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Novel Oximes Having 5-Benzyl-2,4-thiazolidinedione as Antihyperglycemic Agents: Synthesis and Structure–Activity Relationship

Hiroaki Yanagisawa,[a,*] Makoto Takamura,[a] Eriko Yamada,[a] Sachie Fujita,[a] Toshihiko Fujiwara,[b] Makoto Yachi,[b] Aya Isobe[b] and Yuka Hagisawa[b]

[a]*Medicinal Chemistry Research Laboratories, Sankyo Co., Ltd., Hiromachi, Shinagawa-ku, Tokyo 140, Japan*
[b]*Pharmacology and Molecular Biology Research Laboratories, Sankyo Co., Ltd., Hiromachi, Shinagawa-ku, Tokyo 140, Japan*

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Abstract—Oximes having 5-benzyl-2,4-thiazolidinedione were prepared, and their PPAR γ agonistic activities and blood glucose lowering activities were evaluated. Biaromatic and methyl groups, attached to the oxime moiety, and the ethylene bridge between oxime and phenoxy groups are favorable to biological activities.

Introduction

Type II diabetes (non-insulin dependent diabetes mellitus; NIDDM) is one of the major causes of several chronic diseases, such as retinopathy, nephropathy, neuropathy and cardiovascular diseases.[1] Long-term hyperglycemia, caused by insufficient insulin secretion from pancreas and/or insulin resistance in muscle, liver and adipose tissues, brings about an aggravation of diabetes. Therefore, it is important to regulate the blood glucose level in order to control diabetes.[2–4] Treatment of diabetes has been carried out with a combination of diet, exercise and hypoglycemic agents, such as sulfonylureas, which stimulate pancreatic β-cells and increases secretion of insulin to lower the blood glucose level.[5,6] However, sulfonylureas often cause severe hypoglycemia and weight gain, and become poorly effective as a long-term treatment.[7]

Recently new types of agents, troglitazone (**1**),[8] pioglitazone (**2**)[9] and rosiglitazone (**3**),[10] which have a thiazolidine-2,4-dione (TZD) moiety, are available at the clinical stage. These drugs are believed to be ligands for the peroxisome proliferator-activated receptor γ (PPAR γ) and improve insulin resistance in the insulin target organs.[11,12] There have been many reports concerning derivatives of TZD, which have a wide variety of substituents at the *p*-position of 5-benzyl-TZD.[13] The X-ray structure analysis of apo-PPAR γ ligand-binding domain (LBD) and the ternary complex consisting of PPAR γ-LBD, rosiglitazone and SRC-1, have been reported and the pyridine ring of rosiglitazone occupies the relatively non-specific hydrophobic pocket.[14]

Here we will describe the synthesis of 5-benzyl-Tz **4** having iminoxyalkoxy groups at the *p*-position, their biological activity and spatial requirements for the activity.

Synthesis

The synthetic procedure of the iminoxyethoxy derivatives **4a–o** is shown in Scheme 1. Reaction of *N*-(2-hydroxyethoxy)phthalimide **5** with 5-(4-hydroxybenzyl)-3-tritylthiazolidine-2,4-dione **6** using the Mitsunobu reagent followed by the removal of the trityl group gave **7**. Treatment of **7** with hydrazine afforded **8**, which was then condensed with carbonyl compounds to afford **4a–o**.

The iminopropoxy compound **4p** was prepared as shown in Scheme 2. *O*-Alkylation of the oxime **9** with **10** followed by removal of the THP group gave the propanol **11**, which was converted to **4p** by the same procedure as the preparation of **7** from **5**.

*Corresponding author. Tel.: +81-3-3492-3131; fax: +81-3-5436-8563; e-mail: hyanag@shina.sankyo.co.jp

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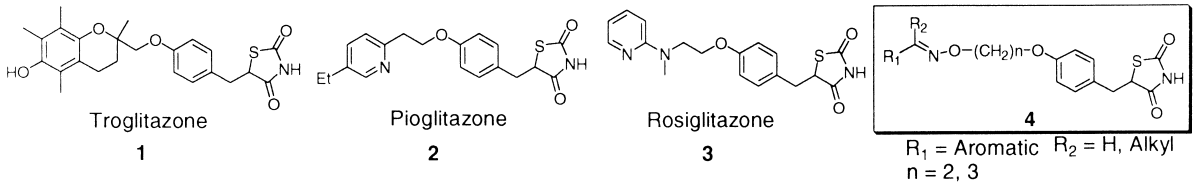


All compounds were obtained as a single isomer. The geometrical structure of **4f** was determined to be (*E*)-isomer by the X-ray analysis. Other oxime compounds are considered to be (*E*)-isomers which are thermodynamically more stable than the corresponding (*Z*)-isomer.

Biological Results and Discussion

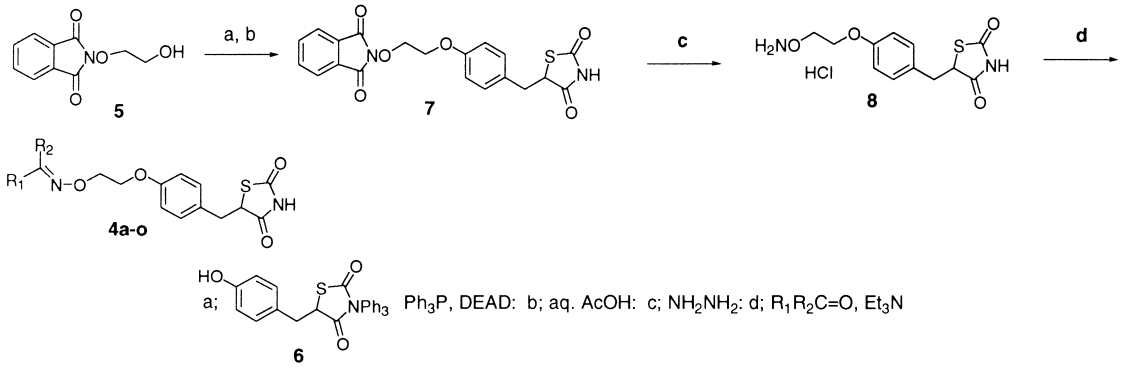
The oxime compounds prepared above were evaluated for their PPAR γ agonistic activity and for their blood glucose lowering activity in hyperglycemic kk mice. The results are summarized in Table 1 compared with the hydrochloride salt of **2** and the maleate salt of **3**.

Phenyl and pyridyl compounds **4a**–**d** activated PPAR γ with EC_{50} values in the range of 1.7 to 7.9 μM, of which **4d** was the weakest. Addition of the phenyl or pyridyl group to **4a**,**4b** and **4c** improved the activity (**4a**→**4f**, **4i**, **4m**–**o**; **4b**→**4k**; **4c**→**4l**) except for **4j**, which could not activate PPAR γ. Biphenyls **4f**, **4i** and 6-phenyl-3-pyridine **4l** were more active than **3**, and 4-(2- and 3-pyridyl)phenyl derivatives **4m**, **4n** were as active as **3**. 4-(4-pyridyl)phenyl derivative **4o** was less potent than the other pyridylphenyl derivatives **4m**, **4n**. Shortening (**4e**) or lengthening (**4g**, **4h**) of R_2 in **4f** diminished the PPAR γ agonistic activity, of which **4e** and **4h** were inactive at 100 μM. Also, elongation (**4p**) of the carbon chain between the oxime oxygen atom and phenolic oxygen atom of **4f** lost the PPAR γ agonistic activity.

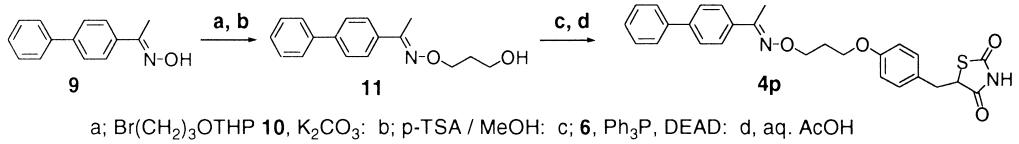
The blood glucose lowering activity of **4a** was weaker than **3** but more potent than **2**. 2-Pyridine **4b** had more potent activity than 3- and 4-pyridines **4c**, **4d**. In the 4-biphenylyl series (**4e**–**h**), the compounds where R_2 are methyl (**4f**) and ethyl (**4g**) had the excellent blood glucose lowering activity, whereas **4h** (R_2 = Pr) showed the weak activity and **4e** (R_2 = H) was inactive. 3-Biphenyl **4i** was less active than 4-biphenyl **4f** but still had an efficacy equivalent to **2**. 2-Biphenyl **4j** was the least active among the biphenylyl series (**4f**, **4i**, **4j**) having R_2 = Me. Phenylpyridines **4k**, **4l** had an efficacy comparable to **4a**. 4-(2-pyridyl)phenyl derivative **4m** had the most potent lowering activity in the pyridylphenyl derivatives (**4m**–**o**). Trimethylene analogue **4p** of **4f** showed the weak blood glucose lowering activity.

A good correlation of PPAR γ agonistic activity with antihyperglycemic activity had been observed in the thiazolidinedione series.[15] Potent PPAR γ agonists **4f**, **4l**, **4m** effectively lowered blood glucose and the weak agonists **4e**, **4h**, **4j**, **4p** did not show significant blood glucose lowering activity. However, **4i** and **4n** had moderate blood glucose lowering activity in spite of their potent PPAR γ agonistic ability and, on the other hand, **4b** and **4g** showed potent blood glucose lowering activity despite moderate PPAR γ agonistic activity. The moderate deviations observed in these compounds may be caused by their metabolism and/or bioavailability.

In conclusion, the favorable features of the oxime series for promoting the PPAR γ activity are as follows:



Scheme 1.



Scheme 2.

Table 1. PPAR γ agonistic activity and antihyperglycemic activity of oxime derivatives

Compound	R_1	R_2	mp	PPAR γ[a] EC_{50} (μM)	ΔBG[b] (%)
4a	Ph	Me	134–136	1.7	57
4b	2–Pyridyl	Me	119–121	2.8	67
4c	3–Pyridyl	Me	180–182	2.8	43
4d	4–Pyridyl	Me	171–172	7.9	48
4e	4–Ph–Ph	H	125–127	>100	7
4f	4–Ph–Ph	Me	164–166	0.40	67
4g	4–Ph–Ph	Et	157–159	1.6	67
4h	4–Ph–Ph	Pr	82–83	>100	29
4i	3–Ph–Ph	Me	Na salt	0.33	42
4j	2–Ph–Ph	Me	Na salt	>100	23
4k	5–Ph–2–pyridyl	Me	136–138	1.1	61
4l	6–Ph–3–pyridyl	Me	186–187	0.19	58
4m	4–(2–Pyridyl)–Ph	Me	177–179	0.64	58
4n	4–(3–Pyridyl)–Ph	Me	182	0.80	42
4o	4–(4–Pyridyl)–Ph	Me	234–235	1.6	44
4p			86–87	>100	20
2[c]				7.6	42
3[d]				0.73	66

[a]Activity was determined using transient transfection assays. See ref 16.
[b]The test compounds were mixed with powdered feed F-2 (Funabashi Farms) in a ratio of 0.01% (about 10 mg/kg/day). The mixture was administered orally to hyperglycemic male kk mice (4–6 months of age) for 3 days. Values (mean ± SE) are the % change in plasma glucose concentration of the drug-treated mice relative to vehicle controls. All values are the mean of $n = 4$ or 5.
[c]The hydrochloride salt of **2** was used.
[d]The maleate salt of **3** was used.

1. introduction of an aromatic group to the *m*- or *p*-position of acetophenone oxime or acetylpyridine oxime
2. methyl group as R_2
3. ethylene bridge ($n = 2$) between the oxygen atoms of the oxime moiety and phenoxy group.

The potential candidates are **4f** and **4l** which have more potent PPAR γ agonistic activity than rosiglitazone and show strong blood glucose lowering activity.

References and Notes

1. Porte, Jr., D.; Schwartz, M. W. *Science* **1996**, *272*, 699.
2. Feldt-Rasmussen, B.; Mathiesen, E. R.; Deckert, T. *Lancet* **1986**, *II*, 300.
3. Dahl-Jørgensen, K.; Brinchmann-Hansen, O.; Hanssen, K. F.; Ganes, T.; Kierulf, P.; Smeland, E.; Sandvik, L.; Aagenaes, Ø. *Br. Med. J.* **1986**, *293*, 1195.
4. The Diabetes Control and Complications Trial Research Group *New Engl. J. Med.* **1993**, *329*, 977.
5. Isley, W. L. *Drugs Today* **1990**, *26*, 59.
6. UK Prospective Diabetes Study Group. *Diabetes* **1995**, *44*, 1249.
7. Melander, A.; Bitzén, P.-O.; Faber, O.; Groop, L. *Drugs* **1989**, *37*, 58.
8. Yoshioka, T.; Fujita, T.; Kanai, T.; Aizawa, Y.; Kurumada, T.; Hasegawa, K.; Horikoshi, H. *J. Med. Chem.* **1989**, *32*, 421.
9. Momose, Y.; Meguro, K.; Ikeda, H.; Hatanaka, C.; Oi, S.; Sohda, T. *Chem. Pharm. Bull.* **1991**, *39*, 1440.
10. Cantello, B. C. C.; Cawthorne, M. A.; Cottam, G. P.; Duff, P. T.; Haigh, D.; Hindley, R. M.; Lister, C. A.; Smith, S. A.; Thurlby, P. L. *J. Med. Chem.* **1994**, *37*, 3977.
11. Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkison, W. O.; Willson, T. M.; Kliewer, S. A. *J. Biol. Chem.* **1995**, *270*, 12953.
12. Berger, J.; Bailey, P.; Biswas, C.; Cullinan, C. A.; Doebber, T. W.; Hayes, N. S.; Saperstein, R.; Smith, R. G.; Leibowitz, M. D. *Endocrinology* **1996**, *137*, 4189.
13. Hulin, B.; McCarthy, P. A.; Gibbs, E. M. *Curr. Pharm. Des.* **1996**, *2*, 85.
14. 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.; Milburn, M. V. *Nature* **1998**, *395*, 137.
15. 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.; Lermann, J. M. *J. Med. Chem.* **1996**, *39*, 665.
16. A cDNA encoding the ligand binding domain (amino acids 175-475) of human PPARγ was obtained with reverse transcript-polymerase chain reaction. A GAL4-PPARγ chimeric expression construct, pM-PPARγ, was generated by insertion of the cDNA into the GAL4 expression plasmid pM (Clontech Laboratories, Inc.) at the BamHI-HindIII site. HepG2 cells were transfected with pM-PPARγ and a GAL4-responsive reporter plasmid pFR-Luc (Stratagene Cloning Systems) using FuGENE™6 Transfection Reagent (Boehringer Mannheim GmbH) according to the manufacturer's instructions. After 2 h, the cells were seeded in 96-well plates followed by an additional 24 h of cultivation. Then, the medium was exchanged to DME medium supplemented with 10% delipided fetal calf serum and the test compound in the appropriate concentration. After 48 h, luciferare activity in the cells was measured using LucLite™ Luciferase Reporter Gene Assay Kit (Packard BioScience B.V.). EC_{50} equals the concentration of compound required to induce 50% of the maximum luciferase activity. All values are the mean of $n = 4$.