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RESEARCH-ARTICLE

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Design, synthesis and hypoglycemic activity of 3-methyl-1-phenyl-4-{4-[(5-methyl-2-phenyloxazol-4-yl)methoxy]benzylene (benzyl)}-2-pyrazol-5-one

Abstract Based on the SAR (structure activity relationship) of TZDs (thiazolidinediones), 3-methyl-1-phenyl-2-pyrazoline-5-one was selected as a substitute for TZD. Compounds of 3-methyl-1-phenyl-4-{4-[(5-methyl-2-phenyloxazol-4-yl)methoxy]benzylene(benzyl)}-2-pyrazol-5-one were designed and synthesized to find some more hypoglycemic active agents and further investigate the SAR of this class of compounds. Butanedione monoxime reacted with (substituted) benzaldehyde *via* cyclization and chlorination to give 4-(chloromethyl)-5-methyl-2-phenyloxazole derivatives, which condensed with 4-hydroxybenzaldehyde or vanillin, and was followed by the Knoevenagel reaction with 3-methyl-1-phenyl-2-pyrazol-5-one to give compounds Ia–Ih. Compounds Ia–Ih were hydrogenated with Pd–C to give IIa–IIh, and their hypoglycemic activity was evaluated with a glucose oxidase kit and insulin load test on normal mice. Sixteen new target compounds were synthesized. All the compounds were characterized by ^{1}H NMR, IR, MS and elemental analysis. The preliminary pharmacological tests show that the compounds have good hypoglycemic activity and can enhance the action of insulin, especially Ib, Id and If.

Keywords pyrazolone derivative, synthesis, hypoglycemic activity, insulin sensitizers

1 Introduction

Insulin resistance (IR) is an important nosogenesis causing non-insulin-dependent diabetes mellitus (type 2 diabetes mellitus) [1]. Insulin sensitizers have become popular in researching antidiabetic agents because they can improve IR. The representative drugs that have come into the market are Pioglitazone and Rosiglitazone. Their mechanism is to activate PPARγ (peroxisome proliferator-activated receptor γ) [2]. Both have the structure of thiazolidinediones (TZDs), which have once been thought to be necessary pharmacophores. More evidence has accumulated showing that there are other structures that have more potent activity compared to TZDs. The increased potency of these PPARγ agonists has been advanced into clinical trials for the treatment of type 2 diabetes [3,4]. On the other hand, modern medical studies find that a lot of diseases are connected with free oxygen radicals, especially non-viral and non-bacterial diseases. Oxygen free radicals not only affect the occurrence and development of diabetes chronic complications, but also contribute to insulin resistance. Free oxygen radicals accumulate too much in vivo, which will break pancreatic cells and disturb the normal saccharide metabolism [5]. The diabetic mellitus animal model indicates that anti-oxidation agents can improve insulin sensitivity by getting rid of excess free radicals in vivo to prevent the destruction of islet cells and also stimulate β-cells, which are partially functionless to excrete insulin [6].

The basic structure of insulin sensitizers consists of three parts (Fig. 1). The research on SAR illuminates that R_1 group of part A influences the hydrophobic interaction between insulin sensitizers and receptors and also adjusts the pharmacokinetic behavior. The research shows the compounds with 4-oxazole display high activity. Part B is normally 4-benzen-oxo-benzyl, which is regarded as the key hypoglycemic function group and reduces blood fat. Other research [7] found that the derivatives of 5-(3,4-diarylbenzyl)-TZD have higher bioactivity than 5-(4-arylbenzyl)-TZD. The R_2 group in part C presents all kinds of acidic heterocycle and non-cycle function groups (normally having carbonyl groups and/or other hetero atoms), which are an important

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pharmacophores. When the volume of the R_2 group is bigger than TZDs, the group is easier to link to receptors [8,9]. Part B is normally connected to part C with a carbon-carbon single bond. The compounds with a double bond also have hypoglycemic activity.

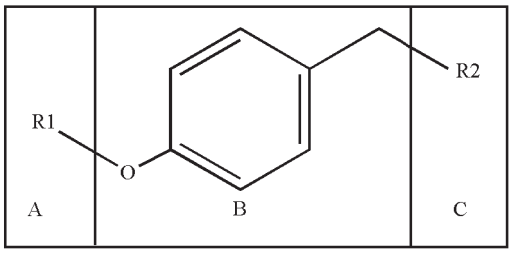


Fig. 1 Basic structure of insulin sensitizers

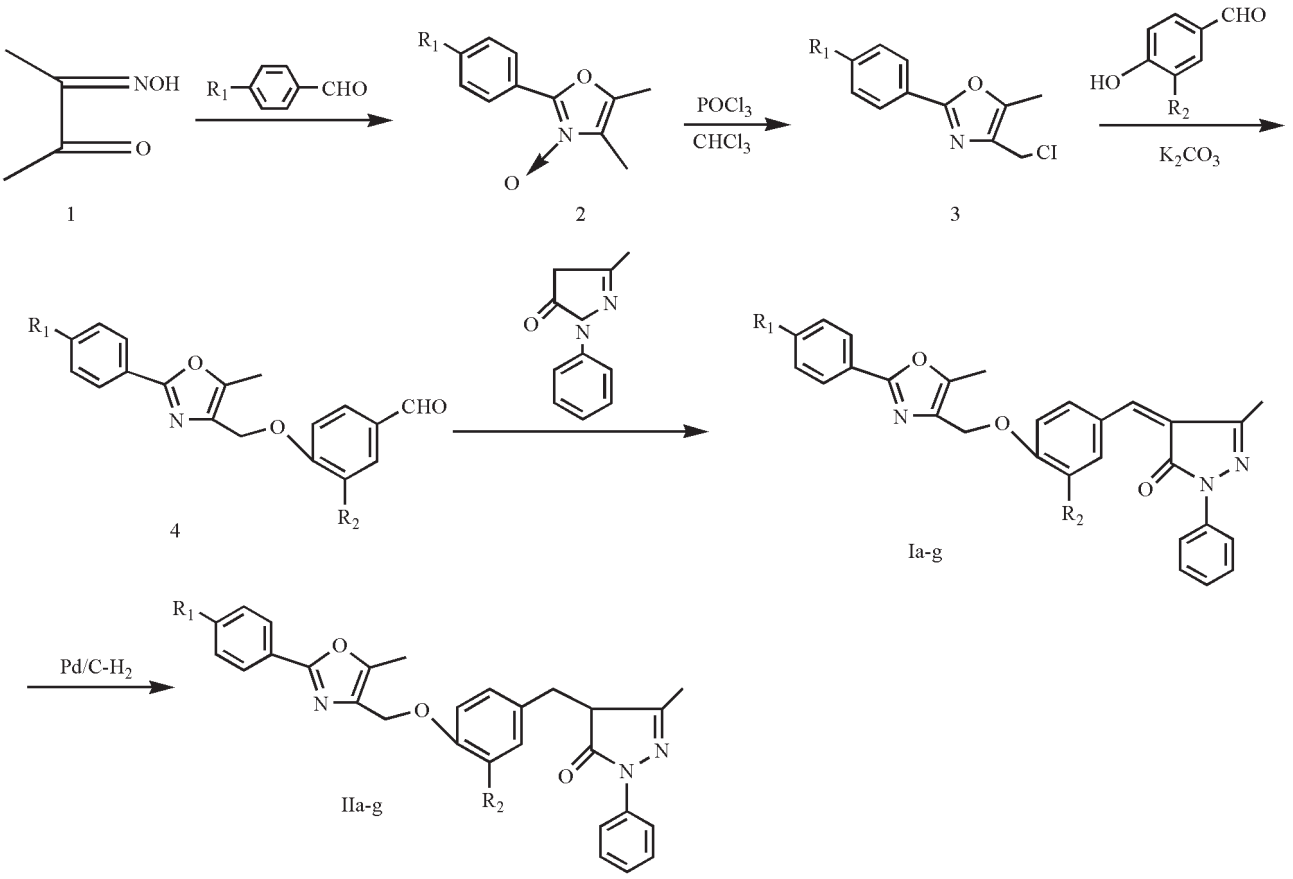
To find a novel high activity compound, with 4-(5-methyl-2-(substituted)phenyl-1,3-oxazole-4-yl)methoxybenzylene(benzyl) as the basic structure of part A and part B and high anti-radical activity 3-methyl-1-phenyl-2-pyrrozoline-5-one as part C to displace TZDs, we designed and synthesized 16 new chemical entities for the screening of new insulin sensitizers. The reaction route is as follows (Scheme 1).

2 Results and discussion

2.1 Chemistry

According to a work-up of compound 2 in the literature [10], water was poured into the reaction mixture, then the mixture was extracted with ethyl ether to get rid of the remaining benzaldehyde. In our experiment however, many white floccules appeared after the addition of water, which is difficult to dissolve in ethyl ether and will cause inconvenience for extraction and loss on yield. After optimization, high pure compound 2 was obtained by filtering and washing with ethyl ether.

According to the literature [11], the reaction time for compound 3 is 30 min at reflux temperature. In fact, the product is not pure after 30 min because there are two close spots in TLC. Monitoring the reaction, the higher polar spot can be converted into the lower polar one, which may suggest that the reaction takes two steps: a



Scheme 1 Synthetic routes of the target compounds Ia–Ig and IIa–Iig
R_1 = H, Cl, F, CH_3, R_2 = H, OMe

reduction which removes the O connected to N, followed by chlorination on the methyl group. As a result, prolonging time can enhance conversion of the reaction.

According to the literature [12], compound 4 was purified by column chromatography [hexane:ethyl acetate = 4 : 1, *V*/*V*] to remove the remaining 4-hydroxy-benzaldehyde. 4-Hydroxy-benzaldehyde has hydroxyl group and can be removed by converting into sodium salt in aqueous phase, while compound 4 can remain in the organic phase. The concentration of aqueous sodium hydroxide is important for the formation of the sodium salt of 4-hydroxy-benzaldehyde. We found the optimal concentration at 2.5 mol/L. The advanced method avoids column chromatography and the yield is 10%, which is higher than that the literature reported.

2.2 Bioactivity

The biological activities of the compounds prepared were tested using genetically modified mice. The results are shown in Tables 1 and 2.

Results show that the tested compounds do not have significant difference compared with the control groups on the impact of sugar loads, but the inhibition of glucose increased tendency is obvious. In insulin load tests, after 2 h the blood sugar level has picked up in CMC control groups, while the hypoglycemic effect is obvious in the tested compounds. This means the tested compounds can significantly strengthen and extend the exogenous insulin to lower the blood glucose, in which the Ib, Id and If are more prominent compared with the control groups. We could now give a preliminary estimation that the target compounds have a certain hypoglycemic activity, which may enhance the role of insulin sensitivity in tissue.

3 Experimental

3.1 Instruments and reagents

Melting points were determined on an Mtl-temp apparatus. Elementary analysis was performed on an Elementar Vario EL III analyzer. ^{1}H NMR spectra were recorded on a Bruker AV-300 using tetramethylsilane as the internal standard. ESI/MS spectra were recorded on an Agilent 1100 apparatus.

All TLC plates were made by mixing 30 g silica gel GF_{254} with 100mL aqueous CMC-Na (sodium carboxymethyl cellulose, 0.8%, *W*/*W*). This mixture was spread as a thick slurry on a glass sheet and the resultant plate was dried and activated by heating in an oven for 1 hour at 105–110°C and preserved in a desiccator. The wavelength of UV lamp is 254 nm. All materials were purchased from commercial suppliers and used without further purification except for butanedione (analytical pure), 4-hydroxy-benzalhyde (analytical pure), 3-methyl-1-phenyl-2-pyrrozoline-5-one (analytical pure).

3.2 4,5-Dimethyl-2-phenyl-3-oxo-oxazole (2a)

Synthesized according to the literature [10], the yield is 85.5%, m.p. 90–92°C (in literature [8] yield is 84.5%). Compound 2b, 2c and 2d were synthesized with a similar method.

Table 1 Hypoglycemic effect of the target compounds in mice ($x \pm$ SD, $n = 10$)

group	dose/mg·kg^{-1}	hypoglycemic effect*		
		0h	1h	2h
CMC	–	0.155±0.017	0.192±0.026(23↑)	0.169±0.021(9↑)
Ia	10	0.138±0.039	0.141±0.041(2↑)	0.113±0.027(18↓)
Ib	10	0.139±0.019	0.159±0.041(14↑)	0.0125±0.022(10↓)
Id	10	0.132±0.036	0.157±0.064(19↑)	0.0125±0.045(5↓)
If	10	0.152±0.031	0.199±0.037(30↑)	0.163±0.052(7↑)
IIc	10	0.131±0.027	0.181±0.019(38↑)	0.164±0.027(20↑)

*The values in parentheses are the percentage change; ↑ expresses the ascension; ↓ expresses the drop

Table 2 Effect of the target compounds on blood glucose under insulin load in mice ($x \pm$ SD, $n = 10$)

group	dose/mg·kg^{-1}	hypoglycemic effect*		
		0h	1h	2h
CMC	–	0.120±0.035	0.078±0.014(35↓)	0.131±0.048(9↑)
Ia	10	0.154±0.023	0.081±0.036(47↓)	0.104±0.029(32↓)
Ib	10	0.134±0.049	0.047±0.021(64↓)	0.088±0.031(34↓)
Id	10	0.136±0.025	0.068±0.019(50↓)	0.107±0.039(21↓)
If	10	0.181±0.030	0.076±0.016(56↓)	0.112±0.042(37↓)
IIc	10	0.143±0.034	0.075±0.030(47↓)	0.119±0.032(16↓)

* The values in parentheses are the percentage change; ↑ expresses the ascension; ↓ expresses the drop

3.3 4-Chloromethyl-5-methyl-2-benzyl-oxazole (3a)

Synthesized according to the literature [11], the yield is 62.0%. m.p. 82–84°C. Compound 3b, 3c and 3d were synthesized with a similar method.

3.4 4-(5-Methyl-2-phenyl-oxazole-4-yl)methoxy-benzalhyde (4a)

According to the work-up in the literature [12], the reaction mixture was poured into 0.5 vol of water and extracted with ethyl acetate twice. The organic layers were combined and washed with water to pH 7, and then washed with brine and dried with Na_2SO_4. The extract was filtered and evaporated to dryness. The residue was reslurried with 2.5 mol/L a.q.NaOH. and filtered, washed with water to pH 7 and dried to give 7.51 g of yellow solid. The yield is 96.7%, m.p. 112–114°C.

3.5 3-Methoxy-4-(5-methyl-2-phenyl-oxazole-4-yl) methoxy-benzalhyde (4b)

According to 4a, compound 4b was synthesized from compound 3 and vanillin. Compound 4b is slightly yellow solid, the yield is 72.1%, and m.p. is 120–122°C. Compound 4c–4h was synthesized with a similar method. The physical character, yields and the data of elemental analysis of compound 2–4 are listed in Table 3.

3.6 3-Methyl-1-phenyl-4-{[4-(5-methyl-2-benzyl-oxazole-4-yl)methoxy]-benzene}2-pyroline-5-one (Ia)

Into the mixture of compound 4a (0.71 g, 2.4 mmol), 3-methyl-1-phenyl-2-pyrroline-5-one (0.42 g, 2.4 mmol) and abs. ethanol (20 mL) were added, catalyzing the amount of pyridine. The mixture was refluxed for 5 hours. A significant solid precipitated after cooling the mixture. The mixture was filtered, washed with ethyl ether and dried to give orange solid 0.31 g. The yield is 29%, m.p. 128–130°C.

Compound Ib–Ih was synthesized with a similar method. The physical character, yields and data of elemental analysis of compound 2–4 are listed in Table 4. The data of IR, MS and ^{1}H NMR are listed in Table 5.

3.7 3-Methyl-1-phenyl-4-{[4-(5-methyl-2-benzyl-oxazole-4-yl)methoxy]-benzyl}-2-pyrrozoline-5-one (IIa)

Pd/C (5%, *W*/*W*) was added to the solution of compound Ia (1.2 g, 2.7 mmol) and dioxane. The mixture was stirred at hydrogen atmosphere at normal pressure and at ambient temperature. The reaction was stopped when the absorption of hydrogen ceased. The mixture was then filtered, and the filtrate was evaporated to dryness. The residue was recrystallized from methanol and dried to give 0.48 g of white solid. The yield is 39.4%, while m.p. is 137–138°C. Compound IIb–IIh was synthesized with a similar method. Their physical character, yields and the data of elemental analysis are listed in Table 4. The data of IR, MS and ^{1}H NMR are listed in Table 5.

3.8 Biological activity tests

Mice weighing 18–22 g, half male and half female, were given commercial feed and arbitrary drinking water in the laboratory for three days for adaptation. In general the mice with agile responses and without injury on skin could be used for testing.

Table 3 Physical data, yields and elemental analysis data of compounds 2,3 and 4

compd.	R_1	R_2	m.p./°C	yield/%	elemental analysis/(%, calcd.)		
					C	H	N
2a	H		90–92	85.5	69.20(69.83)	6.05(5.86)	7.28(7.40)
2b	Cl		136–138	60.0	58.76(59.07)	5.01(4.51)	6.48(6.26)
2c	F		136–137	60.6	63.70(63.76)	4.95(4.86)	6.36(6.76)
2d	CH_3		123–125	71.4	71.04(70.92)	6.23(6.45)	6.64(6.89)
3a	H		80–84	62.0	63.82(63.62)	4.72(4.85)	6.91(6.75)
3b	Cl		96–98	63.0	54.35(54.57)	4.01(3.75)	5.45(5.79)
3c	F		136–137	84.2	58.33(58.55)	4.39(4.02)	6.06(6.21)
3d	CH_3		115–117	58.6	65.47(65.02)	5.23(5.46)	6.47(6.32)
4a	H	H	112–114	96.7	73.41(73.71)	4.94(5.15)	4.73(4.78)
4b	H	CH_3O	120–122	72.1	70.23(70.58)	5.61(5.30)	4.12(4.33)
4c	Cl	H	120–122	89.6	66.06(65.96)	4.04(4.31)	4.68(4.27)
4d	F	H	105–107	96.5	69.13(69.45)	4.22(4.53)	4.76 (4.50)
4e	Cl	CH_3O	150–152	96.8	63.70(63.78)	4.58(4.51)	4.06(3.91)
4f	F	CH_3O	130–132	80.0	67.05(66.86)	4.51(4.72)	4.39(4.10)
4g	CH_3	H	138–141	82.0	74.66(74.25)	5.21(5.58)	4.26(4.56)
4h	CH_3	CH_3O	156–158	85.3	71.37(71.20)	5.59(5.68)	4.37(4.15)

Table 4 Physical data, yields and elemental analysis data of compounds **I** and **II**

compd.	R_1	R_2	m.p./°C	yield/%	elemental analysis/(%, calcd.)		
					C	H	N
Ia	H	H	128–130	29.0	74.52(74.82)	4.96(5.16)	9.23(9.35)
Ib	H	OCH_3	192–193	78.8	71.78(72.64)	5.10(5.25)	8.29(8.76)
Ic	Cl	H	191–192	87.1	69.47(69.49)	4.29(4.58)	8.38(8.68)
Id	Cl	OCH_3	184–185	86.2	67.56(67.77)	4.40(4.71)	7.77(8.18)
Ie	F	H	140–142	87.7	71.68(71.94)	4.68(4.74)	8.95(8.99)
If	F	OCH_3	184–185	86.2	69.71(70.01)	4.55(4.86)	8.10(8.45)
Ig	CH_3	H	178–181	81.4	75.38(75.14)	5.21(5.44)	8.95(9.07)
Ih	CH_3	OCH_3	164–166	79.8	73.22(73.01)	5.23(5.51)	8.78(8.51)
IIa	H	H	137–138	39.4	74.25(74.48)	5.64(5.58)	9.03(9.31)
IIb	H	OCH_3	180–181	30.2	71.96(72.33)	5.93(5.65)	8.80(8.73)
IIc	Cl	H	176–178	69.7	69.03(69.20)	4.98(4.98)	8.38(8.65)
IId	Cl	OCH_3	176–178	24.0	67.87(67.50)	5.36(5.08)	7.62(8.14)
IIe	F	H	170–172	70.5	71.80(71.63)	5.33(5.15)	8.71(8.95)
IIf	F	OCH_3	192–194	17.4	69.30(69.73)	5.33(5.25)	8.10(8.41)
IIg	CH_3	H	152–153	73.6	74.65(74.82)	5.68(5.85)	9.16(9.03)
IIh	CH_3	CH_3O	183–187	53.2	72.49(72.71)	5.94(5.90)	8.34(8.48)

Table 5 Spectra data of compounds **I** and **II**

compd	IR/cm^{-1}	ESI-MS*	^{1}H NMR (DMSO-d_6 or $CDCl_3$) δ
Ia	1680	450	2.34(s,3H,CH_3),2.46(s,3H,CH_3),5.11(s,2H,CH_2),7.12–7.16(d,2H,Ar–H),7.17–7.20(d,1H,Ar–H),7.33(s,1H,CH), 7.38–7.47(m,5H,Ar–H),7.96–7.99(d,2H,Ar–H),8.01–8.04(q,2H,Ar–H),8.59–8.62(d,2H,Ar–H)
Ib	1675	480	2.35(s,3H,CH_3),2.46(s,3H,CH_3),4.03(s,3H,CH_3),5.18(s,2H,CH_2),7.17–7.21(m,2H,Ar–H),7.33(s,1H,CH), 7.39–7.46(m,5H,Ar–H),7.69–7.72(q,1H,Ar–H),7.94–7.97(d,2H,Ar–H),8.00∼8.03(q,2H,Ar–H),9.01–9.02 (d,1H,Ar–H)
Ic	1675	484	2.36(s,3H,CH_3),2.47(s,3H,CH_3),5.08(s,2H,CH_2),7.12–7.19(t,2H,Ar–H),7.21(s,1H,CH),7.35–7.44(t,5H,Ar–H), 7.94–7.98(q,4H,Ar–H),8.60–8.63(d,2H,Ar–H)
Id	1675	514	2.35(s,3H,CH_3),2.46(s,3H,CH_3),4.03(s,3H,CH_3),5.16(s,2H,CH_2),7.16–7.21(t,2H,Ar–H),7.33(s,1H,CH), 7.39–7.44(q,4H,Ar–H),7.70–7.73(d,1H,Ar–H),7.93–7.96(d,2H,Ar–H),9.00(s,1H,Ar–H)
Ie	1678	468	2.34(s,3H,CH_3),2.51(s,3H,CH_3),5.18(s,2H,CH_2),7.19–7.22(t,2H,Ar–H),7.24(s,1H,CH),7.34–7.46(m,4H,Ar–H), 7.77(s,1H,Ar–H),7.92∼7.94(d,2H,Ar–H),7.97–8.02(q,4H,Ar–H),8.71–8.74(d,2H,Ar–H)
If	1678	498	2.34(s,3H,CH_3),2.51(s,3H,CH_3),3.87(s,3H,CH_3),5.17(s,2H,CH_2),7.20–7.22(t,2H,Ar–H),7.34(s,1H,CH), 7.36–7.47(m,4H,Ar–H),7.90–7.93(d,1H,Ar–H),7.98–8.02(q,2H,Ar–H),8.82(s,1H,Ar–H)
Ig	1678	464	2.35(s,6H,CH_3),2.48(s,3H,CH_3),5.12(s,2H,CH_2),7.02–7.09(t,2H,Ar–H),7.31(s,1H,CH),7.35–7.44(m,5H,Ar–H), 7.94–7.98(q,4H,Ar–H),8.40–8.43(d,2H,Ar–H)
Ih	1675	494	2.34(s,6H,CH_3),2.50(s,3H,CH_3),4.18(s,3H,CH_3),5.22(s,2H,CH_2),7.16–7.21(t,2H,Ar–H),7.35(s,1H,CH), 7.39–7.44(q,4H,Ar–H),7.70–7.73(d,1H,Ar–H),7.93–7.96(d,2H,Ar–H),8.90(s,1H,Ar–H)
IIa	2922	452	2.34(s,3H,CH_3),2.44(s,3H,CH_3),2.82(dd,1H,CH),3.21(dd,1H,CH),3.57(m,1H,CH),5.16(s,2H,CH_2), 7.12–7.16(d,2H,Ar–H),7.17–7.20(d,1H,Ar–H),7.38–7.48(m,5H,Ar–H),7.96–7.99(d,2H,Ar–H),8.02–8.06 (q,2H,Ar–H),8.56–8.60(d,2H,Ar–H)
IIb	3057	482	2.15(s,3H,CH_3),2.48(s,3H,CH_3),3.15(d,2H,CH_2),3.60(t,1H,CH),4.21(s,3H,CH_3),5.18(s,2H,CH_2),7.17–7.21 (m,2H,Ar–H),7.39–7.46(m,5H,Ar–H),7.69–7.72(q,1H,Ar–H),7.94–7.97(d,2H,Ar–H),8.00–8.03(q,2H, Ar–H),9.01–9.02(d,1H,Ar–H)
IIc	3088	486	2.35(s,3H,CH_3),2.47(s,3H,CH_3),3.18(d,2H,CH_2),3.82(t,1H,CH),5.18(s,2H,CH_2),7.12–7.19(t,2H,Ar–H), 7.35–7.44(t,5H,Ar–H),7.94–7.98(q,4H,Ar–H),8.60–8.63(d,2H,Ar–H)
IId	3063	516	2.35(s,3H,CH_3),2.46(s,3H,CH_3),3.12(d,2H,CH_2),3.64(t,1H,CH),4.13(s,3H,CH_3),5.20(s,2H,CH_2),7.16–7.21 (m,2H,Ar–H),7.39–7.44(m,2H,Ar–H),7.70–7.73(m,2H,Ar–H),7.93–7.96(m,2H,Ar–H),9.00(s,1H,Ar–H)
IIe	3067	470	2.35(s,3H,CH_3),2.56(s,3H,CH_3),3.21(d,2H,CH_2),3.98(t,1H,CH),5.18(s,2H,CH_2),7.19–7.22(t,2H,Ar–H), 7.34–7.46(m,4H,Ar–H),7.77(s,1H,Ar–H),7.92–7.94(d,2H,Ar–H),7.97–8.02(q,4H,Ar–H),8.71–8.74 (d,2H,Ar–H)
IIf	3076	500	2.34(s,3H,CH_3),2.51(s,3H,CH_3),3.20(d,2H,CH_2),3.76(t,1H,CH),4.23(s,3H,CH_3),5.17(s,2H,CH_2),7.20–7.22 (t,2H,Ar–H),7.36–7.47(m,4H,Ar–H),7.80–7.93(d,1H,Ar–H),7.98–8.02(q,2H,Ar–H),8.62(s,1H,Ar–H)
IIg	3073	466	1.94(s,3H,CH_3),2.35(s,3H,CH_3),2.48(s,3H,CH_3),3.12(d,2H,CH_2),3.61(t,1H,CH),5.12(s,2H,CH_2),7.02–7.09 (t,2H,Ar–H),7.35–7.44(m,5H,Ar–H),7.94–7.98(q,4H,Ar–H),8.40–8.43(d,2H,Ar–H)
IIh	3080	496	2.34(s,6H,CH_3),2.50(s,3H,CH_3),3.21(t,1H,CH),3.68(d,2H,CH_2),4.18(s,3H,CH_3),5.22(s,2H,CH_2),7.16–7.21 (t,2H,Ar–H),7.39–7.44(q,4H,Ar–H),7.70–7.73(d,1H,Ar–H),7.96–8.03(d,2H,Ar–H),8.95(s,1H,Ar–H)

*It is the m/z $[M+H]^+$ peak of MS

Subject compounds were 0.5 mg/mL suspensions in 0.5% aqueous CMC. The mice were treated in oral administration with delivery volume of 0.2 mL/10 g, a dose of 10 mg/kg, once daily.

Method 1. Healthy mice were randomly divided as follows: 10/group, half male and half female: CMC control groups; Ia, Ib, Id, If and IIc treatment groups. These groups were given dosages of 10 mg/kg for 7 day administrations until the night of the final day, then fasted for about 12 h, respectively. Prior to and after the sugar loads, the mice were measured with 20 μL of serum from orbital venous plexus blood using a glucose oxidase method.

Method 2. According to the above methods mice were divided into six groups (10/group, half male and half female). The mice received oral administration for 14 consecutive days, fasted for 12 h from the last delivery of the final day to the next morning, and then blood was taken from the orbital venous plexus. Each group was immediately injected with an insulin load 0.2 μ/kg subcutaneously. After injection of insulin for 1 and 2 h, the blood samples were taken again. The measurements for the insulin changes in mice before and after glucose loads were the same as above.

Statistical Methods: Data presented as $x \pm$ SD, with t tests for the differences between the group tests and SAS software used for data processing.

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