3 and τ_4-τ_5 of **1**, respectively. The biphenylyl group of this structure was located in the downward pocket, although it shifted toward the outside of the pocket by approximately 1.8 Å compared with that of **1** (Color Plate 3). It is considered that for the biphenylyl groups in these structures, the hydrophobic interactions with the surrounding atoms were weakened because they could not occupy the more preferable position as seen in **1** and **2**.

Structure–Activity Relationship

In the most stable structures of the active compounds **1**, **2**, and **5**, the biphenylyl group was located in a similar position to the pyridine ring of rosiglitazone in the crystal structures. It became clear that the biphenylyl group prefers this position. It was found that the biphenylyl group of **3** and **7** cannot adopt the same position as those of the active compounds. This can be considered as the reason for their loss of activity. The size-limited hydrophobic interaction of R_2 to the receptor residues was also found to be essential for the activity. This interaction is absent in compound **4** which has no substituent and canceled out in compound **6**, which has an n-propyl group extending to a hydrophilic site. Their loss in activity can be ascribed to the loss of the favorable interaction of the R_2 group with the receptor. Thus, the structures of compounds **1**–**7** complexed with the PPARγ LBD corresponded well to their activities.

The Tail-up and -down Configurations

Both the tail-up and tail-down configurations were obtained by the docking of **1**–**6** to the receptor (Color Plate 4). The differences of the molecular mechanics energies between the tail-up and tail-down configurations were 0.4, 1.8, and 1.0 kcal/mol (i.e., tail-down was preferable) for compounds **1**–**3**, and -1.4 and -1.6 kcal/mol (tail-up was preferable) for **4** and **6**, respectively. The energies were almost the same for both configurations for compound **5**, and no structure in the tail-up configuration was found for **7**. Structures with the tail-up configuration were also found in the docking models of the rosiglitazone complex, for which the energy difference was 0.7 kcal/mol. It should be noted that neither solvent water molecules nor any kind of solvation terms were included in this calculation. The effect of solvation should also be taken into account to pre-

cisely evaluate which of the two configurations is more preferable. Although both pockets have mainly hydrophobic characteristics, there were several hydrophilic sidechains in the upward pocket including the carboxy group of E295 and the guanidino group of R288, and the upward pocket was occupied by more solvent water molecules than the downward pocket in the apo-PPARγ LBD crystal structure.[8] Therefore, the downward pocket can be considered to be more hydrophobic than the upward pocket. We concluded that for molecules **1**–**7,** the tail-down configuration, which is adopted by rosiglitazone in its crystal structures when complexed with the LBD, is more likely than the tail-up configuration. The hydrophobic biphenylyl group of the compounds can more favorably interact with the surrounding sidechain atoms in the tail-down configuration.

However, the appearance of the tail-up configuration among the lowest energy conformations is very interesting. In the crystal structures of the PPARδ LBD complexed with EPA and the synthetic fibrate GW2433,[16] EPA adopts both tail-up and tail down configurations, and two tails of GW2433, the 2-(2-chloro-6-fluolo-phenyl)ethyl group and the 2,3-dichlorophenyl group, are positioned in the upward and the downward pocket, respectively. The large ligand-binding pocket of PPARs allows such binding in multiple configurations, and this flexibility in binding is responsible for the variety of fatty acids recognized by PPARs,[16–19] and also possibly accounts for the various functions activated by the receptor. In this way, one may speculate that the absence of the activity for compounds **4** and **6** can be associated with their relative preference for the tail-up configuration. Further investigation into the binding mode and the structure–activity relationships of PPARγ ligands would be necessary, however, to determine the physiological significance of the multiple configurations.

Most of the TZDs with potent agonistic activity have an aromatic group in their tail part.[20] Our results suggest that the aromatic group of the TZDs occupies a common binding position when bound to the PPARγ. The interactions appear to be essential for the strong agonistic activity. Such information about the structure–activity relationships would be important to understand the mechanism of the activation of the receptor as well as to design new ligands.

ACKNOWLEDGMENT

We thank Dr. Andrew A. Bogan for his comments and corrections to the manuscript.

REFERENCES

1 Day, C. Thiazolidinediones: a new class of antidiabetic drugs. *Diabet. Med.* 1999, **16**, 179–192
2 Spiegelman, B.M. PPAR-γ: adipogenic regulator and thiazolidinedione receptor. *Diabetes* 1998, **47**, 507–514
3 Lehmann, J.M., Moore, L.B., Smith-Oliver, T.A., Wilkison, W.O., Willson, T.M., and Kliewer, S.A. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPAR γ). *J. Biol. Chem.* 1995, **270**, 12953–12956
4 Willson, T.M., Cobb, J.E., Cowan, D.J., Wiethe, R.W., Correa, I.D., Prakash, S.R., Beck, K.D., Moore, L.B., Kliewer, S.A., and Lehmann, J.M. The structure–activity relationship between peroxisome proliferator-activated receptor γ agonism and the antihyperglycemic activity of thiazolidinediones. *J. Med. Chem.* 1996, **39**, 665–668
5 Lowell, B.B. PPARγ: an essential regulator of adipogenesis and modulator of fat cell function. *Cell* 1999, **99**, 239–242
6 Rocchi, S., and Auwerx, J. Peroxisome proliferator-activated receptor-γ: a versatile metabolic regulator. *Ann. Med.* 1999, **31**, 342–351
7 Okuno, A., Tamemoto, H., Tobe, K., Ueki, K., Mori, Y., Iwamoto, K., Umesono, K., Akanuma, Y., Fujiwara, T., Horikoshi, H., Yazaki, Y., and Kadowaki, T. Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats. *J. Clin. Invest.* 1998, **101**, 1354–1361
8 Nolte, R.T., Wisely, G.B., Westin, S., Cobb, J.E., Lambert, M.H., Kurokawa, R., Rosenfeld, M.G., Willson, T.M., Glass, C.K., and Milburn, M.V. Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor-γ. *Nature* 1998, **395**, 137–143
9 Uppenberg, J., Svensson, C., Jaki, M., Bertilsson, G., Jendeberg, L., and Berkenstam, A. Crystal structure of the ligand binding domain of the human nuclear receptor PPARγ. *J. Biol. Chem.* 1998, **273**, 31108–31112
10 Oberfield, J.L., Collins, J.L., Holmes, C.P., Goreham, D.M., Cooper, J.P., Cobb, J.E., Lenhard, J.M., Hull-Ryde, E.A., Mohr, C.P., Blanchard, S.G., Parks, D.J., Moore, L.B., Lehmann, J.M., Plunket, K., Miller, A.B., Milburn, M.V., Kliewer, S.A., and Willson, T.M. A peroxisome proliferator-activated receptor γ ligand inhibits adipocyte differentiation. *Proc. Natl. Acad. Sci. U. S. A.* 1999, **96**, 6102–6106
11 Weatherman, R.V., Fletterick, R.J., and Scanlan, T.S. Nuclear-receptor ligands and ligand-binding domains. *Annu. Rev. Biochem.* 1999, **68**, 559–581
12 Gampe, R.T., Jr., Montana, V.G., Lambert, M.H., Miller, A.B., Bledsoe, R.K., Milburn, M.V., Kliewer, S.A., Willson, T.M., and Xu, H.E. Asymmetry in the PPARγ/RXRα Crystal Structure Reveals the Molecular Basis of Heterodimerization among Nuclear Receptors *Mol. Cell* 2000, **5**, 545–555
13 Yanagisawa, H., Takamura, M., Yamada, E., Fujita, S., Fujiwara, T., Yachi, M., Isobe, A., and Hagisawa, Y. Novel oximes having 5-benzyl-2,4-thiazolidinedione as antihyperglycemic agents: synthesis and structure–activity relationship. *Bioorg. Med. Chem. Lett.* 2000, **10**, 373–375
14 Berman, H.M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T.N., Weissig, H., Shindyalov, I.N., and Bourne, P.E. The Protein Data Bank. *Nucleic Acids Res.* 2000, **28**, 235–242
15 QUANTA97/CHARMm23.2, 1997, Molecular Simulations Inc., San Diego, California.
16 Xu, H.E., Lambert, M.H., Montana, V.G., Parks, D.J., Blanchard, S.G., Brown, P.J., Sternbach, D.D., Lehmann, J.M., Wisely, G.B., Willson, T.M., Kliewer, S.A., and Milburn, M.V. Molecular recognition of fatty acids by peroxisome proliferator-activated receptors. *Mol. Cell* 1999, **3**, 397–403
17 Forman, B.M., Tontonoz, P., Chen, J., Brun, R.P., Spiegelman, B.M., and Evans, R.M. 15-Deoxy-Δ 12, 14-prostaglandin J2 is a ligand for the adipocyte determination factor PPAR γ. *Cell* 1995, **83**, 803–812
18 Kliewer, S.A., Sundseth, S.S., Jones, S.A., Brown, P.J., Wisely, G.B., Koble, C.S., Devchand, P., Wahli, W.,

Willson, T.M., Lenhard, J.M., and Lehmann, J.M. Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors α and γ. *Proc. Natl. Acad. Sci. U.S.A.* 1997, **94**, 4318–4323

19 Nagy, L., Tontonoz, P., Alvarez, J.G., Chen, H., and Evans, R.M. Oxidized LDL regulates macrophage gene expression through ligand activation of PPARγ. *Cell* 1998, **93**, 229–240

20 Hulin, B., McCarthy, P.A., and Gibbs, E.M. The glitazone family of antidiabetic agents *Curr. Pharm. Des.* 1996, **2**, 85–102