Communication

Synthesis and Insulin-sensitizing Activity of a Series of 2-Benzyl-1,3-dicarbonyl Derivatives

TANG, Lei(汤磊) **LENG, Ying**(冷颖) **WANG, Huo-Quan**(王火权) **FENG, Ying**(冯颖)
YANG, Yu-She*(杨玉社) **JI, Ru-Yun**(嵇汝运)
State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 200031, China

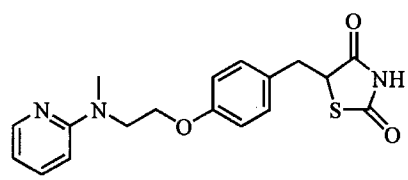
A series of 2-benzyl-1,3-dicabonyl derivatives was synthesized. Their insulin-sensitizing activity was evaluated in 3T3-L1 preadipocyte cells. Compounds 3, 26 and 27 were found to possess strong insulin-sensitizing activity *in vitro* and were selected for further hypoglycemic evaluation *in vivo*.

Keywords insulin-sensitizing activity, 3T3-L1 cells, type 2 diabetes

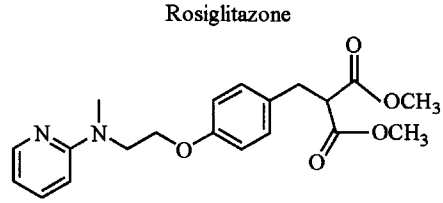
Introduction

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] which greatly increase the risk of heart attack, blindness, kidney failure, stroke and amputation. Therefore, it is important to maintain an appropriate blood glucose level, especially during the early stage of the disease. The therapy for NIDDM is caloric restriction and aerobic exercise, but the most widely used is oral pharmacological agents.[2] Since the pioneer ciglitazone improves glycemic control in insulin resistant animal model of NIDDM by increasing insulin sensitivity,[3] three insulin sensitizers, troglitazone,[4] piglitazone[5] and rosiglitazone[6] have been launched into market for the treatment of type 2 diabetes. However, possibly due to their common thiazolidinedione group, these compounds are associated with a poor safety profile.[7]

We were interested in developing a series of non-thiazolidinedione insulin sensitizer, which might surmount the hepatic toxicity problems associated with thiazolidinediones. Non-thiazolidinedione compound **1** was reported to be able to decrease blood glucose level in ob/ob mice.[8] We now report the synthesis and insulin-sensitizing activity of 34 new compounds based on compound **1**.



Rosiglitazone

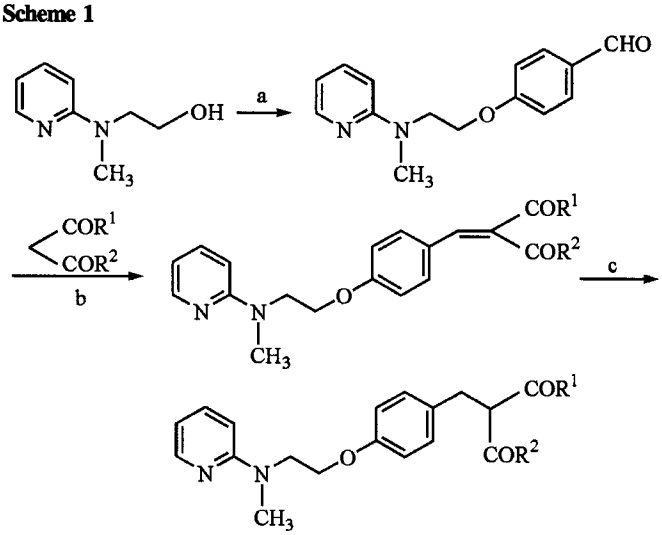


1

Chemistry

Knoevenagel condensations between the 4-[2-(methyl-2-pyridylamino)ethoxy]-benzaldehyde[6] and corresponding malonate derivatives followed by catalytic hydrogenation with 10% Pd/C give compounds **1**—**8**, **11**—**16** and **18** (Scheme 1).

Scheme 1



1—8, 11—16, 18

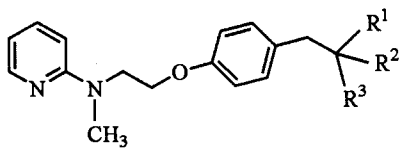
Reagents: (a) NaH, 4-fluorobenzaldehyde, DMF; (b) piperidinium acetate, toluene, reflux; (c) H_2, 10% Pd-C.

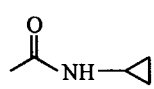
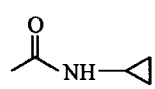
* E-mail: ysyang@mail.shcnc.ac.cn; Tel.: 021-64311833-346
Received September 18, 2002; revised December 19, 2002; accepted January 6, 2003.

Coupling of compound **1** with hydroxylamine and hydrazine gave compounds **9** and **10**. The diamide **17** or **19** was prepared from **1** with methylamine hydrochloride or cyclopropylamine in basic conditions. The triesters **20** or **21** was prepared by coupling **1** and methyl chloroacetate or ethyl chloroacetate. Compound **22** was obtained by reduction of compound **1** with $LiAlH_4$. Treatment of **22** with formic acid or acetic anhydride yields compounds **23** or **24** (Scheme 2).

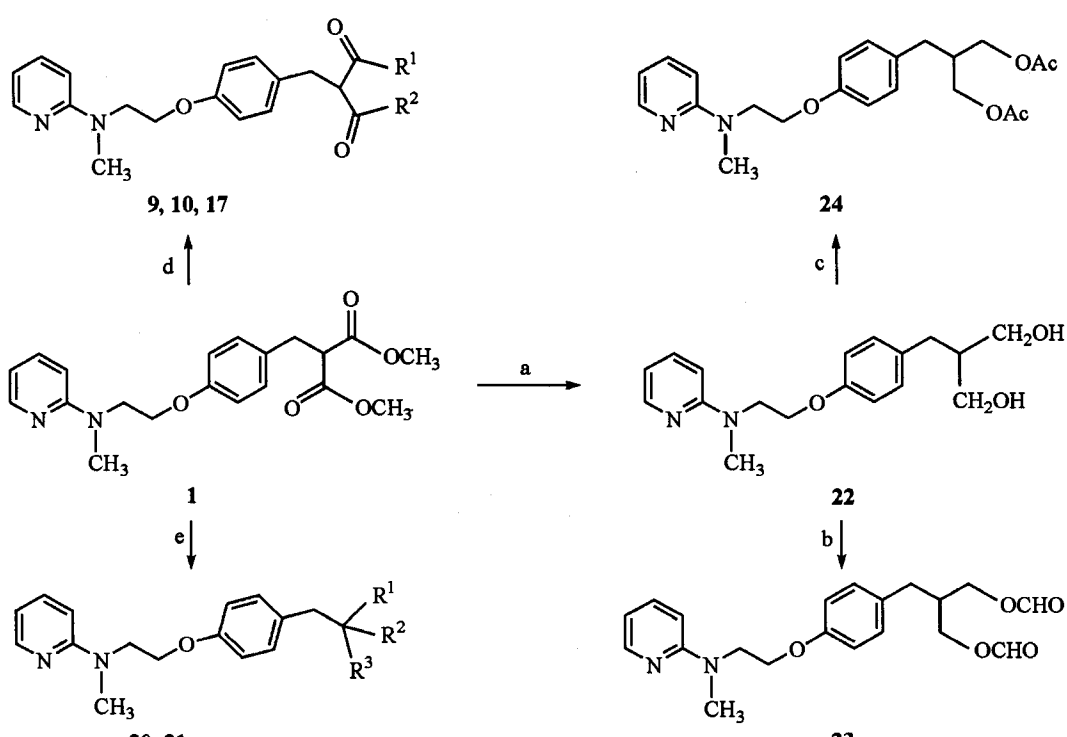
Mitsunobu reactions beteween indole-alkyl alcohol and dimethyl 2-(4-hydroxybenzyl) malonate give compounds **25**—**32** and **34**. Reduction of **31** with 10% Pd/C in formic acid give compounds **33** (Scheme 3). The structures of compounds **1**—**34** can be seen in Tables 1 and 2.

Table 1 Structure of compounds **1**—**24**



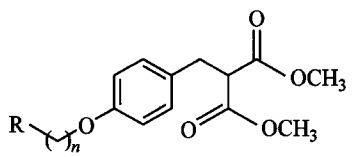
Compd	R^1	R^2	R^3	Compd	R^1	R^2	R^3
1	CO_2CH_3	CO_2CH_3	H	**13**	CO_2CH_3	CONH-4-Py	H
2	CO_2Et	CO_2Et	H	**14**	CO_2Et	CONH-2-Py	H
3	CO_2-Pr-*i*	CO_2-Pr-*i*	H	**15**	CO_2Et	CONH-3-Py	H
4	CO_2-*t*-Bu	CO_2-*t*-Bu	H	**16**	CO_2Et	CONH-4-Py	H
5	$-CO_2-C(CH_3)_2-CO_2-$		H	**17**	$CONHCH_3$	$CONHCH_3$	H
6	$COCH_3$	CO_2Et	H	**18**	CONH-Ph	CONH-Ph	H
7	$COCH_3$	CO_2CH_3	H	**19**			H
8	CO-*n*-Pr	CO_2Et	H	**20**	CO_2CH_3	CO_2CH_3	CO_2CH_3
9	CONHOH	CONHOH	H	**21**	CO_2CH_3	CO_2CH_3	CO_2Et
10	$CONHNH_2$	$CONHNH_2$	H	**22**	CH_2OH	CH_2OH	H
11	CO_2CH_3	CONH-2-Py	H	**23**	CH_2OCHO	CH_2OCHO	H
12	CO_2CH_3	CONH-3-Py	H	**24**	CH_2OAc	CH_2OAc	H

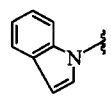
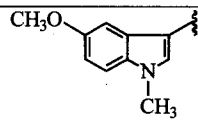
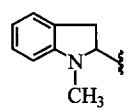
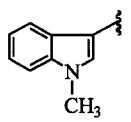
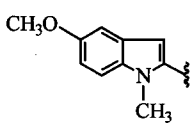
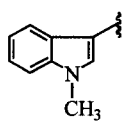
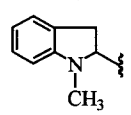
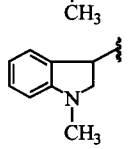
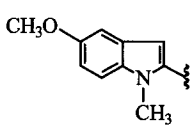
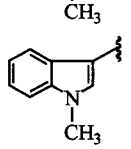
Scheme 2



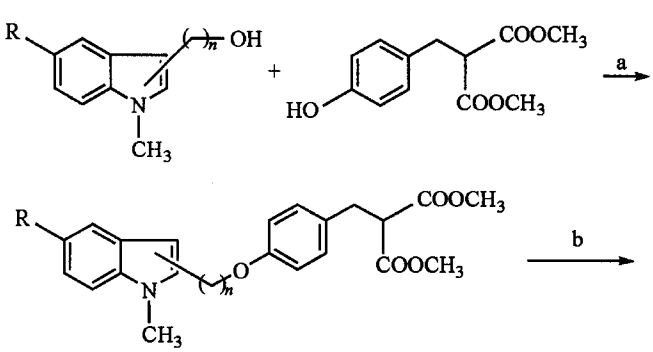
Reagents: (a) $LiAlH_4$; (b) HCOOH, reflux; (c) Ac_2O, pyridine, reflux; (d) 5 equiv. of hydroxylamine hydrochloride or hydrazine hydrate, Na_2CO_3, reflux; (e) NaH, methyl chloroformate or ethyl chloroformate, $CHCl_3$.

Table 2 Structure of compounds **25—34**

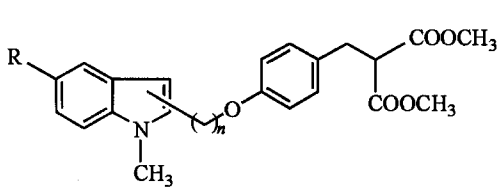


Compd	R	n	Compd	R	n
25		2	**30**		1
26		1	**31**		2
27		1	**32**		1
28		1	**33**		2
29		1	**34**		4

Scheme 3



25—32, 34



33

Reagents: (a) Ph_3P, DEAD, Et_2O; (b) 10% Pd-C, HCOOH.

Results and discussion

All compounds prepared were identified with ^1H NMR spectra, mass spectra, elemental analyses and infrared spectra. Insulin-sensitizing activity were evaluated by the effect on insulin-regulated cell differentiation, which was monitored from the enhancement of triglyceride accumulation in 3T3-L1 cells.[9] Rosiglitazone was selected as positive control compound (Tables 3 and 4).

Table 3 Percentage enhancement of triglyceride accumulation in 3T3-L1 cells[a]

Compound	Concentration of test compound (μmoL/L)		
	0.01	0.1	1
1	31.34	45.53	39.8
2	26.81	39.54	36.49
3	14.06	71.07	73.73
4	5.17	-8.87	-3.56
5	ND[c]	ND	ND
6	-0.16	24.28	55.79
7	-8.1	-7.06	14.25
8	-9.69	9.57	31.9
9	1.88	2.67	8.21
10	0.27	0.44	3.24
11	-2.81	10.52	13.85
12	3.08	12.48	20.6
13	3.64	14.75	18.91
14	-6.88	4.34	17.01
15	6.36	19.57	18.87
16	6.23	14.06	24.47
17	ND	16.09	3.20
18	5.38	13.17	11.11
19	2.53	-5.68	11.09
20	1.20	3.73	2.36
21	-4.77	21.60	25.83
22	6.21	4.62	5.41
23	14.44	-5.02	19.80
24	-23.51	-17.96	-18.08
25	2.01	20.1	23.36
26	26.24	54.36	50.14
27	13.78	50.66	57.01
28	13.27	34.81	41.18
29	-5.49	-2.85	12.85
30	-5.03	13.09	16.04
31	3.95	17.01	53.3
32	2.29	3.07	12.64
33	15.64	34.56	48.38
34	20.97	23.83	31.46
rosiglitazone[b]	31.45 ± 16.57	40.07 ± 13.77	38.99 ± 11.67

[a] mean, $n = 3$. [b] mean ± SD, $n = 22$. [c] ND: not done.

Table 4 EC_{25}[a] and EC_{50}[a] (μmoL/L) of compounds **1**, **3**, **26** and **27**

Compound	**1**	**3**	**26**	**27**	ros.
EC_{25}	0.07	0.016	0.034	0.022	0.0063
EC_{50}	1.90	0.1	0.38	NG[b]	0.086

[a] Effective concentration for 25% (EC_{25}) or 50% (EC_{50}) enhancement of insulin-induced triglyceride accumulation in 3T3-L1 cells. [b] NG: not got the accumulation of 50% enhancement.

Among all diester derivatives, compound **3** (EC_{50} 0.1 μmoL/L) exhibited almost equal insulin-sensitizing activity to rosiglitazone (EC_{50} 0.086 μmoL/L), and a higher potency

compared to leading compound **1** (EC_{50} 1.9 μmoL/L). Diamide or mono-amide compounds lead to decreased activity. The propanediol derivative **22** also showed weak activity. This might mean that high-polarity group is not favorable for the insulin-sensitizing activity of these compounds. The electronic-isomeric **23**, **24** of compound **1** were hardly active, indicating that the 1, 3-dicarbonyl structure is essential for insulin-sensitizing activity. The tricarbonyl derivatives **20**, **21** also showed decreased potency. All indole derivative compounds **26** (EC_{50} 0.38 μmoL/L) and **27** (EC_{25} 0.022 μmoL/L) showed satisfactory insulin-sensitizing activity.

In summary, we have found non-thiazolidinedione compounds **3**, **26** and **27** which show potent insulin-sensitizing activity in 3T3-L1 cells. According to the conclusion that compounds with good potency in the lipogenesis assay have antihyperglycemic and antihyperlipidemic activity in rodent models of type 2 diabetes,[10] compounds **3**, **26** and **27** were selected for further tests *in vivo* in KKAy mice.

References

1 Porte, D., Jr.; Schwartz, M. W. *Science* **1996**, *272*, 699.

2 Taylor, S. I.; Accili, D.; Imai, Y. *Diabetes* **1994**, *43*, 735.

3 Sohda, T.; Mizuno, K.; Imamiya, E.; Sugiyama, Y.; Fujita, T.; Kawamatsu, Y. *Chem. Pharm. Bull.* **1982**, *30*, 3580.

4 Yoshioka, T.; Fujita, T.; Kanai, T.; Aizawa, Y.; Kurumada, T.; Hasegawa, K.; Horikoshi, H. *J. Med. Chem.* **1989**, *32*, 421.

5 Momose, Y.; Meguro, K.; Ikeda, H.; Hatanaka, C.; Oi, S.; Sohda, T. *Chem. Pharm. Bull.* **1991**, *39*, 1440.

6 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.

7 Henry, R. R. *Endocrinol. Metab. Clin. North Am.* **1997**, *26*, 553.

8 David, H; Kantilal, R. H. *WO 9413650*, **1994** [*Chem. Abstr.* **1994**, *121*, 134132].

9 Kletzien, R. F.; Clarke, S. D.; Ulrich, R. G. *Mol. Pharm.* **1991**, *41*, 393.

10 Henke, B. R.; Blanchard, S. G.; Brackeen, M. F.; Brown, K. K.; Cobb, J. E.; Collins, J. L.; Harrington, W. W.; Hashim, J. M. A.; Hull-Ryde, E. A.; Kaldor, I.; Kliewer, S. A.; Lake, D. H.; Leesnitzer, L. M.; Lehmann, J. M.; Lenharrd, J. M.; Orband-Miller, L. A.; Miller, J. F.; Mook, R. A.; Noble, S. A.; Oliver, W.; Parks, D. J.; Plunket, K. D.; Szewczyk, J. R.; Willson, T. M. *J. Med. Chem.* **1998**, *41*, 5020.

(E0209181 PAN, B. F.; ZHENG, G. C.)