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SYNTHESIS AND HYPOGLYCEMIC EFFECT OF STILBENE DERIVATIVES

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ABSTRACT

The synthesis of stilbene derivatives *via* the Wittig reaction using Benzyl-triphenyl-phosphonium chloride was successfully carried out and seven (7) molecules were obtained. The products were characterized by MS and NMR analysis. The effect on blood glucose of its compounds was evaluated on *wistar Kyoto* rats. At the dose of 3 mg/kg *per os*, RD02 (anthraldehyde derivative) and RD05 (benzaldehyde derivative) induced a powerful and persistent hypoglycemic effect. The blood glucose respectively varied from 0.89±0.02 to 0.65±0.04 g/L ($p<0.05$, n=5) and 0.87±0.02 to 0.71±0.02 g/L ($p<0.05$, n=5). Under the same conditions, the similar hypoglycemic effect was observed with RD04 (benzaldehyde derivative) (0.67±0.04 vs 0.93±0.03 g/L) ($p<0.05$, n=5). Conversly, stilbenes derived from cinnamaldehyde (SS014, SS015) do not modify baseline blood glucose levels in normoglycemic rats. This study reports the synthesis of stilbene derivatives and its effects on blood glucose in normoglycemic rats. RD02, RD04 and RD05 are potential candidates for the synthesis of structural analogs of interest in blood glucose regulation.

KEYWORD:- Wittig reaction, Anthraldehyde, Benzaldehyde, Cinnamaldehyde, Blood glucose.

1. INTRODUCTION

Diabetes is a metabolic disease characterized by a chronic hyperglycemia resulting either from a deficiency in insulin secretion or an abnormality in the action of insulin on the target tissues, or from both them. This disease is manifested by symptoms specific to diabetes (polyuro-polydipsia syndrome) and by organ damage such as the retina, kidneys, coronary arteries, due to the toxicity of the acetone produced during a rapid degradation of the fats occuring in case of insulin failure leading to major hyperglycemia.[1] The trans (-) stilbene form is more stable and bioactive. It is generally found more abundantly in the different stilbene-producing plant species.[2,3] Many pharmacological properties of stilbenes have been demonstrated, making resveratrol one of the most studied natural substances.[4-14] The discovery of resveratrol in wine has contributed to taking a new-look at the molecule thanks to its various biological properties as anti-carcinogenic, cardio-protective, detoxification of drugs, influence on the lifespan of different organisms, antioxidant, anti-inflammatory and anti-diabetic.[15-21] Stilbenes have aroused many interests over the past few decades. This study reports the synthesis of new molecules derived from stilbenes and study their effect on blood glucose in *wistar Kyoto* rat normoglycemic model.

2. MATERIAL AND METHODS

2.1 Experimental details of the synthesis of molecules

General: Commercial reagents were used without purification. Prior to use, CH_3CN, DMSO and Methanol were dried using a pure solvent drying system over aluminum oxide under an argon atmosphere. All anhydrous reactions were carried out under nitrogen atmosphere. Analytical thin layer chromatography was performed on SDS silica gel 60F254 aluminium plates (0.2 mm layer) and was revealed by UV light and/or by phosphomolybdic acid. All flash chromatography separations were performed with SDS silica gel 60. Melting points (mp) were determined on a Tottoli apparatus and were uncorrected. Infrared (IR) spectra were obtained as neat films and were recorded on Bruker Vector 22 spectrophotometer. 1H and 13C spectra were recorded in CD_3OD or $CDCl_3$ either on a Bruker Avance 300 or 600 MHz and 75 or 150 MHz, respectively. Chemicals shifts (δ) are reported in ppm relative to TMS

for ^{1}H and ^{13}C NMR spectra. The following abbreviations are used to indicate the multiplicities: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet). GC/MS conditions: Analyses were performed using a 5890 gas chromatogram connected to a G 1019 A mass spectrometer (both from Hewlett Packard) operating in the electro spray ionization mode (ESI).

General Procedure for the wittig Réaction of Benzyltriphenylphosphonium chloride **2** with the aldehydes dérivatives. A solution of aldehyde derivatives (1 equiv.), Benzyltriphenylphosphonium chloride 2 (1 equiv.) and NaOH (20%) (3.96 mL) in THF or CCl_4 or CH_2Cl_2 was stirred for 24h at rt and under Ar. The reaction solvent is evaporated off and then 5 ml of distilled water and ethyl acetate are added. The aqueous phase is extracted with 3x5 mL of ethyl acetate. The organic phases are combined, dried over $MgSO_4$ then filtered and concentrated under vacuum pressure. Purification of the residue on silica gel (Cyclohexane/AcEt 7:3).

2.2 Synthesis of *(E)-1-bromo-4-styrylbenzene* (3b)
Following the general procedure, aldehyde derivatives 1b (R1=H, R2=Br, R3=H) (300 mg, 1.63 mmol) reacted with Benzyl-triphenyl-phosphonium chloride 2 (632.78 mg, 1.63 mmol), and NaOH (20 %) (3.96 ml) in THF (4,58 ml). Purification of the residue on silica gel (Cyclohexane/AcEt 7:3) give a yellow powder (273.51 mg (65 %)).

2.3 Synthesis of *(E)-1,2-dichloro-4-styrylbenzène* (3c)
Following the general procedure, aldehyde derivatives 1c (R1=Cl, R2=Cl, R3=H) (300 mg, 1.724 mmol) reacted with Benzyl-triphenyl-phosphonium chloride 2 (668.91 mg, 1.724 mmol), and NaOH (20 %) (3.96 mL) in THF (4,58 ml). Purification of the residue on silica gel (Cyclohexane/AcEt 7:3) give a yellow powder (299 mg (70 %)).

***2.4* Synthesis of *1-chloro-4-((1E, 3E)-4-phénylbuta-1,3-dièn-1-yl) benzène* (5a)**
Following the general procedure, aldehyde derivatives 4a (R1=Cl) (300 mg, 1.80 mmol) reacted with Benzyl-triphenyl-phosphonium chloride 2 (690 mg, 1.80 mmol)), and NaOH (20 %) (3.96 mL) in THF (4,58 ml). Purification of the residue on silica gel (Cyclohexane/AcEt 7:3) give a white powder (294 mg (68 %)).

***2.5* Synthesis of *1-méthoxy-4-((1E, 3E)-4-phénylbuta-1,3-dièn-1-yl) benzène* (5b)**
Following the general procedure, aldehyde derivatives 4b (R1=OMe) (300 mg, 1.85 mmol) reacted with Benzyl-triphenyl-phosphonium chloride 2 (717.8 mg, 1.85mmol)), and NaOH (20 %) (3.96 mL) in THF (4,58 ml). Purification of the residue on silica gel (Cyclohexane/AcEt 7:3) give a white powder 262.11 mg (60 %)).

2.6 Synthesis of *(E)-9-styrylanthracene* (7a)
Following the general procedure, aldehyde derivatives 6a (R1=H) (200 mg, 0.971 mmol) reacted with Benzyl-triphenyl-phosphonium chloride 2 (376.7 mg, 0.971 mmol), and NaOH (20 %) (0.45 ml) in CH_2Cl_2 (1.05 ml). After stirring, the organic phase is recovered and the aqueous phase is extracted with 2×5 mL of CH_2Cl_2. The solvent is evaporated under vacuum and the residue recrystallized from isopropanol, which gives a powder 0.1559 g (78 %).

***2.7* Synthesis of *(E)-9-chloro-10-styrylanthracene* (7b)**
Following the general procedure, aldehyde derivatives 6a (R1=H) (200 mg, 0.971 mmol) reacted with Benzyl-triphenyl-phosphonium chloride 2 (376.7 mg, 0.971mmol), and NaOH (20 %) (0.40 ml) in CCl_4 (1 ml). After stirring, the organic phase is recovered and the aqueous phase is extracted with 2×5 mL of CH_2Cl_2. The solvent is evaporated under vacuum and the residue recrystallized from isopropanol giving a green powder 0.192 g (63 %).

2.8 Tests in normoglycemic rats
Wistar Kyoto strain rats had been fasted for 12 hours. They were divided into groups of 5 rats. At time T0, a blood sample was taken from the retro-orbital sinus. Physiological water (10 ml/kg, *per os*) or stilbene derivatives (3 mg/kg, *per os*) were administered. Blood samples were taken every hour during 4 hours. The rats were distributed as follows:

- Control group: physiological water (10 ml/kg, *per os*)
- Lot 1: RD01 (3 mg/kg, *per os*)
- Lot 2: RD02 (3 mg/kg, *per os*)
- Lot 3: RD04 (3 mg/kg, *per os*)
- Lot 4: RD05 (3 mg/kg, *per os*)
- Lot 5: RD06 (3 mg/kg, *per os*)

2.9 Analysis and Expression of results
Results were expressed as mean ± standard error of the mean (mean±esm). n = 5 is the number of experiments in each group. The variations in blood glucose reduction were compared to the baseline value. A value of $p<0.05$ is considered significant.

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Synthesis of stilbene derivatives from benzaldehydes

In this synthesis, the target compounds are obtained through nucleophilic addition. Indeed, the condensation of Benzyl-triphenyl-phosphonium chloride **2** *via* its anion with aldehydes **1** using sodium hydroxide (NaOH) at room temperature gave compounds **3** (60-70 %) after 24 hours in dichloromethane (**Fig. 1**) (**Table 1**).

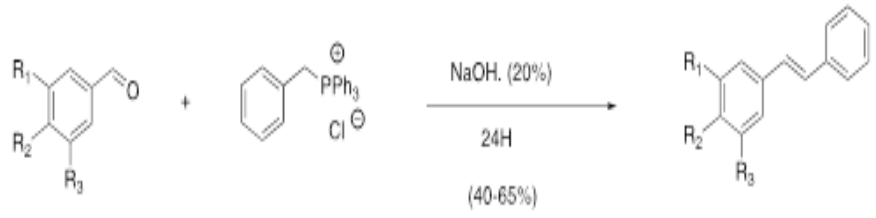

Figure 1: Synthesis of stilbene derivatives from benzaldehydes.

Table 1: The products of the synthesis of 3.

Entry	Compounds	R1	R2	R3	Yields %
1	3a (RD04)	H	H	H	60
2	3b (RD05)	H	Br	H	65
3	3c (RD06)	Cl	Cl	H	70

3.1.2 Synthesis of stilbene derivatives from cinnamaldehydes

The wittig[22,23] reaction between cinnamaldehydes **4** and Benzyl-triphenyl-phosphonium chloride **2** in THF yielded compounds 5 (60-68%) (**Fig. 2**) (**Table 2**). The characterization is based on the analysis of the proton and carbon NMR spectra of compounds **5a** and **5b**.

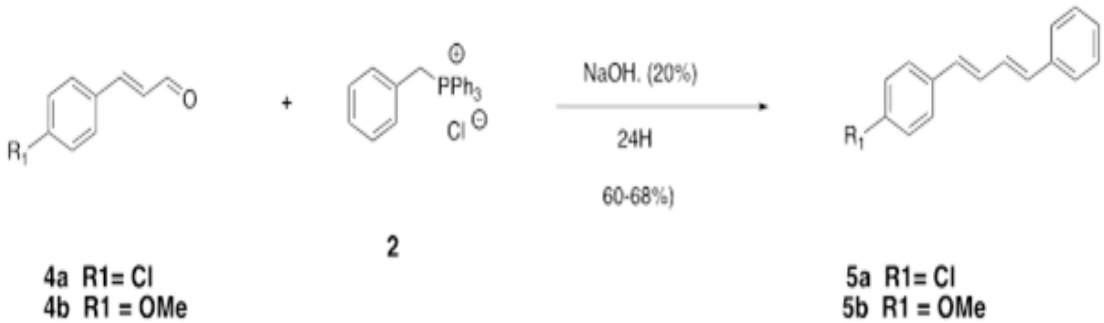

Figure 2: Synthesis of stilbene derivatives from cinnamaldehydes.

Table 2: The products of the synthesis of 5 recorded.

Entry	Compounds	R1	Yields %
1	5a (SS014)	Cl	68
2	5b (SS015)	OMe	60

3.1.3 Synthesis of stilbene derivatives from antraldehydes

The wittig reaction leading to compounds **7a** (RD01) and **7b** (RD02) was carried out under the same experimental conditions as that described above. However, the solvents tetrachloromethane and tetrahydrofuran were respectively used as reaction solvent (**Fig. 3**) (**Table 3**).

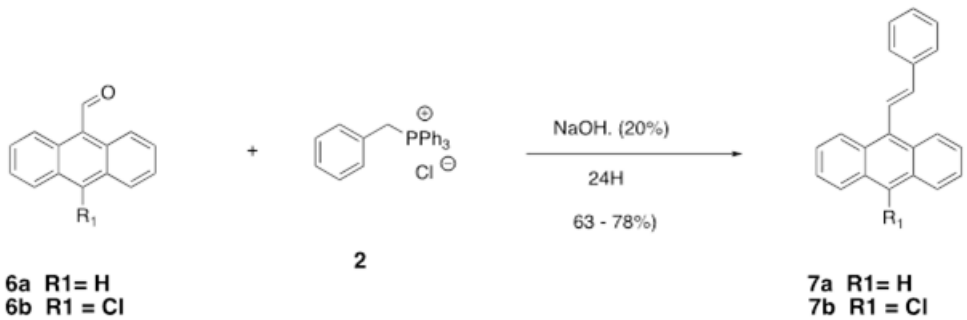

Figure 3: Synthesis of stilbene derivatives from anthraldehydes.

Table 3: The products of the synthesis of 7.

Entry	Compounds	R1	Yields %
1	7a (RD01)	H	78
2	7b (RD02)	Cl	63

(E)-1-bromo-4-styrylbenzene **(3b):** ^{1}H MMR (600 MHz, $CDCl_3$) δ: 6.90 (d, H, CH); 7.30 (d, H, CH), 7.44 (dd, 2H, CH_{Ar}), 7.32-7.73 (m, 5H, CH_{Ar}), 7.82 (d, 2H, CH_{Ar}). ^{13}C MMR (150 MHz, $CDCl_3$) δ: 113.4 (C_{Ar}-Br), 125.48 (CH_{Ar}), 126.46 (2×CH), 137.50 (CH_{Ar}), 127.75 (CH_{Ar}), 128.60 (2xCH_{Ar}), 128.76 (2xCH_{Ar}), 131.50 (2xCH_{Ar}), 136.50 (C), 137.50 (C). MS (ESI) m/z : 259.05 $[M+1]^+$.

(E)-1,2-dichloro-4-styrylbenzène **(3c):** ^{1}H MMR (600 MHz, $CDCl_3$) δ: 6.8 (d, H, CH), 7.1 (d, H, CH), 7.25 (m, 2H, CH_{Ar}), 7.4 (m, 3H, CH_{Ar}), 7.59 (dd, 3H, CH_{Ar}). ^{13}C MMR (150 MHz, $CDCl_3$) δ : 115.86 (CH_{Ar}), 119.34 (CH_{Ar}), 123.7 (2×CH), 126.25 (2×CH_{Ar}), 127.32 (2×CH_{Ar}), 128.7 (2×CH_{Ar}), 137.3 (2×C), 155.2 (2×C). MS (ESI) m/z : 249.02 $[M+1]^+$.

1-chloro-4-((1E, 3E)-4-phénylbuta-1,3-dièn-1-yl) benzène **(5a):** ^{1}H MMR (600 MHz, $CDCl_3$) δ: 6.65 (dd, 2H, 2CHéthy), 7.1 (m, 2H, 2CHAr), 7.25 (t, H, CHAr), 7.35 (t, 2H, 2CHAr), 7.4 (d, 2H, 2CH_{Ar}), 7.53 (t, 4H, 4CH_{Ar}). ^{13}C MMR (150 MHz, $CDCl_3$) δ: 126.42 (2×CH), 127.80 (2×CH_{Ar}), 127.98 (3×CH_{Ar}), 128.80 (4×CH_{Ar}), 129.20 (2xCH), 130.32 (C), 131.26 (C), 133.29 (C). MS (ESI) m/z : 241.12 $[M+1]^+$.

1-méthoxy-4-((1E, 3E)-4-phénylbuta-1,3-dièn-1-yl) benzène **(5b):** ^{1}H MMR (600 MHz, $CDCl_3$) δ : 3.75 (s, 3H, CH_3), 6.75 (dd, 2H, 2×CH), 7.1 (m, 2H, 2×CH_{Ar}), 7.25 (t, H, CHAr), 7.35 (t, 2H, 2CH_{Ar}), 7.4 (d, 2H, 2CH_{Ar}), 7.53 (t, 4H, 4CH_{Ar}). ^{13}C MMR (150 MHz, $CDCl_3$) δ : 55.18 (OCH_3), 114.27 (2×CH_{Ar}), 126.17 (2×CH), 127.22 (2×CH_{Ar}), 127.39 (2×CH_{Ar}), 128.85 (C), 129.73 (CH_{Ar}), 131.38 (2×CH_{Ar}), 132.51 (2×CH), 137.25 (C), 159.01 (C). MS (ESI) m/z : 237.13 $[M+1]^+$.

(E)-9-styrylanthracene **(7a):** ^{1}H MMR (600 MHz, $CDCl_3$) δ: 6.9 (d, 1H, CH), 7.9 (d, 1H, CH), 7.2-9.2 (m, 14H, 13CH_{Ar}). ^{13}C MMR (150 MHz, $CDCl_3$) δ: 124.56 (CH_{Ar}), 125.30 (2×CH_{Ar}), 125.83 (2×CH_{Ar}), 126.64 (2×CH_{Ar}), 126.80 (2×CH_{Ar}), 127.70 (2×C), 127.52 (CH), 128.59 (2×CH_{Ar}), 129.04 (2×CH_{Ar}), 129.15 (CH_{Ar}), 132.65 (C), 134.30 (CH), 137.17 (C), 138.14 (2×C). MS (ESI) m/z : 281.10 $[M+1]^+$.

(E)-9-chloro-10-styrylanthracene **(7b):** ^{1}H MMR (600 MHz, $CDCl_3$) δ: 6.9 (d, 1H, CH), 7.9 (d, 1H, CH) ; 7.2-9 (m, 13H, 13CH_{Ar}). ^{13}C MMR (150 MHz, $CDCl_3$) δ : 124.56 (CH_{Ar}), 125.30 (2×CH_{Ar}), 125.83 (2×CH_{Ar}), 126.64 (2×CH_{Ar}), 126.80 (2×CH_{Ar}), 127 (2×C), 127.5 (CH), 128.59 (2×CH_{Ar}), 129.04 (2×CH_{Ar}), 130.36 (C), 132.6 (C), 134.30 (CH), 137.17 (C), 138.14 (2×C).MS (ESI) m/z : 315.09 $[M+1]^+$.

3.1.4 Administration of physiological water (10 ml/kg, *per os*) in normo-glycemic control group

Oral administration of physiological water at a dose of 10 ml/kg does not modify the baseline blood glucose levels of normo-glycemic rats. Glycemia remains stable after 4 hours of observation (0.89±0.05 g/L vs 0.98±0.05 g/L), (ns, n=5).

3.1.5 Hypoglycemic effect of stilbenes derived from Benzaldehyde and Anthraldehyde

3.1.5.1 Stilbenes derived from benzaldehyde (RD04, RD05, RD06)

Oral administration of RD04 (3 mg/kg) is associated with significant hypoglycemia. Blood glucose varied from 0.93±0.03 to 0.67±0.04 g/L ($p<0.05$, n=5). Similar results of variation in blood glucose were observed, 2 h after administration of RD05 (3 mg/kg, *per os*) (0.71±0.02 vs 0.87±0.02 g/L) ($p<0.05$, n=5). RD06 (3 mg/kg, *per os*), also a stilbene derived from benzaldehyde, does not modify the baseline glycemia of normo-glycemic rats (0.81±0.07 vs 0.82±0.05g/L) (ns, n=5).

3.1.5.2 Stilbenes derived from anthraldehyde (RD01, RD02)

The administration of RD01 (3 mg/kg, *per os*) does not significantly modify baseline blood glucose in normoglycemic rats (0.83±0.02 vs 0.80±0. 06 g/L) (ns, n=5). On the other hand, under the same conditions, RD02 (3 mg/kg, *per os*) induced significant hypoglycemia (0.65±0.04 vs 0.89±0.02 g/L) ($p<0.05$, n=5).

3.1.5.3 Stilbenes derived from cinnamaldehyde (SS014, SS015)

The administration of SS014 (10 mg/kg, *per os*) showed a tendency towards a slight decrease in baseline blood glucose at T2h and T4h. The variation of the drop in blood glucose is equal to 0.17±0.05 g/L after 4 h (0.85±0.05 *vs* 1.03±0.04 g/L) ($p<0.05$, n=5). However, SS015 (10 mg/kg, *per os*) do not modified the baseline blood glucose levels of normoglycemic rats. We observed a trend towards a drop in blood glucose at T2h (0.82±0.08 *vs* 0.99±0.04 g/L), followed by a return to the baseline after 4h (0. 92±0.08 *vs* 0.99±0.04 g/L) (ns, n=5).

4. DISCUSSION

This study aims to evaluate the effect of stilbene derivatives on blood glucose. The experiments were carried out in normoglycemic rats to demonstrate a possible hypoglycemic action. In normoglycemic rats, RD02, RD04 and RD05 induce significant hypoglycemia, most likely suggesting the involvement of insulin secretion, by stimulating its receptor at the level of skeletal muscle cells, promotes glucose uptake by a

mechanism involving an increase in the expression of the Glut 4 glucose transporter. This mechanism involves an activation of phosphatidylinositol kinase (PI3K) and the AKT protein.[24]

Previous work had highlighted the interest of stilbene derivatives in the regulation of glycemia by improving either insulin secretion or by reducing insulin resistance of peripheral tissues. Resveratrol, a stilbene derivative, promotes glucose uptake in skeletal muscle cells by a mechanism involving the activation of AMPkinase and the increase in the intrinsic activity of the glucose transporter Glut 4. [25,26] In the present study, the effect on blood glucose of stilbene derivatives could involve an increase in glucose uptake dependent on its transporter Glut 4. Like stilbene derivatives of interest in the regulation of glycemia, the hypoglycemic action of RD02, RD04 and R05 could involve the insulin secretion pathway.

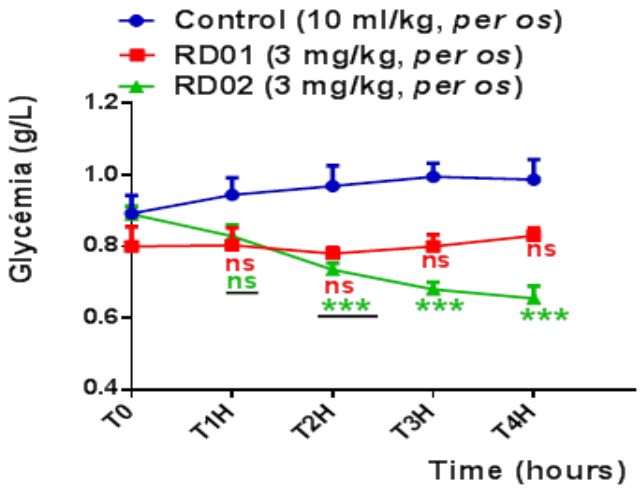

Figure 4: Hypoglycemic effect of RD02 in normoglycemic rats. *p<0.05 *vs* baseline value. n = 5. ns: not significant vs baseline value.

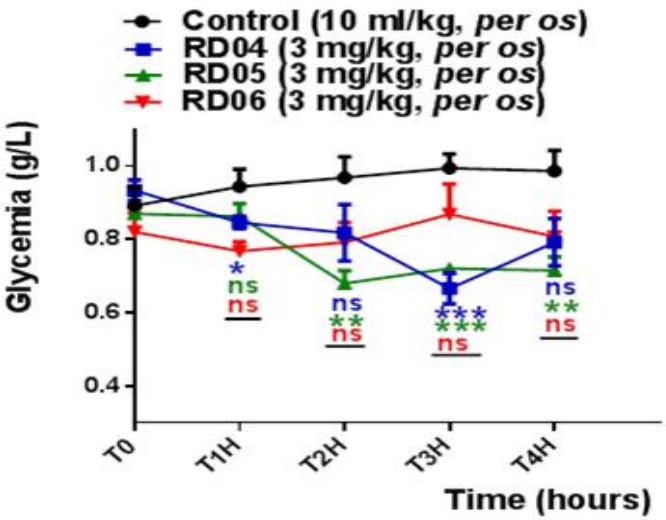

Figure 5: Powerful and Persistent hypoglycemic effect of RD05. *p<0.05 vs baseline value. n = 5. ns: not significant vs baseline value.

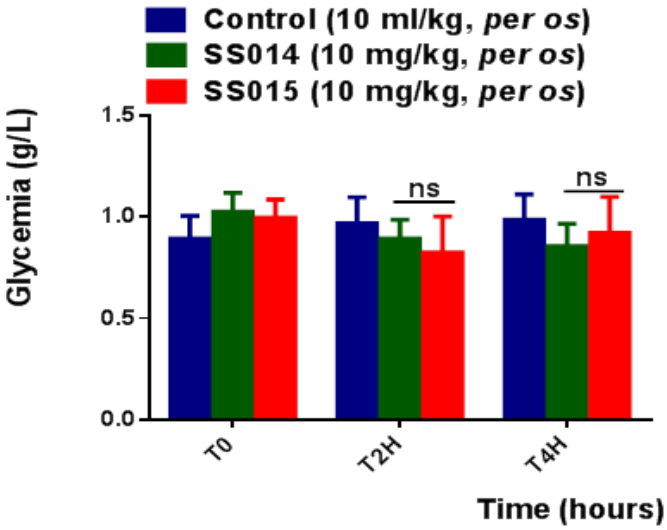

Figure 6: Absence of hypoglycemic effect of SS014 and SS015. ns: not significant *vs* baseline value.

5. CONCLUSION

The present study reports the synthesis of stilbene derivatives and a bioactive study of their hypoglycemic activity. Seven new derivatives stilbene were prepared in good yield. The results of this study showed that the compounds have a potent and persistent hypoglycemic activity. The best results are obtained with compounds RD02, RD04 and RD05.

Conflicts of interest

Authors declare no conflict of interest.

REFERENCES

1. Guthrie RA, Guthrie DW. Pathophysiology of diabetes mellitus. Crit Care Nurs Qart, 2004; 27(2): 113-125.
2. Mérillon JM, Fauconneau B, Teguo PW, Barrier L, Vercauteren J, Huguet F. Antioxidant activity of stilbene Astringin, newly extracted from *Vitis vinifera* Cell Cultures. Clin Chem, 1997; 43: 1092-1093.
3. Brandi A, Cicchi S, Cordero FM, Goti A. Heterocycles from alkylidene cyclopropenes. Chem Rev, 2003; 103: 1213-1270.
4. Hart JH. Role of phytostilbenes in decay and disease resistance. Annu Rev Phytopathol, 1981; 19: 437-58.
5. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the *in vivo* evidence. Nat Rev Drug Discov, 2006; 5: 493-506.
6. Nakao S, Mabuchi M, Wang S, Kogure Y, Shimizu T, Noguchi K, Tanaka A, Dai Y. Synthesis of resveratrol derivatives as new analgesic drugs through desensitization of the TRPA1 receptor. Bioorg Med Chem Lett, 2017; 27: 3167-3172.
7. Ismail T, Shafi S, Srinivas J, Sarkar D, Qurishi Y, Khazir J, Alam MS, Kumar HMS. Synthesis and tyrosinase inhibition activity of trans-stilbene derivatives. Bioorg Chem, 2016; 64: 97-102.
8. Albert S, Horbach R, Deising HB, Siewert B. Synthesis and antimicrobial activity of (*E*) stilbene derivatives. Bioorg Med Chem, 2011; 19: 5155-5166.
9. Keitaro H, Nobuyoshi K, Yusuke Y, Ryou-u T, Fumitaka T, Takahiro O. Stilbene derivatives promote Ago2-dependent tumour-suppressive microRNA activity. Sci Rep, 2012; 2: 314-321.
10. Hanna K. The stilbene derivatives, nucleosides, and nucleosides modified by stilbene derivatives. Bioorg Chem, 2019; 90: 103073.
11. Cagir A, Odaci B, Varol M, Akcok I, Okur O, Koparal AT. Evaluation of multifunctional hybrid analogs for stilbenes, chalcones and flavanones. Anticancer Agents Med Chem, 2018; 17: 1915-1923.
12. Heynekamp JJ, Weber WM, Hunsaker LA, Gonzales AM, Orlando RA, Deck LM, Vander J, David L. Substituted *trans*-stilbenes, including Analogues of the natural product resveratrol, inhibit the human tumor necrosis factor alpha-induced activation of transcription factor nuclear factor KappaB. J Med Chem, 2006; 49: 7182-7189.
13. Bunce NJ, Landers JP, Schneider UA, Safe SH, Zacharewski TR. Chlorinated *trans* stilbenes: Competitive binding to the ah receptor, induction of cytochrome p-450 monooxygenase activity and partial 2,3,7,8-TCDD antagonism. Toxicol Environ Chem, 1990; 28: 217-229.
14. Baur JA, Sinclair D. Therapeutic potential of resveratrol: the *in vivo* evidence. Nat Rev Drug Discov, 2006; 5: 493-506.
15. Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CWW, Fong HH, Farnsworth NR, Kinghorn AD, Mehta RG, Moon RC, Pezzuto JM. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science*, 1997; 275: 218-220.
16. Frombaum M, Le CClanche S, Bonnefont-Rousselot D, Borderie D. Antioxidant effects of resveratrol and

other stilbene derivatives on oxidative stress and NO bioavailability: Potential benefits to cardiovascular diseases. Biochem, 2012; 94: 269-76.
17. Bertelli AA, Giovannini L, Giannessi D, Migliori M, Bernini W, Fregoni M, Bertelli A. Antiplatelet activity of synthetic and natural resveratrol in red wine. Int J Tissue React, 1995; 17: 1-3.
18. Cao Z, Li Y. Potent induction of cellular antioxidants and phase 2 enzymes by resveratrol in cardiomyocytes: protection against oxidative and electrophilic injury. Eur J Pharmacol, 2004; 489: 39-48.
19. Howitz K, Bitterman K, Cohen H, Lamming D, Lavu S, Wood JREZ, Chung P, Kisielewski A, Zhang L, Scerer B, and Sinclair D. Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. Nature, 2003; 425: 191-196.
20. Martinez J, Moreno JJ. Effect of resveratrol, a natural polyphenolic compound, on reactive oxygen species and prostaglandin production. Biochem Pharmacol, 2000; 59: 865-870.
21. Bing W, Teng L, Zhongyu W, Lei Z, Jie S, and Xiaojing W. Synthesis and biological evaluation of stilbene derivatives coupled to NO donors as potential antidiabetic agents. J Enzyme Inhib Med Chem, 2018; 33(1): 416-423.
22. Saiyed AS, Patel KN, Kamath BV, Bedekar AV. Synthesis of Stilbene Analogues by One-Pot Oxidation-Wittig and Oxidation-Wittig-Heck Reaction. Tetrahedron Lett, 2012; 53: 4692-4696.
23. Peter AB, Declan GG. The modern interpretation of the Wittig reaction mechanism. Chem Soc Rev, 2013; 42: 6670-6696.
24. Kim W, Khil LY, Clark R, Bok SH, Kim EE, Lee S, Jun HS, Yoon JW. Naphtalenemethylester derivative of dihydroxyhydrocinnamic acid, a component of cinnamon, increases glucose diposal by enhancing translocation of glucose transporter 4. Diabetol, 2006; 49(10): 2437-2448.
25. Goh KP, Lee HY, Lau DP, Supaat W, Chan YH, Koh AF. Effects of resveratrol in patients with type 2 diabetes mellitus on skeletal muscle SIRT1 expression and energy expenditure. Int J Sport Nutr Exerc Metab, 2014; 24: 2-13.
26. Leon D, Uribe E, Zambrano A, Salas M. Implications of resveratrol on glucose uptake and metabolism. Molecules, 2017; 22(3): 398-408.