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Synthesis and Insulin-Sensitizing Activity of a Novel Kind of Benzopyran Derivative

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Abstract—A series of benzopyran derivatives was synthesized and their insulin-sensitizing activities were evaluated in 3T3-L1 cells. Compounds **6** and **11** exhibited more potent insulin-sensitizing activity than rosiglitazone.

Non-insulin-dependent diabetes mellitus (NIDDM) is a metabolic disorder characterized by hyperglycemia as well as insulin resistance and/or impaired insulin secretion. Hyperglycemia often leads to several complications such as neuropathy, retinopathy, nephropathy and premature atherosclerosis.[1] Therefore, it is important to maintain an appropriate blood glucose level, especially during the early stage of the disease. The therapy for NIDDM is often by a combination of diet, exercise, or with pharmacological agents.[2] Since the pioneer thiazolidinedione compound, ciglitazone, was reported improving blood glucose level by increasing insulin sensitivity,[3] several new thiazolidine-2,4-diones such as troglitazone,[4] piglitazone,[5] rosiglitazone[6] were launched into market since 1997 (Chart 1). However, possibly due to their common thiazolidine-2,4-dione group, thiazolidinedione compounds are associated with a poor safety profile.[7] The first-marketed troglitazone was even called back from the market for its severe hepatic toxicity in 1999. The research of non-thiazolidinedione insulin sensitizer has attracted much more attention in recent years.

We were interested in developing a series of non-thiazolidinedione insulin sensitizer, which might surmount the hepatic toxicity problems associated with the known thiazolidinediones. Of all non-thiazolidinedione insulin sensitizers, 1,3-dicarbonyl compounds **1** and JTP-20993 (Chart 1) were reported decreasing blood glucose level in ob/ob mice[8] and increasing insulin-sensitizing activity in 3T3-L1 cells respectively.[9] Meanwhile, we found that compound **2** possesses weak insulin sensitizing activity in our previous research (not published). Both two compounds contain a alkoxyphenyl structure, which intrigued us to design a series of benzopyran agents on the base of them (Chart 2). Coumarin-3-carboxylic methyl acid ester was selected as the core structure in our original design. Some of the known heterocycle structures in thiazolidinedione insulin sensitizer were attached to this core structure with the link of the alkyloxy group.

Condensation of 7-hydroxy-coumarin-3-carboxylic acid methyl acid ester **3** with the desired heterocyclic alcohol

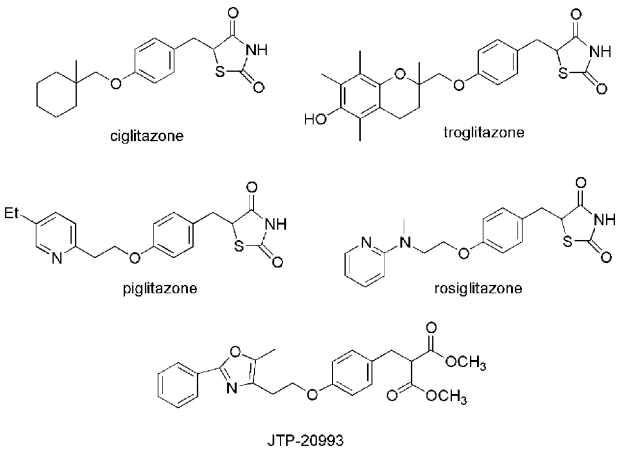

Chart 1.

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via Mitsunobu reaction yielded compounds **4–6**. Saponification of **4–6** with NaOH afforded compounds **7–9**, respectively. Catalytic hydrogenation of compounds **4** and **6** gave compounds **10** and **11** (Scheme 1). Compound **13** was prepared from compound **12** via Mitsunobu reaction. Hydrogenation of compound **13**, and then removal of *tert*-butyl group with trifluoroacetic acid gave compound **14** (Scheme 2). The procedure for the synthesis of compound **16** was outlined in Scheme 3. Condensation of compound **3** with 2-(*N*-*tert*-butoxycarbonyl-*N*-methlyamino)ethanol afforded compound **15**. Catalytic hydrogenation of compound **15** followed by removal of the Boc group and addition to 2-chlorobenzoxazole gave compound **16**. Compounds **17** and **18** were prepared from 6-hydroxy-coumarin-3-carboxylic acid methyl ester via the procedure similar to that in Scheme 1.

All compounds were screened for insulin-sensitizing activity by measuring the triglyceride accumulation

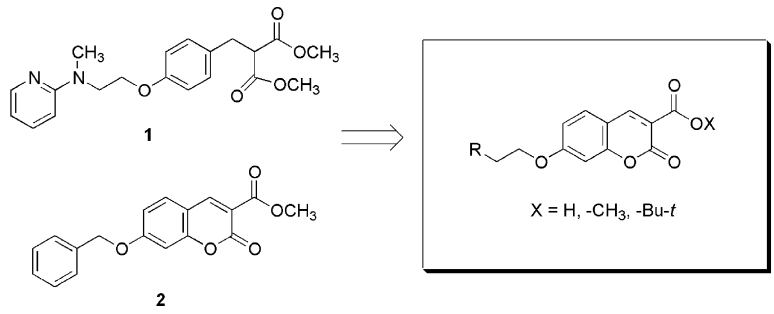
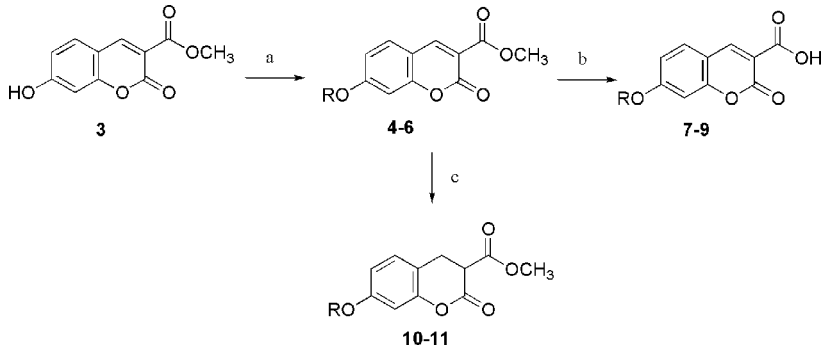
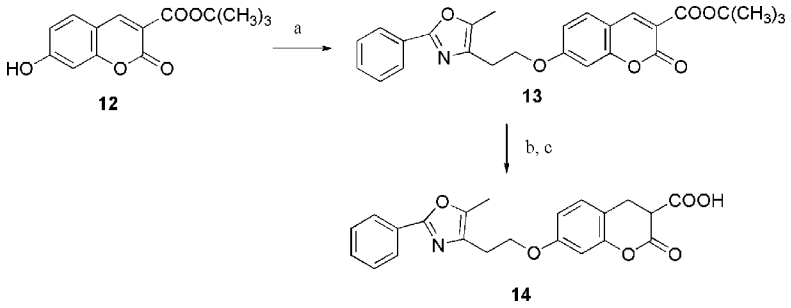


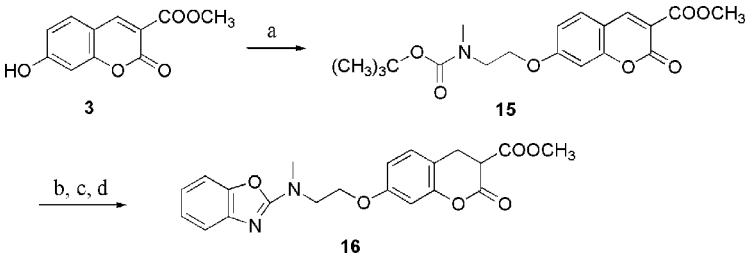
Chart 2.



Scheme 1. Reagents: (a) R-OH, Ph_3P, DEAD, THF; (b) 10% NaOH aqueous; (c) H_2-Pd/C, MeOH/dioxane (3:1).



Scheme 2. Reagents: (a) 2-(5-methyl-2-phenyl-oxazol-4-yl)ethanol, Ph_3P, DEAD, THF, 36%; (b) H_2-Pd/C, MeOH/dioxane (1:1); (c) trifluoroacetic acid, CH_2Cl_2, 70% for two steps.

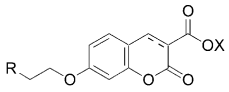


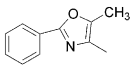
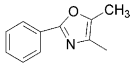
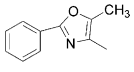
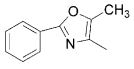
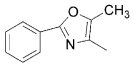
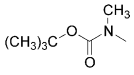
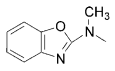
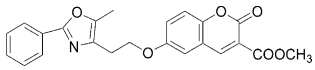
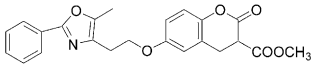
Scheme 3. Reagents: (a) Ph_3P, DEAD, 2-(*N*-Boc-*N*-methlyamino)ethanol, THF, 73%; (b) H_2-Pd/C, dioxane; (c) trifluoroacetic acid, CH_2Cl_2; (d) 2-chlorobenzoxazole, triethylamine, 50% for three steps.

resulting from insulin-regulated differentiation of 3T3-L1 cells.[9] The marketed insulin-sensitizing drug rosiglitazone was selected as positive control. All compounds' activities in Table 1 are given as a percentage of rosiglitazone response for insulin-sensitizing activity at 1 μM concentration, and the EC_{30} values (effective concentration for 30% enhancement of insulin-induced triglyceride accumulation in 3T3-L1 cells) of some compounds are also given.

As indicated in Table 1, compounds **6**[10] and **11**[11] exhibited more potent insulin-sensitizing activity than

Table 1. Screening data of insulin-sensitizing activity for benzopyran derivatives



Compd	R	X	Double bond [a]	Insulin-sensitizing activity	
				Triglyceride accumulation at 1 μM[b]	EC_{30}[c] (M)
4		CH_3	Yes	46	
5		CH_3	Yes	108	3.44×10^{-7}
6		CH_3	Yes	129	8.00×10^{-9}
7		H	Yes	15	
8		H	Yes	25	
9		H	Yes	103	3.00×10^{-7}
10		CH_3	No	27	
11		CH_3	No	132	1.56×10^{-8}
13		Bu-*t*	Yes	89	3.82×10^{-7}
14		H	No	98	1.10×10^{-7}
15		CH_3	Yes	115	
16		CH_3	No	108	2.19×10^{-7}
17				33	
18				28	
Rosiglitazone				100	2.03×10^{-8}

[a]Yes: 3,4-double bond; No: 3,4-single bond.
[b]% activity of rosiglitazone at 1 μM. Values are means of three experiments.
[c]Effective concentration (M) for 30% enhancement of insulin-induced triglyceride accumulation in 3T3-L1 cells.

rosiglitazone according to their EC_{30} values. By comparing compound **4** with **10**, and **6** with **11**, the single-bond and double-bond derivatives did not show much difference on activity. The activities of those compounds with a free carboxy group were lower than their corresponding methyl ester derivatives. Replacement of methyl group in compound **6** with *tert*-butyl group (compound **13**) resulted in a dramaticly reduced activity. The example of compounds **17** and **18** suggested that position of substituent have important effect on activity. Both these synthesized compounds and JTP-20993 contain a 1,3-dicarbonyl group, which suggests this kind of structure is important in the search of non-thiazolidinedione insulin-sensitizing agents.

In summary, we have discovered a novel class of benzopyran derivatives which possessing potent insulin-sensitizing activity. This could be used as a lead structure in the search of non-thiazolidinedione insulin-sensitizing agents.

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10. Data of **6**: colorless crystals, mp 139–140, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.36 (s, 3H), 3.02 (t, $J=6.6$ Hz, 2H), 3.91 (s, 3H), 4.34 (t, $J=6.5$ Hz, 2H), 6.80 (d, $J=2.2$ Hz, 1H), 6.85 (dd, $J=8.7$ Hz, 2.3 Hz, 1H), 7.35–7.42 (m, 3H), 7.46 (d, $J=8.8$ Hz, 1H), 7.90–7.98 (m, 2H), 8.50 (s, 1H). EI-MS (*m*/*z*): 405 (16, M^+), 186 (100).
11. Data of **11**: colorless crystals, mp 128–131, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 2.97 (t, $J=6.5$ Hz, 2H), 3.08 (dd, $J=15.9$ Hz, 6.1 Hz, 1H), 3.34 (dd, $J=15.7$ Hz, 8.6 Hz, 1H), 3.65-3.78 (m, 4H), 4.22 (t, $J=6.4$ Hz, 2H), 6.60 (d, $J=2.2$ Hz, 1H), 6.64 (dd, $J=8.5$ Hz, 2.3 Hz, 1H), 7.06 (d, $J=8.4$ Hz, 1H), 7.30–7.48 (m, 3H), 7.92–8.05 (m, 2H). EI-MS (*m*/*z*): 407 (20, M^+), 186 (100).