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Design and Synthesis of Novel Arctigenin Analogues for the Amelioration of Metabolic Disorders

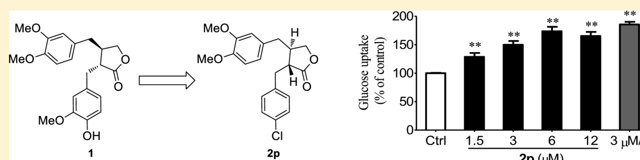
Shudong Duan,[†,§] Suling Huang,[†,§] Jian Gong,[†] Yu Shen,[†] Limin Zeng,[†] Ying Feng,[†] Wenming Ren,[†] Ying Leng,*[,†] and Youhong Hu*[,†,‡]

[†]State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai 201203, China

[‡]ZJU-ENS Joint Laboratory of Medicinal Chemistry, Zhejiang Province Key Laboratory of Anti-Cancer Drug Research, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China

Supporting Information

ABSTRACT: Analogues of the natural product (−)-arctigenin, an activator of adenosine monophosphate activated protein kinase, were prepared in order to evaluate their effects on 2-deoxyglucose uptake in L6 myotubes and possible use in ameliorating metabolic disorders. Racemic arctigenin **2a** was found to display a similar uptake enhancement as does (−)-arctigenin. As a result, the SAR study was conducted utilizing racemic compounds. The structure−activity relationship study led to the discovery of key substitution patterns on the lactone motif that govern 2-deoxyglucose uptake activities. The results show that replacement of the *para*-hydroxyl group of the C-2 benzyl moiety of arctigenin by Cl has a pronounced effect on uptake activity. Specifically, analogue **2p**, which contains the *p*-Cl substituent, stimulates glucose uptake and fatty acid oxidation in L6 myotubes.



KEYWORDS: *Natural product, arctigenin analogues, 2-deoxyglucose uptake in L6 myotubes, amelioration of metabolic disorders*

Type 2 diabetes is a metabolic disorder characterized by high blood glucose levels in the context of insulin resistance and impaired insulin secretion.[1,2] Because it is the main target tissue of insulin action, skeletal muscle plays an important role in the regulation of glucose metabolism, accounting for 80% of whole-body glucose disposal under insulin stimulation.[3] Observations made in a number of studies indicate that reducing glucose uptake in skeletal muscle results in type 2 diabetes and a related metabolic syndrome.[4−6] Thus, therapies that regulate glucose uptake are promising strategies for the treatment of metabolic disorders.

Natural products are important sources for lead substances in drug discovery.[7] In a recent effort, we screened an in house library of natural products and natural product-like substances for their ability to increase 2-deoxyglucose uptake in L6 myotubes. This study led to the identification of the dibenzyl-γ-lactone, (−)-arctigenin (**1**, Figure 1), as a potent indirect activator of adenosine monophosphate-activated protein kinase (AMPK) in the regulation of glucose and lipid homeostasis, through inhibition of mitochondria complex I.[8,9] AMPK is a major regulator of energy homeostasis, and pharmacological activation of AMPK improves glucose and lipid metabolism in insulin-resistant state. Taking together the pleiotropic beneficial functions of AMPK, targeting AMPK appears as a promising tool for treating metabolic disorder and diabetes.[10] Other investigations have shown that arctigenin and its derivatives have antitumor,[11] anti-HIV,[12,13] anti-inflammation[14] activities, and AMPK activating effects.[15,16] However, only limited systematic SAR studies of the lactone scaffold of this natural product have been carried out thus far.[11−13,15] Below, we describe the design and synthesis of a series of novel arctigenin analogues and the results of a structure−activity relationship (SAR) investigation, which has led to the identification of a substance possessing the lactone motif that is a potent promoter of 2-deoxyglucose uptake in L6 myotubes.

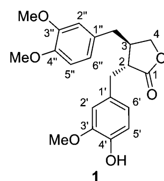


Figure 1. Structure of (−)-arctigenin.

The general procedure employed for the synthesis of the arctigenin analogues is shown in Scheme 1.[17,18] The routes begin with condensation of a substituted benzaldehyde **3** with dimethyl succinate to afford **4**, which undergoes hydrogenation to give **5**. The acid **5** is then transformed to its potassium salt **6**, which is selectively reduced using $NaBH_4$ giving γ-hydoxyacid that cyclizes to generate the lactone intermediate **7**. Treatment of **7** with LDA at −78 °C followed by reaction of the resulting

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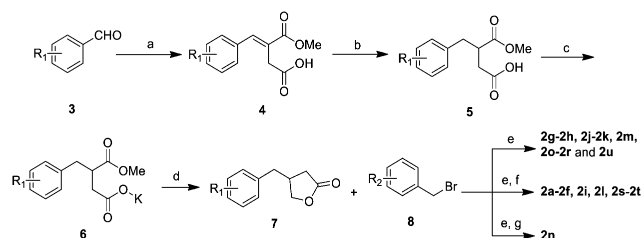
Scheme 1. Synthesis of Arctigenin Analogues 2a–2u[a]



[a]Reagents and conditions: (a) dimethyl succinate, *t*-BuOK, *t*-BuOH, 25 °C. (b) H_2, palladium 10% on carbon, MeOH, 25 °C. (c) *t*-BuOK, EtOH, 25 °C. (d) (1) $NaBH_4$, $CaCl_2$, EtOH, −10 °C to −78 °C; (2) conc. HCl, 80 °C. (e) LDA, THF, −78 to 25 °C. (f) H_2, palladium 10% on carbon, MeOH, 25 °C. (g) Fe, CH_3COOH, EtOH, 80 °C.

enolate with a commercially available or prepared benzyl bromide **8**[12,19] then forms the desired analogues **2g–2h**, **2j–2k**, **2m**, **2o-2r**, and **2u**. Catalytic hydrogenolysis of the lactones generated from the corresponding oxygen-protected benzyl bromides produces the phenol analogues **2a–2f**, **2i**, **2l**, **2s**, and **2t** and reduction of the corresponding nitro-benzyl products forms the desired aniline derivatives **2n**. By using this approach, racemic arctigenin **2a** was also produced. It should be noted that, as expected, the benzyl groups in the synthetic analogues are trans-disposed.

The results of a preliminary study of the dose-dependent increase in glucose uptake in L6 myotubes show that natural (−)-arctigenin and its racemic analogue **2a** display similar enhancement properties (Figure 2). Glucose uptake was

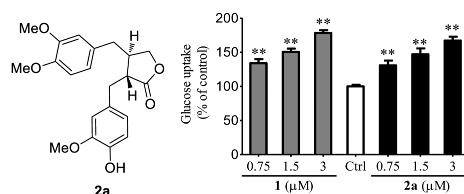
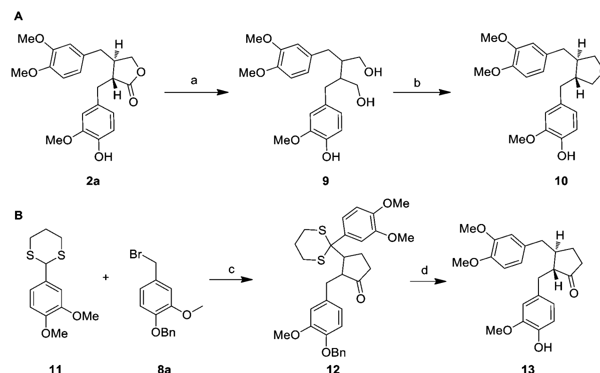


Figure 2. Structure of **2a** and dose-dependent increase in glucose uptake by L6 myotubes exposed to **1** and **2a** at the indicated concentrations for 2 h. Results are expressed as mean ± SEM, $n = 3$ independent experiments. $^{**}p < 0.01$ vs control.

measured as described in Supporting Information. Glucose uptake increases by 1.62-fold compared to that of a control when 3 μmol/L of **2a** is present, whereas the same dose of (−)-arctigenin causes a 1.75-fold uptake enhancement. Furthermore, **2a** displays the same dose dependence as does (−)-arctigenin. These results indicate that a SAR study with racemic arctigenin analogues would generate informative results.

To investigate the impact of the lactone moiety in arctigenin on glucose uptake, the tetrahydrofuran **10** and cyclopentanone **13** analogues were synthesized using the methods outlined in Scheme 2A,B, respectively. Preparation of **10** utilized a route that begins with the reduction of **2a** to give diol **9**, which is cyclized to form **10** (Scheme 2A).[12] The scheme for synthesis of **13**, described earlier by Ziegler,[20] begins by treatment of dithiane **11** with *n*-butyllithium followed by conjugate addition of the resulting anion to cyclopent-2-enone. The formed cyclopentanone is then α-alkylated with substituted benzyl bromide **8a** to give the intermediate **12**, which upon catalytic

Scheme 2. Synthesis of Arctigenin Analogues 10 and 13[a]



[a]Reagents and conditions: (a) $LiAlH_4$, THF, 70 °C. (b) PTSA, DCM, 40 °C. (c) (1) *n*-BuLi, cyclopent-2-enone, THF, −78 °C; (2) HMPA. (d) Raney nickel, EtOH, 80 °C.

hydrogenolysis and desulfurization with the Raney nickel gives **13**.

The results of biological studies show that **10** has only a maximum 1.31-fold stimulating effect on 2-deoxyglucose uptake in L6 myotubes at a dose of 6 μmol/L. This value is much lower than that of **1** (Figure S1A, see Supporting Information). In contrast, compound **13** exhibits a moderate 2.08-fold enhancement of uptake activity at 3 μmol/L (2 h), which is close to the 2.76-fold increase promoted by **1** under identical conditions (Figure S1B, see Supporting Information). These data indicate the potency of lactone motif in keeping compound activity.

To probe the influence of substituents on the arene ring of the C-3 benzyl moiety in the arctigenin analogues, **2b–2e** were synthesized using an approach that is identical to the one shown in Scheme 1. Investigations of the effects of these substances on glucose uptake at different concentrations (see Supporting Information) demonstrate that the glucose uptake activities of **2b** with a *meta*-methoxy-phenyl and **2d** with a 3,4,5-trimethoxy-phenyl group have no significant effect (Table 1). Furthermore, **2e**, in which the 3,4-dimethoxyl group on the C-3 benzyl moiety in **2a** is changed to 3,4-dioxole, also has a dramatically lower uptake activity. Only **2c**, possessing a *para*-methoxy group, has a ca. 2.4-fold effect at 24 μmol/L that is close to that of **1** at 3 μmol/L.

On the basis of the above results, our attention turned to SAR studies of analogues that contain various substituents on the phenyl group in the C-2 benzyl moiety (i.e., **2f–2u**). Analysis of the results arising from studies of **2f–2u** (Table 1) show that introduction of an ortho or meta electron donating and withdrawing group on this ring (**2f–2k**) results in no effect on glucose uptake activity. Only **2i**, with a *meta*-OH group, displays a moderate activity. Significantly, substitution at the para position of the phenyl group of the C-2 benzyl moiety brings about a remarkable change in the glucose uptake activity in L6 myotubes. For example, **2l** with a *p*-hydroxyl group has the close activity at 12 μmol/L as does (−)-arctigenin at 3 μmol/L. However, **2m**, in which the *p*-hydroxyl is changed to methoxyl, has a greatly diminished glucose uptake activity. Furthermore, electron donating (−NH_2) and withdrawing group (−CN) substitution at this position results in a decrease in activity. Interestingly, in contrast to other related halogen substituted substances (**2q** and **2r**), the *para*-chloro substituted analogue **2p** displays the highest activity of the substances

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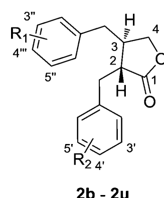
Table 1. Enhancement of Glucose Uptake in L6 Myotubes Induced by Compounds 2b−2u



compd.	R_1	R_2	concentration (μM)[a]	effect on glucose uptake in L6 myotubes (%)	effect on glucose uptake [3 μM] of 1 in L6 myotubes[b] (%)	ratio[c]
2b	3″-OMe	3′-OMe-4′-OH	1.5	121.2 ± 3.0	241.0 ± 13.6	0.503
2c	4″-OMe	3′-OMe-4′-OH	24	235.1 ± 11.7	262.4 ± 3.6	**0.896**
2d	3″,4″,5″-OMe	3′-OMe-4′-OH	6	128.8 ± 3.3	233.9 ± 16.0	0.551
2e	3″,4″-OCH_2O−	3′-OMe-4′-OH	1.5	131.7 ± 4.5	265.3 ± 10.8	0.496
2f	3″,4″-OMe	2′-OH	1.5	137.6 ± 1.5	237.6 ± 8.8	0.579
2g	3″,4″-OMe	2′-OMe	3	97.4 ± 6.3	190.1 ± 9.7	0.512
2h	3″,4″-OMe	2′-Cl	3	112.4 ± 4.0	206.4 ± 6.5	0.545
2i	3″,4″-OMe	3′-OH	24	180.3 ± 23.3	217.8 ± 13.5	**0.828**
2j	3″,4″-OMe	3′-OMe	12	119.2 ± 1.3	211.3 ± 9.1	0.564
2k	3″,4″-OMe	3′-Cl	3	114.8 ± 0.7	212.4 ± 6.6	0.540
2l	3″,4″-OMe	4′-OH	12	179.5 ± 21.1	200.6 ± 10.9	**0.895**
2m	3″,4″-OMe	4′-OMe	1.5	108.4 ± 6.5	182.1 ± 1.1	0.595
2n	3″,4″-OMe	4′-NH_2	3	126.6 ± 11.0	205.4 ± 2.6	0.616
2o	3″,4″-OMe	4′-CN	3	136.7 ± 4.3	258.7 ± 9.4	0.528
2p	3″,4″-OMe	4′-Cl	6	173.7 ± 7.7	185.5 ± 4.8	**0.936**
2q	3″,4″-OMe	4′-F	1.5	116.4 ± 5.7	239.6 ± 19.6	0.486
2r	3″,4″-OMe	4′-Br	6	176.0 ± 6.7	269.2 ± 11.7	0.654
2s	3″,4″-OMe	3′-OH-4′-OMe	1.5	100.4 ± 5.9	188.9 ± 10.7	0.531
2t	3″,4″-OMe	3′,4′-OH	3	243.2 ± 29.9	238.9 ± 21.2	**1.018**
2u	3″,4″-OMe	3′,4′-OMe	3	137.1 ± 14.0	237.6 ± 8.8	0.577
(2*R*,3*R*)-2p	3″,4″-OMe	4′-Cl	6	191.1 ± 6.2	185.5 ± 4.8	**1.030**
(2*S*, 3*S*)-2p	3″,4″-OMe	4′-Cl	1.5	103.1 ± 3.8	208.9 ± 10.7	0.494

[a]The effect on glucose uptake by L6 myotubes exposed to **2b−2u** at a series of concentrations for 2 h, including 1.5, 3, 6, 12, and 24 μM (see Supporting Information), and the maximum enhancement was displayed. [b]Compound **1** was employed as a positive control at 3 μM. [c]The ratio of the activity between the test compound with **1** was calculated.

explored in this effort. More importantly, **2s**, in which the positions of the 3′-hydroxyl and 4′-methoxyl in **1** are exchanged does not exhibit any uptake activation effects.

The combined observations clearly suggest that *para*-hydroxyl or -chloro groups on the phenyl ring of the C-2-benzyl moiety play critical roles in the enhancement of glucose uptake in L6 myotubes. In accord with this finding is the observation that **2t**, bearing 3′,4′-dihydroxy groups, has an excellent activity in comparison to that of **2u**.

Considering the potential metabolic problem for phenol group, **2p** was chosen for the separation to obtain the two isomers in ∼1:1 ratio. These exhibited quite different effects on glucose uptake in L6 myotubes. **(2*R*,3*R*)-2p**, with the configuration matching (see Supporting Information) (−)-arctigenin, maintained the stimulation and reached maximal effect at 6 μmol/L equal to (−)-arctigenin at 3 μmol/L, while isomer **(2*S*,3*S*)-2p** did not possess any activity on glucose uptake (Table 1). However, the racemic **2p** and **(2*R*,3*R*)-2p** show the identical dose−effect tendency (Figure S4, see Supporting Information).

Because it has a remarkably high glucose uptake stimulating effect in skeletal muscle cells, the chloro-substituted analogue **2p** along with racemic arctigenin (**2a**) were selected for further investigation. We have previously demonstrated that (−)-arctigenin mildly depolarizes the mitochondrial membrane potential ($\Delta\psi m$) and increases AMPK phosphorylation. In the current effort, we observed that both **2a** and **2p** depolarize $\Delta\psi m$ in a moderate dose-dependent manner (Figure 3A). Because mitochondrial function is linked with AMPK activation, the effect of these analogues on AMPK phosphorylation in L6 myotubes was determined (Figure 3B). As expected, AMPK phosphorylation is significantly enhanced by **2a** and **2p** in association with increased phosphorylation of acetyl-CoA carboxylase (ACC), a downstream target of AMPK. In accordance with the effects on glucose uptake, **(2*S*,3*S*)-2p** did not stimulate AMPK and ACC phosphorylation. To determine whether **2a** and **2p** stimulation of glucose uptake involves activation of AMPK, the effects of the AMPK inhibitor, compound C,[21] on the abilities of **2a** and **2p** to stimulate glucose uptake in L6 myotubes were probed. As the results displayed in Figure 3C show, increases in glucose uptake caused by **2p** and **2a** are completely blocked by compound C. Thus, the increased glucose uptake in skeletal muscle stimulated by **2a** or **2p** is mediated by activation of AMPK in a similar manner as has been observed for **1**.

It has been reported that acute activation of AMPK in skeletal muscle cells increases fatty acid oxidation by decreasing malonyl-CoA concentrations through the inhibition ACC and activation of malonyl-CoA decarboxylase (MCD).[22,23] Our studies (Figure 4A) demonstrate that **2a** significantly induces fatty acid oxidation at a dose of 6 μmol/L. Treatment with 3 or 6 μmol/L of **2p** also enhances fatty acid oxidation in L6 myotubes, whereas pretreatment with compound C fully blocks

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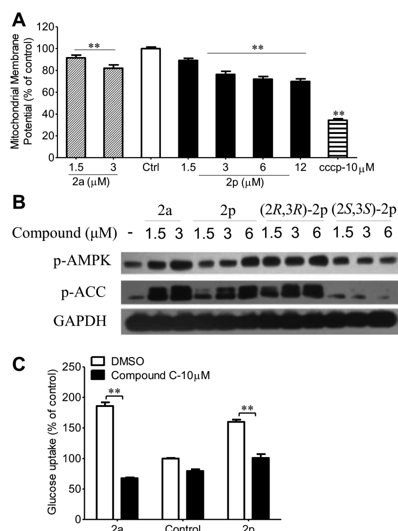

Figure 3. Compound **2p**, like **2a**, stimulates glucose uptake through AMPK. (A) Dose-dependent depolarization of $\Delta\psi m$ in L6 myotubes by 10 min treatments of **2a** and **2p** with the indicated concentrations. (B) Compounds **2a**, **2p**, and (2*R*,3*R*)-**2p** but not (2*S*,3*S*)-**2p** increase AMPK and ACC phosphorylation (p-AMPK, p-ACC) in L6 myotubes following 2 h treatment at the indicated concentrations. (C) Compounds stimulated glucose uptake in an AMPK-dependent manner. Results are expressed as mean ± SEM, $n = 3$ independent experiments. $^{**}p < 0.01$ vs control.

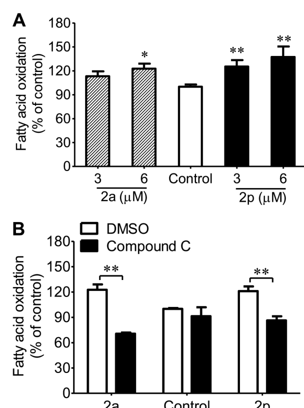

Figure 4. Compound **2a** and **2p** stimulate fatty acid oxidation through AMPK. (A) Compound **2a** and **2p** increase fatty acid oxidation. (B) Compounds stimulated fatty acid oxidation in an AMPK-dependent manner. Results are expressed as mean ± SEM, $n = 3$ independent experiments. $^{*}p < 0.05$, $^{**}p < 0.01$ vs control.

this effect (Figure 4B). The results demonstrate that **2a** and **2p** improve fatty acid oxidation by activating AMPK.

To assess the pharmacokinetic properties of **2a** and **2p**, the compounds were dosed to *ob*/*ob* mice as shown in Figure S5 (see Supporting Information). After administration by intraperitoneal injection, **2a** and **2p** were observed with very fast absorption (t_{max} = 30 min). Comparison of C_{max} and $AUC_{0\text{-}t}$ indicate that **2p** displays higher plasma exposure compared to **2a**, showing a C_{max} of 508 ng/mL and $AUC_{0\text{-}t}$ of 1876 h·ng/mL. It is clear that replacement of the *para*-hydroxyl group of the C-2 benzyl moiety of arctigenin by Cl as **2p** could avoid one of the possible metabolic sites. The compound **2p** was chosen for further investigation in vivo.

Compound **2p** having acute effects on the respiratory exchange ratio (RER) in *ob*/*ob* mice is demonstrated by the plot shown in Figure 5. Because **2p** increases fatty acid oxidation, its effect on whole-body fat oxidation was explored

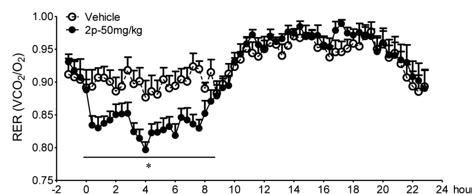

Figure 5. Acute effect of **2p** on RER in *ob*/*ob* mice. Results are expressed as mean ± SEM, $n = 6$. $^{*}p < 0.05$ compared with vehicle.

using undirected calorimetry. The *ob*/*ob* mice were intraperitoneal injected with a single dose of 50 mg/kg of **2p** or a vehicle. The animals were then monitored for oxygen consumption and CO_2 production for 23 h. The observations show that treatment with **2p** results in a rapid decrease in RER that is sustained for 8 h (Figure 5). The finding is consistent with the effect of **2p** on fatty acid oxidation in L6 myotubes, suggesting that this substance induces a switch to fatty acid utilization and an improvement of whole body lipid metabolism.

To assess the in vivo antidiabetic potential of **2p**, *ob*/*ob* mice were intraperitoneal injected with 50 mg/kg of this substance or a vehicle twice per day for 23 d. Mice treated with **2p** display a significant decline in body weight gain after **3d** treatment (Figure 6A) although they have an unaltered feeding behavior

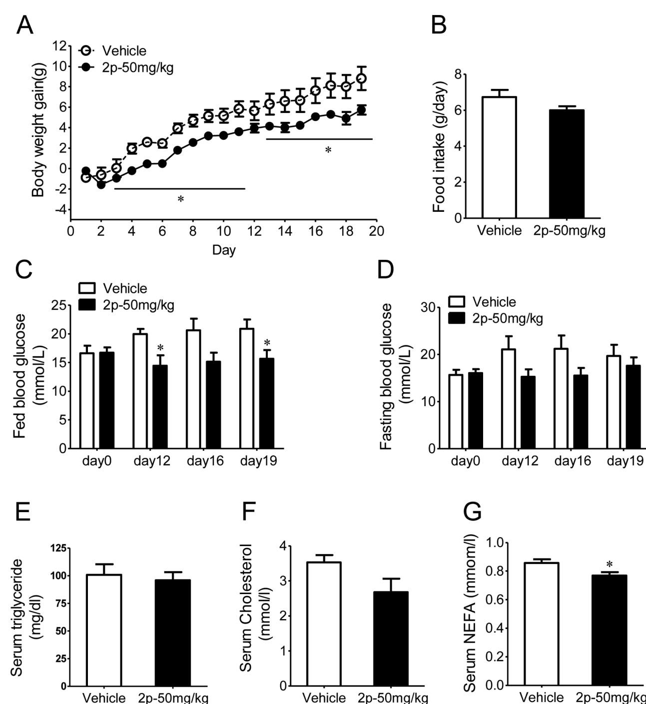

Figure 6. Effect on body weight and blood glucose of *ob*/*ob* mice. (A) Compound **2p** slightly decreases body weights of *ob*/*ob* mice after treatment for 20 d. Body weight (A) and food intake (B) were recorded regularly during the treatment period. Levels of fed blood glucose (C) and fasting blood glucose (D) were determined throughout the treatment. Serum triacylglycerol (E), cholesterols (F), and NEFA (G) concentrations were evaluated at the end of the treatment period. Data are mean ± SEM for $n = 6$–8 mice. $^{*}p < 0.05$ vs vehicle mice.

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(Figure 6B). As the data in Figure 6C show, **2p** has an effect on fed blood glucose levels in *ob*/*ob* mice after 12 d treatment, with reduction rate of 27.7%. Treated mice also display reduced fasting blood glucose levels with a reduction rate of 27.3% at day 12, although a statistical significance ($P = 0.11$) is not reached (Figure 6D). Treatment of mice with **2p** does not alter serum triglyceride levels, but it does cause a 22.4% reduction of the total cholesterol level and a 10% reduction of NEFA (Figure 6E−G). These data indicate that **2p** could possess antidiabetic effects in which blood glucose and dyslipidemia are potentially improved.

In conclusion, the systematic SAR study described above was designed to probe the effect of arctigenin analogues on 2-deoxyglucose uptake in L6 myotubes. The findings show that replacement of the *para*-OH group on the phenyl ring of the C-2 benzyl moiety of the arctigenin framework by Cl leads a substance, **2p**, which displays an excellent uptake activity and avoids one of the possible metabolic issues. This analogue stimulates glucose uptake and fatty acid oxidation through AMPK activation in vitro. Chronic administration of **2p** lowered blood glucose and improved lipid metabolism in *ob*/*ob* mice. Although **2p** displayed higher plasma exposure compared to **2a**, the PK property of **2p** is still poor to cause the weak activity in vivo. The current results of this effort suggest that further optimization based on the SAR of arctigenin analogues needs to be investigated for the amelioration of metabolic disorders.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic details and characterization data for all new compounds reported in this letter. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*(Y.H.) E-mail: yhhu@mail.shcnc.ac.cn.

*(Y.L.) E-mail: yleng@simm.ac.cn.

Author Contributions

[§]S.-D.D. and S.-L.H. contributed equally to this work.

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

SAR, structure−activity relationship; LDA, lithium diisopropylamide; PTSA, *p*-toluenesulfonic acid; THF, tetrahydrofuran; DCM, dichloromethane; HMPA, hexamethylphosphoramide

■ REFERENCES

(1) Semenkovich, C. F. Insulin resistance and atherosclerosis. *J. Clin. Invest.* **2006**, *116* (7), 1813−1822.

(2) Cohen, E. The insulin paradox: aging, proteotoxicity and neurodegeneration. *Nat. Rev. Neurosci.* **2008**, *9* (10), 759−767.

(3) DeFronzo, R. A.; Jacot, E.; Jequier, E.; Maeder, E.; Wahren, J.; Felber, J. P. The effect of insulin on the disposal of intravenous glucose. Results from indirect calorimetry and hepatic and femoral venous catheterization. *Diabetes* **1981**, *30* (12), 1000−7.

(4) Ren, J. M.; Marshall, B. A.; Gulve, E. A.; Gao, J.; Johnson, D. W.; Holloszy, J. O.; Mueckler, M. Evidence from transgenic mice that glucose transport is rate-limiting for glycogen deposition and glycolysis in skeletal muscle. *J. Biol. Chem.* **1993**, *268* (22), 16113−16115.

(5) Hansell, C. A. H.; Schiering, C.; Kinstrie, R.; Ford, L.; Bordon, Y.; McInnes, I. B.; Goodyear, C. S.; Nibbs, R. J. B. Universal expression and dual function of the atypical chemokine receptor D6 on innate-like B cells in mice. *Blood* **2011**, *117* (20), 5413−5424.

(6) Kelley, D. E.; Goodpaster, B.; Wing, R. R.; Simoneau, J.-A. Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity, and weight loss. *Am. J. Physiol.: Endocrinol. Metab.* **1999**, *277* (6), E1130−E1141.

(7) Vasilevich, N. I.; Kombarov, R. V.; Genis, D. V.; Kirpichenok, M. A. Lessons from natural products chemistry can offer novel approaches for synthetic chemistry in drug discovery. *J. Med. Chem.* **2012**, *55* (16), 7003−7009.

(8) Huang, S. L.; Yu, R. T.; Gong, J.; Feng, Y.; Dai, Y. L.; Hu, F.; Hu, Y. H.; Tao, Y. D.; Leng, Y. Arctigenin, a natural compound, activates AMP-activated protein kinase via inhibition of mitochondria complex I and ameliorates metabolic disorders in ob/ob mice. *Diabetologia* **2012**, *55* (5), 1469−81.

(9) Leng, Y.; Tao, Y. D.; Hu, Y. H.; Gong, J.; Huang, S. L.; Yu, R. T. Dihydrofuran-2-one compounds and their preparation, pharmaceutical compositions and use in the treatment of diabetes mellitus and disorders of glucose and lipid metabolism. CN 102451178A, 2012.

(10) Viollet, B.; Lantier, L.; Devin-Leclerc, J.; Hebrard, S.; Amouyal, C.; Mounier, R.; Foretz, M.; Andreelli, F. Targeting the AMPK pathway for the treatment of Type 2 diabetes. *Front. Biosci.* **2009**, *14*, 3380−400.

(11) Chen, G.-R.; Cai, L.-P.; Dou, D.-Q.; Kang, T.-G.; Li, H.-F.; Li, F.-R.; Jiang, N. Synthesis of (−)-arctigenin derivatives and their anticancer activity. *Nat. Prod. Res.* **2011**, *26* (2), 177−181.

(12) Eich, E.; Pertz, H.; Kaloga, M.; Schulz, J.; Fesen, M. R.; Mazumder, A.; Pommier, Y. (−)-Arctigenin as a lead structure for inhibitors of human immunodeficiency virus type-1 integrase. *J. Med. Chem.* **1996**, *39* (1), 86−95.

(13) Yang, L.-M.; Lin, S.-J.; Yang, T.-H.; Lee, K.-H. Synthesis and anti-HIV activity of dibenzylbutyrolactone lignans. *Bioorg. Med. Chem. Lett.* **1996**, *6* (8), 941−944.

(14) Lee, J.; Kim, C. Arctigenin, a phenylpropanoid dibenzylbutyrolactone lignan, inhibits type I−IV allergic inflammation and pro-inflammatory enzymes. *Arch. Pharm. Res.* **2010**, *33* (6), 947−957.

(15) Shen, S.; Zhuang, J.; Chen, Y.; Lei, M.; Chen, J.; Shen, X.; Hu, L. Synthesis and biological evaluation of arctigenin ester and ether derivatives as activators of AMPK. *Biorg. Med. Chem.* **2013**, *21* (13), 3882−3893.

(16) Gu, Y.; Sun, X. X.; Ye, J. M.; He, L.; Yan, S. S.; Zhang, H. H.; Hu, L. H.; Yuan, J. Y.; Yu, Q. Arctigenin alleviates ER stress via activating AMPK. *Acta Pharmacol. Sin.* **2012**, *33* (7), 941−52.

(17) Carnbie, R. C.; Craw, P. A.; Rutledge, P. S.; Woodgate, P. D. Oxidative coupling of lignans. III Non-phenolic oxidative coupling of deoxypodorhizon and related compounds. *Aust. J. Chem.* **1988**, *41* (6), 897−918.

(18) Morimoto, T.; Nagai, H.; Achiwa, K. Lipase-catalyzed esterification of a (±)-2,3-di(arylmethyl)-1,4-butanediol and its application to the synthesis of (S,S)-(+)-hinokinin. *Synth. Commun.* **2005**, *35* (6), 857−865.

(19) Sharma, G. V. M; Rakesh. Development of p-phenylbenzyl as a new protecting group: protection and deprotection of alcohols. *Tetrahedron Lett.* **2001**, *42* (32), 5571−5573.

(20) Ziegler, F. E.; Schwartz, J. A. Synthetic studies on lignan lactones: aryl dithiane route to (.+-.)-podorhizol and (.+-.)-isopodophyllotoxone and approaches to the stegane skeleton. *J. Org. Chem.* **1978**, *43* (5), 985−991.

(21) Zhou, G.; Myers, R.; Li, Y.; Chen, Y.; Shen, X.; Fenyk-Melody, J.; Wu, M.; Ventre, J.; Doebber, T.; Fujii, N.; Musi, N.; Hirshman, M. F.; Goodyear, L. J.; M?ller, D. E. Role of AMP-activated protein kinase in mechanism of metformin action. *J. Clin. Invest.* **2001**, *108* (8), 1167−74.

(22) Ruderman, N. B.; Cacicedo, J. M.; Itani, S.; Yagihashi, N.; Saha, A. K.; Ye, J. M.; Chen, K.; Zou, M.; Carling, D.; Boden, G.; Cohen, R. A.; Keaney, J.; Kraegen, E. W.; Ido, Y. Malonyl-CoA and AMP-activated protein kinase (AMPK): possible links between insulin resistance in muscle and early endothelial cell damage in diabetes. *Biochem. Soc. Trans.* **2003**, *31*, 202−206.
(23) Zhou, R.; Wang, L.; Xu, X.; Chen, J.; Hu, L. H.; Chen, L. L.; Shen, X. Danthron activates AMP-activated protein kinase and regulates lipid and glucose metabolism in vitro. *Acta. Pharmacol. Sin.* **2013**, *34* (8), 1061−9.

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