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(3-Substituted Benzyl)thiazolidine-2,4-diones as Structurally New Antihyperglycemic Agents

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Abstract: A series of 3-[(2,4-dioxothiazolidin-5-yl)methyl]benzamide derivatives was prepared as part of a search for antidiabetic agents . A structure-activity relationship study of these compounds led to the identification of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-methoxy-*N*-[[4-(trifluoromethyl)-phenyl]methyl]benzamide (**KRP-297**) as a candidate drug for the treatment of diabetes mellitus.

Type 2 diabetes (non-insulin-dependent diabetes mellitus) is a metabolic disorder characterized by hyperglycemia and/or insulin resistance, and is often associated with other disorders such as obesity, hypertension, and hyperlipidemia.[1] Extensive evidence points to a positive relationship between hyperglycemia and long-term organ complications, such as neuropathy, nephropathy, retinopathy, and premature atherosclerosis,[2] and to the necessity for tight control of blood glucose levels in the early stages of the disease.[3] However, current therapies to reduce plasma glucose levels have inherent problems, including poor compliance, ineffectiveness, and occurrence of hypoglycemic episodes with insulin and the sulfonylureas.[4] Therefore, there is a need for more effective, orally active agents, particularly ones that normalize both glucose and insulin levels. Since the pioneering discovery of ciglitazone by Takeda group,[5] which effectively reduces insulin resistance by potentiating insulin action in animal models of type 2 diabetes, several benzylthiazolidine-2,4-dione antihyperglycemic agents have been described in the literature,[6-9] and recently troglitazone has been brought onto the market in the US and Japan.[10] In our research directed toward the development of antihyperglycemic agents with thiazolidine-2,4-dione structure, we found that compound (**1**) exhibited antihyperglycemic activity comparable to that of troglitazone.[6] Compound (**1**) is structurally different from classical thiazolidine-2,4-diones, most of which have a hydrophobic group located at the 4-position of the benzene ring of a benzylthiazolidine-2,4-dione moiety; instead, the hydrophobic moiety (4-*tert*-butylphenylaminocarbonyl group) of **1** is located at the 3-position of the benzene ring. Therefore, we prepared a series of 3-[(2,4-dioxothiazolidin-5-yl)methyl]benzamide derivatives of general formula (**A**)

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and evaluated their antihyperglycemic activity. In this paper, we describe the synthesis and structure-antihyperglycemic activity relationship of these compounds.

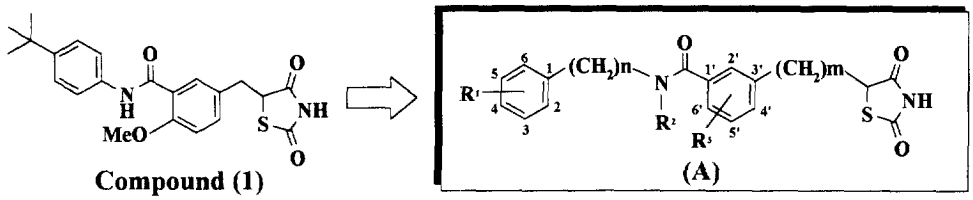
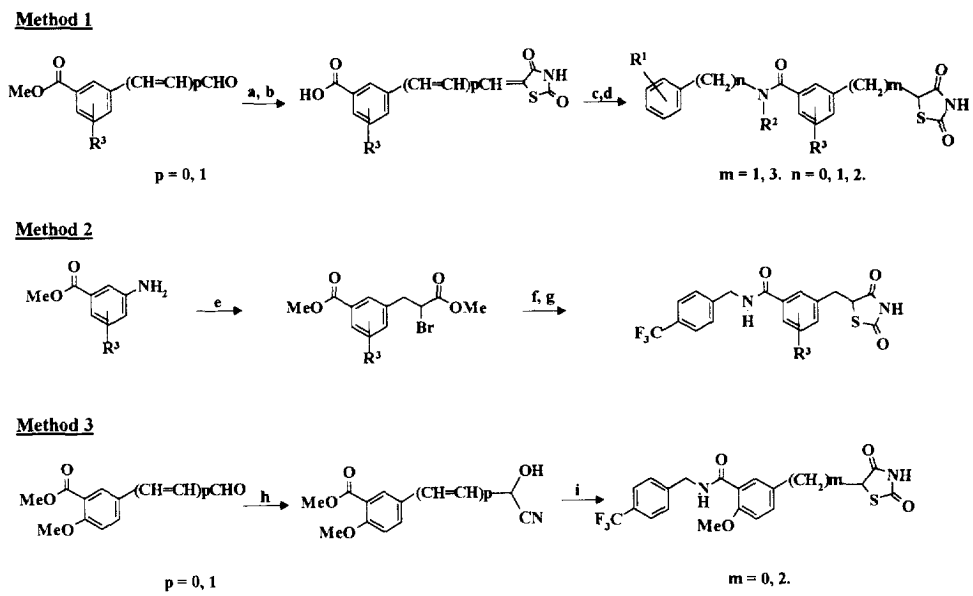


Figure 1. The structure of compound (1) and the general structure of compound (A)

The compounds described in this study were prepared as outlined in chart 1.



a) thiazolidine-2,4-dione, $AcONH_4$, AcOH, benzene; b) c.HCl-AcOH; c) amine, diethyl phosphorocyanidate, triethylamine, *N,N*-dimethylformamide; d) H_2, Pd-C, AcOEt-EtOH; e) (1) $NaNO_2$, HBr, MeOH-acetone, (2) methyl acrylate, Cu_2O; f) (1) thiourea, EtOH, (2) 6N HCl, sulfolane; g) 4-(trifluoromethyl)benzylamine, diethyl phosphorocyanidate, triethylamine, *N,N*-dimethylformamide; h) (1) TMSCN, ZnI_2, CH_2Cl_2, (2) 2N HCl, 1,3-dioxolane; i) (1) H_2, Pd-C, AcOEt-EtOH (in the case of p = 1), (2) CBr_4, Ph_3P, CH_2Cl_2 (in the case of p = 1) or $SOCl_2$, $CHCl_3$ (in the case of p = 0), (3) thiourea, EtOH, (4) H^+, H_2O (5) 4-(trifluoromethyl)benzylamine, diethyl phosphorocyanidate, triethylamine, *N,N*-dimethylformamide.

Chart 1. Synthetic routes to 3-[(2,4-dioxothiazolidin-5-yl)methyl]benzamide derivatives.

The Knoevenagel condensation[11] of appropriate aldehydes and thiazolidine-2,4-dione, followed by amide bond formation and subsequent reduction provided the 3-[(2,4-dioxothiazolidin-5-

yl)methyl]benzamide derivatives and 3-[3-(2,4-dioxothiazolidin-5-yl)propyl]benzamide derivative (Method 1). An alternative method for the preparation of the 3-[(2,4-dioxothiazolidin-5-yl)methyl]benzamide derivatives was the Meerwein arylation[12] of methyl acrylate and anilines in the presence of cuprous oxide, followed by cyclization with thiourea and subsequent amide bond formation (Method 2). The 3-(2,4-dioxothiazolidin-5-yl)benzamide derivative and 3-[2-(2,4-dioxothiazolidin-5-yl)ethyl]benzamide derivative were prepared by the reaction of aldehydes with trimethylsilyl cyanide, followed by halogenation of the resultant cyanohydrin, cyclization with thiourea and subsequent amide bond formation (Method 3).

The test compounds prepared in this study were suspended in a 5% arabia-gum solution and given orally once a day for 5 days to genetically obese (ob/ob) mice. The animals were starved over night, then 2 g/kg of glucose was given orally and blood samples were taken from the tail vein 0, 30, and 60 min thereafter. Blood glucose was determined by using the glucose oxidase method. The decrease in blood glucose level was calculated as the percentage change from the control value. The results are collected in Table 1.

Effect of amide nitrogen substituents (No. 1-15)

The *N*-phenyl derivative (**1**) showed moderate antihyperglycemic activity, while the *N*-benzyl derivatives (except **3**, 7, and **11**) exhibited more potent activity. Further lengthening of the linker methylene chain (**14**) decreased the activity.

Introduction of a trifluoromethyl group at the 4- or 3-position of the benzene ring (**9**, **10**) enhanced the activity, but other substituents decreased the activity as compared to that of the non-substituted derivative (**2**). The existence of the hydrogen atom at the amide portion is important, since the tertiary amide derivative (**15**) showed less potent activity than the secondary amide derivative (**9**).

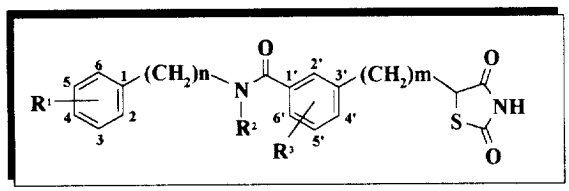
Effect of substituents at the centered benzene ring (No. 16-22, 9)

As can be seen from Table 1, the position and the kind of the substituents introduced onto the center benzene ring greatly influenced the antihyperglycemic activity. 4-Methoxy- and 2-methoxy derivatives (**16**, **17**) were inactive, but the 6-methoxy derivative (**9**) exhibited potent activity. Interestingly, the 6-fluoro derivative (**21**) showed potent activity, but the 6-methyl derivative (**22**) showed less potent activity. These results might indicate that intramolecular hydrogen bonding interaction between hydrogen atom at the amide portion and oxygen atom of methoxy group or fluorine atom located at the 6-position of the center benzene ring is necessary for potent antihyperglycemic activity.

Effect of thiazolidine-2,4-dione linker (No. 23-25, 9)

As for the methylene chain connecting the center benzene ring and the thiazolidine-2,4-dione ring, the methylene chain derivative (**9**) exhibited the most potent antihyperglycemic activity, and shortening or lengthening of the linker chain decreased the activity. But compounds **9**, **23**, **24**, and **25** showed moderate to potent activity, so the linker length might not critical for antihyperglycemic activity.

Table 1. Antihyperglycemic activity of 3-[(2,4-dioxothiazolidin-5-yl)methyl]benzamide derivatives



Compound							Decrease in blood glucose (%)		
No.	R^1	R^2	R^3	m	n	mp (℃)	10 mg/kg	3 mg/kg	1 mg/kg
1	4-*t*-Bu	H	6'-MeO	1	0	217.5-219.0	17		
2	H	H	6'-MeO	1	1	Foam	37	31	19
3	4-*t*-Bu	H	6'-MeO	1	1	135.0-136.0	5		
4	4-Me	H	6'-MeO	1	1	Foam	30		
5	4-MeO	H	6'-MeO	1	1	Foam	21		
6	4-CF_3O	H	6'-MeO	1	1	Foam	34		
7	4-Me_2N	H	6'-MeO	1	1	Foam	12		
8	4-F	H	6'-MeO	1	1	Foam	28		
9	4-CF_3	H	6'-MeO	1	1	176.0-177.5	58	53	35
10	3-CF_3	H	6'-MeO	1	1	145.0-147.0	41		
11	2-CF_3	H	6'-MeO	1	1	179.0-181.0	4		
12	3,4-diMeO	H	6'-MeO	1	1	Foam	30		
13	3,5-diCF_3	H	6'-MeO	1	1	167.0-169.0	30		
14	4-CF_3	H	6'-MeO	1	2	153.0-154.0	3		
15	4-CF_3	Et	6'-MeO	1	1	Foam	31		
16	4-CF_3	H	4'-MeO	1	1	204.0-207.0	3		
17	4-CF_3	H	2'-MeO	1	1	197.0-199.0	0		
18	4-CF_3	H	6'-EtO	1	1	159.0-162.0	34		
19	4-CF_3	H	6'-*i*-PrO	1	1	158.0-158.5	45		
20	4-CF_3	H	6'-OH	1	1	146.0-148.0	34	12	7
21	4-CF_3	H	6'-F	1	1	145.0-146.0	50		
22	4-CF_3	H	6'-Me	1	1	167.0-169.0	16		
23	4-CF_3	H	6'-MeO	0	1	168.0-169.0	48	36	27
24	4-CF_3	H	6'-MeO	2	1	165.5-167.5	43	20	15
25	4-CF_3	H	6'-MeO	3	1	192.0-194.0	39	29	10
26	Troglitazone						9		
27	Pioglitazone						14		

On the basis of its potency as an antihyperglycemic agent, 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-methoxy-*N*-[[4-(trifluoromethyl)phenyl]methyl]benzamide (**9**: **KRP-297**) was selected for further study *in vivo*. The results are shown in Table 2.

Table 2. Biochemical parameters in ob/ob mice treated with KRP-297 and pioglitazone.

	Dosage	Rate of decrease (%)		
Compound	(mg/kg/day)	Glucose	Insulin	Triglyceride
KRP-297	0.3	77	55	67
	1	78	59	80
	3	95	83	122
	10	100	87	130
Pioglitazone	3	64	43	85
	10	75	41	99

*KRP-297 and pioglitazone were administered orally for two weeks, and the glucose, insulin, and triglyceride levels were determined (n = 5).

As can be seen from Table 2, KRP-297 showed potent antihyperglycemic, antihyperinsulinemic, and antihyperlipidemic activity, even at a dosage level of less than 1 mg/kg/day. Its activities were superior to those of pioglitazone. These in *vivo* results clearly indicated that KRP-297 is an effective, orally active agent that normalizes both glucose and insulin levels.

Recent molecular-biological studies have revealed that thiazolidine-2,4-dione antidiabetics bind to peroxisome proliferator-activated receptor (PPAR) γ isoform, the master regulator of adipocyte differentiation.[13] Therefore, we investigated the effect of KRP-297 on PPAR isoforms and found that KRP-297 binds directly to and activates both PPAR α and PPAR γ isoforms (*Kd* values were 228 nM and 326 nM, respectively).[14] In contrast, classical thiazolidine-2,4-diones such as troglitazone,[6] pioglitazone,[7] and rosiglitazone[8] bind to and activate only the PPAR γ isoform. Therefore, the pharmacological effects of KRP-297 might be attributed to its coligand character for both PPAR α and PPAR γ isoforms. Further pharmacological studies of KRP-297 and a structure-activity relationship study of the (3-substituted benzyl)thiazolidine-2,4-diones as coligands of PPAR α and PPAR γ are in progress.

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