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In vitro study and structure-activity relationship analysis of stilbenoid derivatives as powerful vasorelaxants: Discovery of new lead compound

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ABSTRACT

The development of vasorelaxant as the antihypertensive drug is important as it produces a rapid and direct relaxation effect on the blood vessel muscles. Resveratrol (**RV**), as the most widely studied stilbenoid and the lead compound, inducing the excellent vasorelaxation effect through the multiple signalling pathways. In this study, the *in vitro* vascular response of the synthesized *trans*-stilbenoid derivatives, **SB 1-8e** were primarily evaluated by employing the phenylephrine (PE)-precontracted endothelium-intact isolated aortic rings. Herein we report *trans*-3,4,4′-trihydroxystilbene **(SB 8b)** exhibited surprisingly more than 2-fold improvement to the maximal relaxation (R_{max}) of **RV**. This article also highlights the characterization of the aromatic protons in terms of their unique splitting patterns in ^{1}H NMR.

1. Introduction

Owing to the imperceptible symptoms, most of the patients are not conscious of the perseverance of the persistently elevated blood pressure that leads to the progressive end-organ dysfunction and damage [1]. The strong vascular wall stress damages the endothelial and further giving rise to the increased vascular permeability, activation of coagulation factors and platelets as well as the fibrin deposition [1,2]. Therefore, hypertension is often linked to the possibilities in triggering human cardiovascular diseases (CVD) including stroke, coronary artery disease, acute heart failure (AHF), heart attack, angina, peripheral vascular disease, aneurysm, atrial fibrillation and kidney failure [2,3]. Among the nine classes of medications that are used in the treatment for hypertension (diuretics, vasodilators, angiotensin-converting enzyme (ACE) inhibitors, peripheral adrenergic inhibitors, angiotensin receptor blockers, alpha-blockers, beta-blockers, calcium channel blockers and central agonists), the vasodilators (also known as the vasorelaxants) are the common medication for the AHF on top of some hypertensive emergencies [4–6].

Vasorelaxants are referred to as the chemical compounds that interact with the vasomotors found in the vascular smooth muscles (VSMCs) of tunica media and the endothelial cells of tunica intima to stipulate a rapid relaxation effect on the smooth muscle cells within the vessel walls to allow the blood to flow smoothly [7]. The general mechanisms of actions involved were usually the activation of the NO/cGMP pathway, blockade of the Ca^{2+} channels, and activation of the K^{+} channels. More than two hundred of the compounds obtained from plants were studied on their vasorelaxant effects, examples include the polyphenols in red wine, saponins from ginseng, proanthocyanidins from persimmon leaf tea and green tea, xanthones obtained from *Haleniaelliptica*, chalcones isolated from *Angelica keiskei*, alkaloids obtained from *Peganum harmala*, glycosides identified in *Melaleuca quinquenervia* and the macrocyclic bis(bibenzyls) from liverworts [8].

RV (*trans*-3,4′,5-trihydroxystilbene) as the most widely studied stilbenoids had been proven its role to the “French Paradox”, an epidemiological finding that linked the low occurrence of the cardiovascular diseases of French population due to their daily habits of consuming red wine despite their diet were high in saturated fats [9,10]. The popularity of RV was then increased tremendously and nowadays RV that made from the grape extracts can be obtained as the nutritional supplements [11]. Tan et al. reported the vasorelaxant effects of RV were attributed to the endothelium-derived relaxing factors (EDRFs) such as the PGI_2 and NO/sGC/cGMP pathways, followed by the G-protein-coupled β-adrenergic and muscarinic receptor pathways. The signalling pathways comprised both the potassium and calcium channels. RV could suppress not only the extracellular calcium influx, but also the intracellular release of the calcium from the sarcoplasmic reticulum (SR) within the VSMCs [12]. There is another article compared

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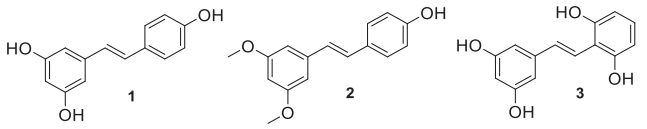


Fig. 1. The chemical structures of resveratrol (**1**) (*trans*-3,4′,5-trihydroxystilbene), pterostilbene (**2**) (*trans*-3,5-dimethoxy-4′-hydroxystilbene) and gnetol (**3**) (*trans*-3,5, 2′, 6′-tetrahydroxystilbene).

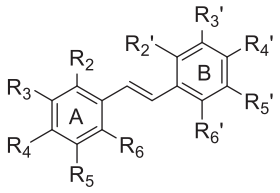


Fig. 2. General structure of the *trans*-stilbenoid

the *in vitro* and *in vivo* capabilities of another two stilbenoids, namely pterostilbene and gnetol (Fig. 1) that were responsible in suppressing cardiomyocyte hypertrophy and enhancing diastolic function [9,13]. The articles suggested RV and the stilbenoids could be the suitable medications for hypertension and human cardiovascular diseases [9,12,13] (see Fig. 2).

Stilbenoids represented a group of naturally occurring phenolic compounds that share a common stilbene backbone structure, C6-C2-C6, but differ in the number, type and position of substituents on the aromatic rings [9,14,15]. Stilbenoids that were formerly functioned as the phytoalexin that responded to stress, injury, ultraviolet irradiation and fungal infection were derived naturally from the coenzyme A derivative of cinnamic acid through the general phenylpropanoid pathway [9,16,17]. The presence of the ethylene bridge joining the two aromatic rings (A- and B- rings) contributed to the formation of the *cis*-isomer, and the relatively more stable *trans*-isomer that displayed most of the beneficial biological activities such as antihypertensive, anticancer, anti-inflammation, antilipidemic, antiplatelet aggregation, antileukaemia, antioxidation, antimicrobial and protein-tyrosine kinase inhibitory [9,16–18].

Although the *trans*-stilbene scaffold of the stilbenoids had been investigated its potential in the vasorelaxation effect of blood vessel, the corresponding SARs data of stilbenoids are insufficient [19]. Notably, the previous vasorelaxation studies focussed mainly on the resveratrol derivatives with the 3-, 5- and 4′- positions of different substituents [19,20]. There are various structural modifications of the *trans*-stilbenoids have been attempted on the other biological activities such as the *in vitro* studies focussed only the anti-cancer and anti-oxidant properties [20–23]. Herein we recognized the significance of the investigation on the structural requirements of the *trans*-stilbenoids that show the *in vitro* vasorelaxation effect as the prerequisite for the future mechanism studies.

This article presents the synthesis scheme (Scheme 1) of the *trans*-stilbenoid derivatives, **SB 1-8e**, and the clean and simple separation of the *trans*-stilbenoid isomers as well as the structural characterizations by FT-IR and NMR. The *in vitro* vascular response of **SB 1-8e** was primarily evaluated by employing the PE-precontracted endothelium-intact isolated aortic rings with the objective to reveal the relationship between the chemical structure of **SB 1-8e** and their resulting vasorelaxant activity.

2. Results and discussion

2.1. Synthesis

Various commercially available benzaldehydes, **4a-f** and **5g-j** were used for the synthesis of the stilbenoid derivatives, **SB 1-8e** employing the formation of the phosphonium salts, **8a-j** under the conventional Wittig reaction method. The synthesis route (outlined in Scheme 1) involves the reduction of the ethoxylated and methoxylated benzaldehydes, **5a-j** to benzyl alcohols, **6a-j** using the granular sodium borohydride prior to the reaction with thionyl chloride to form the benzyl chlorides, **7a-j**. The phosphonium salts, **8a-j**, represented the A-ring structures of the stilbenoid backbone, were synthesized by heating the benzyl chlorides **7a-j** with the triphenylphosphine solid in the adequate amount of the THF solvent.

Gently heating of the phosphonium salts, **8a-j** with base generated the ylide that reacted with the respective benzaldehydes (represented the B-ring structures) to give the final products as the mixture of the *cis*- and *trans*- isomers along with the by product, triphenylphosphine oxide. The *trans*- isomers could readily be obtained in clean solid form by washing the crude with small portion of cold ethanol in few times.

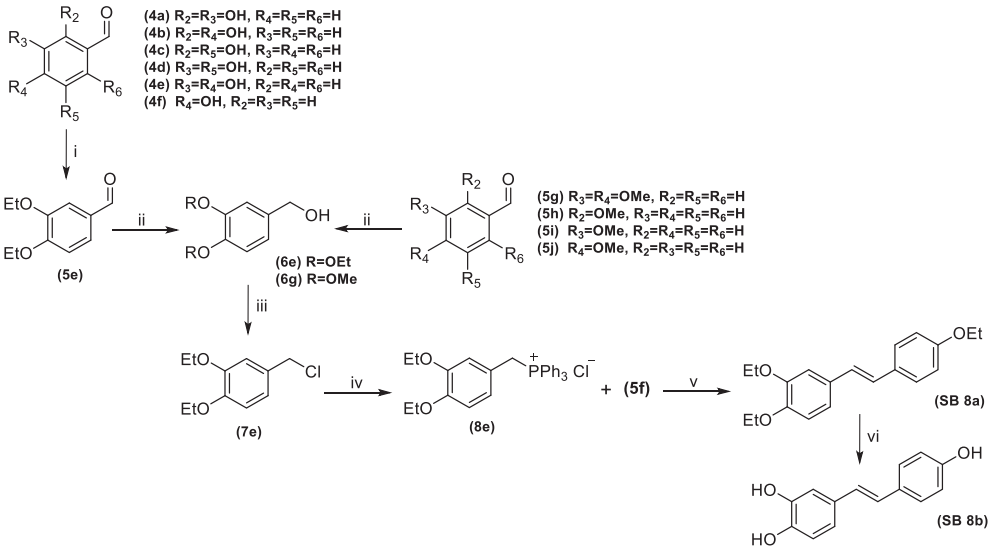
SB 8b was synthesized from **SB 8a** via the poly *O*-dealkylation method using the aluminium trichloride/N,N-dimethylaniline system. The polymeric nature of $AlCl_3$ was disrupted by the amine substrate, thus the reagent system was able to generate a more powerful lewis acid to convert all the ethoxy groups effectively into the hydroxy groups leaving the carbon-carbon double bond undisturbed [24]. **SB 4b**, **SB 6b**, and **SB 8e** were also synthesized using the same method mentioned. The chemical structures of the stilbenoid derivatives, **SB 1-8e** were illustrated in Table 1. The chemical structures of synthesized *trans*- stilbenoid derivatives were further elucidated by FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy.

2.2. Structural characterization

All the alkoxylated stilbenoid derivatives, **SB 1-3**, **SB 4a-8a** and **SB 8c-8d** exhibited a weak C_{sp2}-H stretching band and the three medium C_{sp3}-H stretching bands at 3003–3051 cm^{-1} and 2837–2983 cm^{-1}, respectively. The broad O—H stretching bands of **SB 4b**, **SB 6b**, **SB 8b** and **SB 8e** were appeared at 3265–3338 cm^{-1}. The two peaks observed at 1500 and 1600 cm^{-1} represented the aromatic C=C stretching of the benzene rings. The strong absorption bands near to 1220–1256 cm^{-1} and 1020–1052 cm^{-1} were assigned to the aromatic C—O stretching and saturated C—O stretching, respectively. Notably, the presence of the *trans*- double bond could be confirmed by recognizing a sharp and intense peak fell in the narrow range of 960–970 cm^{-1} that represented the bending of the C_{sp2}-H_{trans} bond [25].

The existence of the *trans*- isomers could also be proven by the presence of the two characterizable doublets with the coupling constant, *J* value of 16.0–16.5 Hz representing the olefinic *trans*- protons in the ^{1}H NMR spectra, except the symmetrical compounds like **SB 3** and **SB 8a-e** that showed the *trans*- proton peaks as a singlet. The presence of 4′-mono-substituted B-ring (except **SB 8e**) could be confirmed by the presence of the two doublets with the similar *J* value of 8.5 Hz. It was also observed that the B-ring's protons of the tri-substituted stilbenoids resonated at more downfield than that of the A-ring, due to the greater number of the alkoxy groups that contributes extra electron density to the A-ring via resonance [26].

The substitution patterns of the tri-substituted A-ring (**SB 4-8**) were more complicated due to long range coupling in the presence of the conjugated π bond. Although the protons located at *ortho*- and *para*-positionsto the alkoxy or hydroxy group are more shielded by the substituents [27], but the chemical shift are insufficient to confirm the position of thatproton on the aromatic rings. Therefore, the *J* value and the recognizable splitting pattern of the proton peaks were used to confirm the substitution patterns of the A-ring. The proton that has the both coupled protons at ortho- positions (e.g. H5 of **SB 4a**) appeared as a triplet with $J = 8.0$ Hz. The coupled protons at ortho- and meta-positions (e.g. H6 of **SB 4a**) split the relative proton peak into doublet of doublet ($J = 8.0$, 2.0 Hz). Table 2 tabulates a few characterizable splitting patterns of the aromatic protons of the stilbenoid derivatives, **SB 1-8e**.



Scheme 1. The synthesis of stilbenoid derivatives (**SB 1-7e**). Reagents and conditions: (i) bromoethane, K_2CO_3, KI, acetone, reflux; (ii) $NaBH_4$, THF-MeOH, reflux; (iii) $SOCl_2$, pyridine, 0 ˚C to r.t; (iv) triphenylphosphine, THF, 120 ˚C; (v) NaOH, DCM, reflux; (vi) $AlCl_3$, N,N-dimethylaniline, 180 ˚C.

Table 1
The chemical structure of the stilbenoid derivatives, **SB 1-8e** with their respective starting materials in step v (ref. Scheme 1).

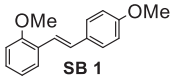
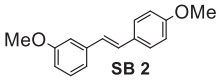
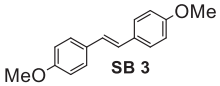
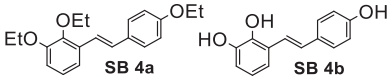
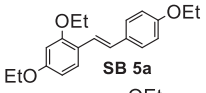
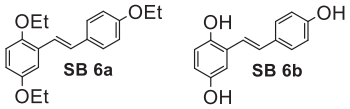
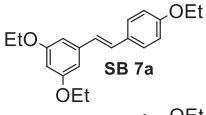
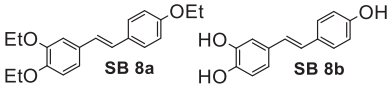
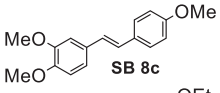
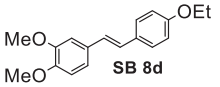
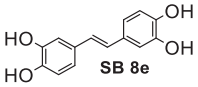
Chemical Structure of stilbenoid derivatives	Starting Materials	
	Phosphonium salt	Benzaldehyde
 SB 1	**8j**	**5h**
 SB 2	**8j**	**5i**
 SB 3	**8j**	**5j**
 SB 4a SB 4b	**8a**	**5f**
 SB 5a	**8b**	**5f**
 SB 6a SB 6b	**8c**	**5f**
 SB 7a	**8d**	**5f**
 SB 8a SB 8b	**8e**	**5f**
 SB 8c	**8g**	**5j**
 SB 8d	**8g**	**5d**
 SB 8e	**8g**	**5g**

Table 2
The relative position of the coupled protons on the aromatic rings with their respective splitting patterns at 500 MHz.

The relative positions of the coupled protons	Splitting patterns of the proton peaks (500MHz)	Assignment of Proton
-ortho and *-ortho*	 t, *J*= 8.0 Hz	H5 (**SB 4a**)
-ortho and *-meta*	 dd, *J*= 8.0, 2.0 Hz	H4 & H6 (**SB 4a**), H5 (**SB 5a**), H4 (**SB 6a**), H6 (**SB8a**)
-ortho and *-para*	 d, *J*= 8.5 Hz	H6 (**SB5a**), H3 (**SB 6a**), H5 (**SB 8a**)
-meta and *-para*	 d, *J*= 2.0 Hz	H3 (**SB 5a**), H6 (**SB 6a**), H2 (**SB 8a**)
-meta and *-meta*	 or t or d, *J*= 2.5 Hz	H2, H4 & H6 (**SB 7a**)

2.3. In vitro aortic rings assay

Rat aortic rings assay is a prominent *in vitro* technique used in the vasculature studies due to their ease of preparation, less vulnerable to damage the intima surface of the endothelium as well as to minimize the orientation change of the VSMCs [28,29]. In this study, a single concentration of each compound was applied to evaluate quantitatively the vasorelaxation potential of the stilbenoid derivatives, **SB 1-8e**. The vascular response elicited by the stilbenoid derivatives, **SB 1-8e** (shown in Table 3) were primarily evaluated from the PE-precontracted endothelium-intact aortic rings.

Table 3
The maximum relaxation (R_{max}) value of the endothelium-intact isolated aortic rings in response to the synthesized stilbenoid derivatives, **SB 1-8e**.

Compound	A-ring	B-ring	R_{max}[a] (%)
SB 1	2- OMe	4′- OMe	−27.99 ± 3.98
SB 2	3- OMe	4′- OMe	−27.59 ± 4.99
SB 3	4- OMe	4′- OMe	−5.32 ± 1.26
SB 4a	2, 3- OEt	4′- OEt	25.99 ± 4.39
SB 4b	2, 3- OH	4′- OH	37.16 ± 3.13
SB 5a	2, 4- OEt	4′- OEt	22.66 ± 2.77
SB 6a	2, 5- OEt	4′- OEt	3.51 ± 4.63
SB 6b	2, 5- OH	4′- OH	−21.79 ± 3.42
SB 7a	3, 5- OEt	4′- OEt	10.98 ± 3.70
SB 8a	3, 4- OEt	4′- OEt	20.25 ± 4.77
SB 8b	3, 4- OH	4′- OH	89.47 ± 3.88
SB 8c	3, 4- OMe	4′- OMe	−20.32 ± 2.30
SB 8d	3, 4- OMe	4′- OEt	−20.17 ± 5.10
SB 8e	3, 4- OH	3′, 4′- OH	31.77 ± 3.97
RV	3, 5- OH	4′- OH	42.90 ± 1.67

[a] R_{max} = maximal relaxation of the test compounds (0.08 mg/mL); data expressed as mean ± S.E.M. (n = 4).

Fig. 3 shows that most of the stilbenoid derivatives with the positive R_{max} value elicited vasorelaxation response to the PE-precontracted aortic rings, except **SB 1-3**, **SB 6b** and **SB 8c-d** that showed the unfavourable vasoconstriction response. The distinctive screening results also revealed that the stilbene backbone of the stilbenoid derivatives alone did not necessarily producea vasorelaxation response, but it greatly depends on the position, type and number of substituentson the A- and B-ring. The vascular relaxation or constriction is dependent on the affinity, specificity and selectivity of the stilbenoid derivatives, **SB 1-8e** binding to the vasodilation- or vasoconstriction-mediated receptors that found on the blood vessel membrane [31] (see Fig. 4).

Among the stilbenoid derivatives that elicited the vasorelaxation response to the PE-precontracted aortic rings, it was found that only **SB 8b** exhibited surprisingly the greater R_{max} than the lead compound, RV. **SB 8b** that displayed the highest R_{max} had the 2-fold increase of the RV's R_{max}, suggesting the chemical structure of **SB 8b** has the potential to be adopted as a new lead compound for drug optimization.

2.4. SARs analysis

All thedisubstituted stilbenoid derivatives, **SB 1-3** (2,4′-, 3,4′-, and 4,4′-dimethoxy group) exerted the unfavourable vasoconstriction responses, whereas the trisubstituted stilbenoid derivatives, **SB 4a-8a** (2,3,4′-,2,4,4′-, 2,5,4′-, 3,5,4′-, and 3,4,4′-triethoxy) had elicited the vasorelaxant response suggesting the trisubstituted structure is more favourable than that of the disubstituted structure. Among the mentioned trisubstituted stilbenoid derivatives, **SB 4a** with the substituents occupied to the *ortho*- position of each other wasrecorded the highest R_{max} while **SB 6a**with the substituents occupied to the *para*- position showed the lowest R_{max}. The precursor of the **RV**, **SB 7a** unexpectedly exhibited a weaker potency compared to **SB 4a**, **SB 5a** and **SB 8a**.

Converting the alkoxy groups (**SB 4a-8a**) into the hydroxyl groups

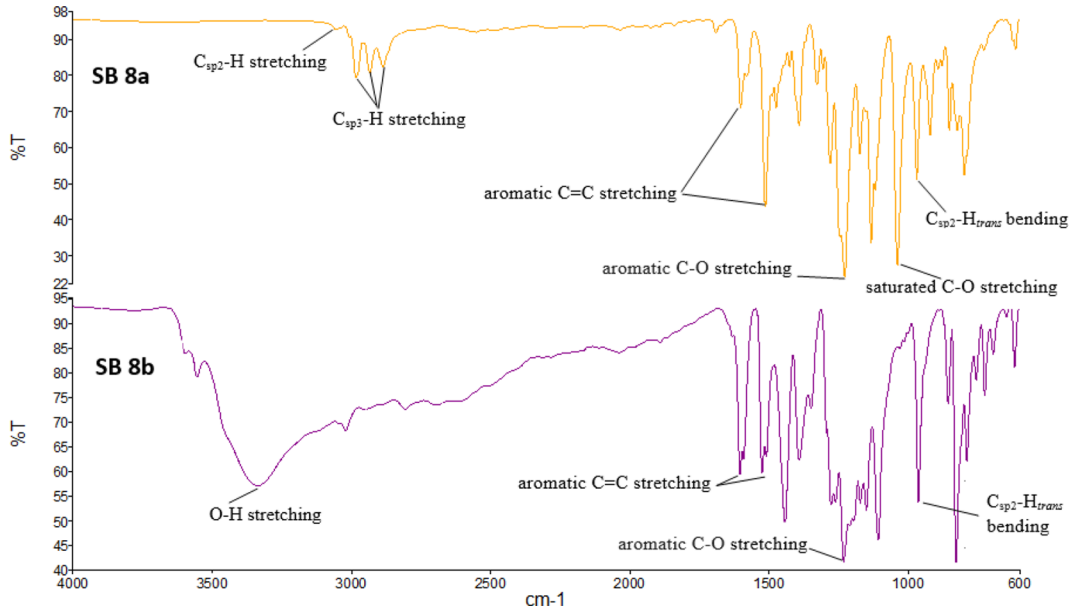


Fig. 3. The IR spectra of the stilbenoid derivatives, **SB 8a** and **Sb 8b**.

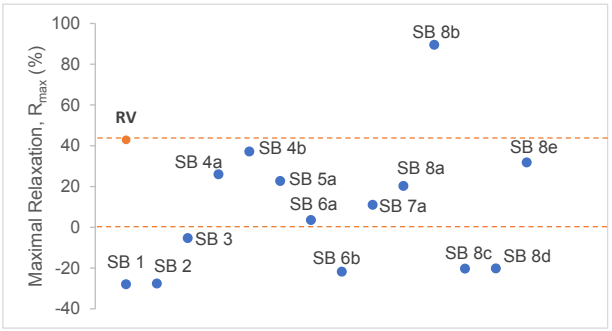


Fig. 4. The R_{max} comparison chart of the RV with **SB 1-8e**.

(**SB 4b-8b**) resulted in a significant enhancement of the vasorelaxant response except for **SB 7b** that elicited the vasoconstriction response. A similar trend was observed that the substituents occupied to the *ortho*-position of each other in **SB 8b** (3,4,4′-trihydroxy) displayed the greatest vasorelaxant effect. We further attempted the 3,4,4′- structure by replacing the substituents to form 3,4,4′-trimethoxy (**SB 8c**) and 3,4-dimethoxy-4′-ethoxy (**SB 8d**) but both structures leaded to the total disappearance of the vasorelaxant effect, demonstrating the hydroxyl functional groups occupied the 3,4- positions of the A-ring are more optimal than that of the alkoxy substituents. It was also observed that the structure with ethoxy groups (**SB 8b**) are more favourable than that of the methoxy groups (**SB 8c**).

After examining the vasorelaxant effect of the substituent positionon the A-ring, we attempted another structure with the B-ring bearing the hydroxyl groups at 3′,4′- positions. However, the modified structure (**SB 8e**) with the additional hydroxyl group at the 3′- position compared to **SB 8b** did not produce an expected increase of the vasorelaxant effect but reduced the vasorelaxant effect by 3 times instead. The overall data illustrated the position, number and type of the substituents on the A- and B-ring were essential in displaying the vasorelaxant effect on the blood vessel, especially the trihydroxy structure with the *ortho*- occupied position to each other was responsible to the significant increase of the vasorelaxant effect.

3. Conclusions

This article demonstrated the simple synthesis, characterization and the preliminary SARs analysis of the stilbenoid derivatives, **SB 1-8e** towards the vasorelaxant effect by employing the *in vitro* aortic rings assay. The trihydroxy structure with the *ortho*- occupied position to each other was responsible to the significant increase of the vasorelaxant effect. **SB 8b** that displayed the remarkable 2-fold improvement of the vasorelaxant effect of RV should be further studied its mechanism of action as well as adopted as a new lead compound for optimization.

4. Experimental section

4.1. Chemistry

All chemicals and solvents were commercially available and used without further purification. FT-IR spectra were recorded using a Perkin Elmer 2000-FTIR spectrophotometer in the range of 4000–600 cm^{-1}. FT-NMR spectra were recorded using a Bruker-Avance 500 MHz ultrashield spectrometer equipped with ultrashield magnets. $CDCl_3$ and DMSO-d_6 were used as NMR solvents with TMS as the internal standard. Reaction monitoring was performed using the thin layer chromatography technique.

4.1.1. General procedure for synthesis of compounds, 5e

Compound **5e** was synthesized from 3,4-dihydroxybenzaldehyde (**4e**) and bromoethane via Williamson etherification. **4e** (2.50 g, 18.1 mmol) and acetone (50 mL) were stirred at 50 °C for half an hour in the presence of potassium carbonate anhydrous (4.0 equiv.) and a catalytic amount of potassium iodide. Bromoethane (2.2 equiv.) was then added into the mixture and refluxed at 80–85 °C for 12 h. The resultant mixture was filtered, excess solvent was evaporated off to yield the desired compound, **5e** as white solid (96% yield) without further purification. **^{1}H NMR (500 MHz, DMSO-d_6)** δ, ppm: 9.83 (s, 1H), 7.53 (dd, J = 8.5, 2.0 Hz, 1H), 7.38 (d, J = 1.5 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 4.17–4.07 (m, 4H), 1.38–1.34 (m, 6H).

4.1.2. General procedure for synthesis of compounds, 6e

Compound **6e** was synthesized from **5e** via reduction using sodium borohydride ($NaBH_4$). A mixture of **5e** (2.00 g, 10.2 mmol) and granular $NaBH_4$ (1.1 equiv.) in THF (25 mL) was refluxed at 100 °C.

Methanol (20 mL) was added dropwise into the mixture over 30 min. The mixture was cooled down to room temperature after 4 h of reflux. The mixture was neutralized by a step-wise addition of 37% HCl. The reaction mixture was filtered, the filtrate was dissolved and extracted with ethyl acetate. Excess solvent was evaporated off to yield the desired compound, **6e** as white solid (95% yield) without further purification. **^{1}H NMR (500 MHz, DMSO-d_6)** δ, ppm: 6.91–6.87 (m, 2H), 6.79 (d, J = 8.5 Hz, 1H), 5.06 (t, J = 6 Hz, 1H), 4.40 (d, J = 5.5 Hz, 2H), 4.02–3.96 (m, 4H), 1.34–1.29 (m, 6H).

*4.1.3. General procedure for synthesis of compounds, **7e***

Compound **7e** was synthesized from **6e** via the reaction with thionyl chloride ($SOCl_2$). In a round bottom flask, **6e** (1.50 g, 7.6 mmol) was dissolved in THF (10 mL), a few drops of pyridine were added into the mixture. The flask was then immersed in an ice bath and stir for 15 min prior to the addition of $SOCl_2$ (1.2 equiv.). After 8 h stirring at room temperature, the resultant mixture was poured into cold distilled water and extracted with diethyl ether. The organic layer was extracted with another portion of distilled water and excess solvent was evaporated off to yield the desired compound, **7e** as yellowish liquid(97% yield) without further purification. **^{1}H NMR (500 MHz, DMSO-d_6)** δ, ppm: 7.02 (s, 1H), 6.96–6.91 (m, 2H), 4.70 (s, 2H), 4.04–3.99 (m, 4H), 1.34–1.31 (m, 6H).

*4.1.4. General procedure for synthesis of compounds, **8e***

Compound **8e** was synthesized from **7e** via the reaction with triphenylphosphine. In a round bottom flask, **7e** (1.00 g, 4.7 mmol) and triphenylphosphine (1.0 equiv.) were dissolved in THF (20 mL). The mixture was refluxed at 150 °C for 12 h until the white solid was observed. The white solid phosphonium salt was filtered and rinsed with THF and a small portion of *n*-hexane to yield the desired compound, **9a** as white solid (86% yield) without further purification. **^{1}H NMR (500 MHz, DMSO-d_6)** δ, ppm: 7.91–7.88 (m, 3H), 7.78–7.74 (m, 6H), 7.69–6.65 (m, 6H), 6.83 (d, J = 8.5 Hz, 1H), 6.56 (dd, J = 8.5, 2.0 Hz, 1H), 6.45 (s, 1H), 5.08 (d, J = 15 Hz, 2H), 3.95 (q, J = 6.5 Hz, 2H), 3.56 (q, J = 6.5 Hz, 2H), 1.28 (t, J = 7.5 Hz, 3H), 1.14 (t, J = 7.0 Hz, 3H); **^{31}P NMR (202 MHz, DMSO-d_6)** δ, ppm: 22.4.

*4.1.5. General procedure for synthesis of compounds, **SB 1-3, SB 4a-8a, SB 8c-8d***

Compound **SB 8a** was synthesized from **8e** and **5f** via the Wittig reaction. In a round bottom flask, **8e** (4.50 g, 10.1 mmol) and **5f** (1.0 equiv.) were dissolved in DCM (50 mL). Sodium hydroxide (3.5 equiv.) was dissolved in distilled water (10 mL) and added into the mixture. The mixture was refluxed at 75–85 °C for overnight. The resultant mixture was neutralized by a step-wise addition of 37% HCl. The resultant mixture was filtered, the filtrate was dissolved in ethyl acetate and extracted with distilled water. Excess solvent was evaporated off. The crude product was washed several times with the small amount of cold ethanol (3x10 mL) to give pure *trans*-isomer of compound **SB 8a** as yellowish crystal. **SB 1-3**, **SB 4a-7a** and **SB 8c-8e** were synthesized according to the described method, wherein phosphonium salt **8e** and benzaldehyde **5f** were replaced by **8a-8g** and **5d-5j** according to Table 1.

*4.1.5.1. (E)-1-Methoxy-2-(4-methoxystyryl)benzene (trans-2,4′-dimethoxystilbene)(**SB 1**).* White solid, yield: 70%, m.p. 85–86 °C (lit. 85–86 °C [32]). **IR (cm^{-1})**: 3003 (C_{sp2}-H stretching), 2962, 2935 and 2837 (C_{sp3}-H stretching), 1597 and 1509 (aromatic C=C stretching), 1237 (aromatic C−O stretching), 1025 (saturated C−O stretching), 967 (C_{sp2}-H_{trans}bending);); **^{1}H NMR (500 MHz, DMSO-d_6)** δ, ppm: 7.51 (d, J = 7.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.28 (d, J_{trans} = 16.5 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 6.99 (d, J_{trans} = 16.5 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 7.0 Hz, 3H), 3.82 (s, 3H), 3.76 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ, ppm: 159.12, 156.74, 130.84, 128.66, 128.24, 127.72, 126.16, 121.38, 120.75, 114.04, 110.92, 55.53, 55.33. **ESI-MS:** 240.30 ($[M+H]^+$).

*4.1.5.2. (E)-1-Methoxy-3-(4-methoxystyryl)benzene (trans-3,4′-dimethoxystilbene) (**SB 2**).* Beige solid, yield: 69%, m.p. 106–107 °C (lit. 107–108 °C [32]). 3007 (C_{sp2}-H stretching), 2972, 2936 and 2837 (C_{sp3}-H stretching), 1585 and 1509 (aromatic C=C stretching), 1243 (aromatic C−O stretching), 1026 (saturated C−O stretching), 968 (C_{sp2}-H_{trans} bending); **^{1}H NMR (500 MHz, DMSO-d_6)** δ, ppm: 7.38 (d, J = 8.5 Hz, 2H), 7.21 (t, J = 8.0 Hz, 1H), 7.03–6.96 (m, 3H), 6.89–6.82 (m, 3H), 6.73 (d, J = 8.0 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ, ppm: 159.89, 159.36, 139.14, 130.05, 129.6, 128.55, 127.77, 126.51, 119.01, 114.15, 112.91, 111.49, 55.35, 55.26.**ESI-MS:** 240.30 ($[M+H]^+$).

*4.1.5.3. (E)-1,2-Bis(4-methoxyphenyl)ethene (trans-4,4′-dimethoxystilbene) (**SB 3**).* White solid, yield: 85%, m.p. 212–213 °C (lit. 212–213 °C [32]). 3016 (C_{sp2}-H stretching), 2960, 2920 and 2838 (C_{sp3}-H stretching), 1601 and 1510 (aromatic C=C stretching), 1244 (aromatic C−O stretching), 1026 (saturated C−O stretching), 967 (C_{sp2}-H_{trans} bending); **^{1}H NMR (500 MHz, DMSO-d_6)** δ, ppm: 7.36 (d, J = 8.0 Hz, 4H), 6.86 (s, 2H), 6.82 (d, J = 8.0 Hz, 4H), 3.75 (s, 6H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ, ppm: 159.01, 130.49, 127.42, 126.19, 114.12, 55.33.**ESI-MS:** 240.30 ($[M+H]^+$).

*4.1.5.4. (E)-1,2-Diethoxy-3-(4-ethoxystyryl)benzene (trans-2,3,4′-triethoxystilbene) (**SB 4a**).* Off-white solid, yield: 68%, m.p. 70–72 °C (lit. 70–72 °C [30]). **IR (cm^{-1})**: 3043 (C_{sp2}-H stretching), 2978, 2927 and 2885 (C_{sp3}-H stretching), 1575 and 1509 (aromatic C=C stretching), 1241 (aromatic C−O stretching), 1032 (saturated C−O stretching), 964 (C_{sp2}-H_{trans} bending); **^{1}H NMR (500 MHz, $CDCl_3$)** δ, ppm: 7.49 (d, J = 8.5 Hz, 2H), 7.38 (d, J_{trans} = 16.5 Hz, 1H), 7.24 (dd, J = 8.0, 1.0 Hz, 1H), 7.09 (d, J_{trans} = 16.5 Hz, 1H), 7.04 (t, J = 8.0 Hz, 1H), 6.92 (d, J = 8.5 Hz, 2H), 6.82 (dd, J = 8.0, 1.0 Hz, 1H), 4.12–4.06 (m, 6H), 1.50–1.43 (m, 9H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ, ppm: 158.63, 152.49, 146.11, 132.21, 130.48, 129.02, 127.79, 123.79, 121.22, 117.53, 114.67, 112.19, 69.16, 64.20, 63.50, 15.78, 14.99, 14.87. **ESI-MS:** 312.40 ($[M+H]^+$).

*4.1.5.5. (E)-2,4-Diethoxy-1-(4-ethoxystyryl)benzene (trans-2,4,4′-triethoxystilbene) (**SB 5a**).* Yellow solid, yield: 76%, m.p. 94–96 °C (lit. 94–96 °C [30]). **IR (cm^{-1})**: 3038 (C_{sp2}-H stretching), 2974, 2929 and 2881 (C_{sp3}-H stretching), 1603 and 1510 (aromatic C=C stretching), 1243 (aromatic C−O stretching), 1042 (saturated C−O stretching), 969 (C_{sp2}-H_{trans} bending); **^{1}H NMR (500 MHz, $CDCl_3$)** δ, ppm: 7.49 (d, J = 8.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.28 (d, J_{trans} = 16.5 Hz, 1H), 7.00 (d, J_{trans} = 16.5 Hz, 1H), 6.90 (d, J = 8.5 Hz, 2H), 6.51 (dd, J = 8.5, 2.0 Hz, 1H), 6.48 (d, J = 2.5 Hz, 1H), 4.11–4.05 (m, 6H), 1.51–1.43 (m, 9H);**^{13}C NMR (125 MHz, $CDCl_3$)** δ, ppm: 159.45, 158.16, 157.24, 131.17, 127.42, 126.97, 126.44, 121.45, 119.86, 114.59, 105.56, 99.95, 63.95, 63.55, 63.47, 14.88.**ESI-MS:** 312.40 ($[M+H]^+$).

*4.1.5.6. (E)-1,4-Diethoxy-2-(4-ethoxystyryl)benzene (trans-2,5,4′-triethoxystilbene) (**SB 6a**).* Off-white solid, yield: 64%, m.p. 82–84 °C (lit. 82–84 °C [30]). **IR (cm^{-1})**: 3036 (C_{sp2}-H stretching), 2973, 2927 and 2872 (C_{sp3}-H stretching), 1602 and 1500(aromatic C=C stretching), 1256 (aromatic C−O stretching), 1044 (saturated C−O stretching), 957 (C_{sp2}-H_{trans} bending); **^{1}H NMR (500 MHz, $CDCl_3$)** δ, ppm: 7.49 (d, J = 8.5 Hz, 2H), 7.37 (d, J_{trans} = 16.5 Hz, 1H), 7.18 (d, J = 3.0 Hz, 1H), 7.10 (d, J_{trans} = 16.5 Hz, 1H), 6.92 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 1H), 6.78 (dd, J = 9.0, 3.0 Hz, 1H), 4.10–4.04 (m, 6H), 1.50–1.44 (m, 9H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ, ppm: 158.58,

153.14, 150.64, 130.61, 128.75, 127.99, 127.80, 121.31, 114.64, 114.01, 113.97, 112.13, 65.02, 64.01, 63.50, 15.10, 15.04, 14.88.**ESI-MS:** 312.40 ($[M+H]^+$).

*4.1.5.7. (E)-1,3-Diethoxy-5-(4-ethoxystyryl)benzene (trans-3,5,4′-triethoxystilbene) (**SB 7a**)*. White solid, yield: 58%, m.p. 70–72 °C (lit. 70–72 °C [33]). **IR (cm^{-1}):** 3024 (C_{sp2}-H stretching), 2981, 2933 and 2875 (C_{sp3}-H stretching), 1588 and 1507(aromatic C=C stretching), 1243 (aromatic C−O stretching), 1052 (saturated C−O stretching), 954 (C_{sp2}-H_{trans} bending);**^{1}H NMR (500 MHz, $CDCl_3$)** δ, ppm: 7.45 (d, J = 8.5 Hz, 2H), 7.05 (d, J_{trans} = 16.0 Hz, 1H), 6.91 (m, 3H), 6.66 (d, J = 2.5 Hz, 2H), 6.39 (t, J = 2.0 Hz, 1H), 4.10–4.06 (m, 6H), 1.46–1.44 (m, 9H);**^{13}C NMR (125 MHz, $CDCl_3$)** δ, ppm: 160.27, 158.75, 139.62, 129.85, 128.63, 127.77, 126.57, 114.69, 104.9, 100.51, 62.5, 14.89, 14.85.**ESI-MS:** 312.40 ($[M+H]^+$).

*4.1.5.8. (E)-1,2-Diethoxy-4-(4-ethoxystyryl)benzene (trans-3,4,4′-triethoxystilbene) (**SB 8a**)*. Pale yellow solid, yield: 90%, m.p. 150–152 °C (lit. 150–152 °C [30]). **IR (cm^{-1}):** 3051 (C_{sp2}-H stretching), 2983, 2931 and 2840 (C_{sp3}-H stretching), 1598 and 1510 (aromatic C=C stretching), 1235 (aromatic C−O stretching), 1020 (saturated C−O stretching), 967 (C_{sp2}-H_{trans} bending); **^{1}H NMR (500 MHz, $CDCl_3$)** δ, ppm: 7.44 (d, J = 9.0 Hz, 2H), 7.08 (d, J = 2.0 Hz, 1H), 7.02 (dd, J = 8.5, 2.0 Hz, 1H), 6.93 (s, 2H), 6.91–6.87 (m, 3H), 4.20–4.06 (m, 6H), 1.52–1.43 (m, 9H);**^{13}C NMR (125 MHz, $CDCl_3$)** δ, ppm: 158.42, 148.85, 148.40, 130.90, 130.28, 127.43, 126.41, 126.35, 119.61, 114.67, 113.47, 111.04, 64.61, 63.49, 14.91, 14.87.**ESI-MS:** 312.40 ($[M+H]^+$).

*4.1.5.9. (E)-1,2-Dimethoxy-4-(4-methoxystyryl)benzene (trans-3,4,4′-trimethoxystilbene) (**SB 8c**)*. White solid, yield: 87%, m.p. 136–138 °C (lit. 136–138 °C [32]).**IR (cm^{-1}):** 3043 (C_{sp2}-H stretching), 2973, 2931 and 2838 (C_{sp3}-H stretching), 1602 and 1509 (aromatic C=C stretching), 1237 (aromatic C−O stretching), 1023 (saturated C−O stretching), 969 (C_{sp2}-H_{trans} bending); **^{1}H NMR (500 MHz, $CDCl_3$)** δ, ppm: 7.36 (d, J = 8.0 Hz, 2H), 6.98–6.95 (m, 2H), 6.86 (s, 2H), 6.82 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.0 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.76 (s, 3H);**^{13}C NMR (125 MHz, $CDCl_3$)** δ, ppm: 159.08, 149.12, 148.64, 130.83, 130.35, 127.46, 126.42, 119.52, 114.14, 111.26, 108.59, 55.97, 55.88, 55.34.**ESI-MS:** 284.35 ($[M+H]^+$).

*4.1.5.10. (E)-4-(4-Ethoxystyryl)-1,2-dimethoxybenzene (trans-3,4-diethoxy-4′-methoxystilbene) (**SB 8d**)*. White solid, yield: 92%, m.p. 142–144 °C.**IR (cm^{-1}):** 3051 (C_{sp2}-H stretching), 2983, 2933 and 2840 (C_{sp3}-H stretching), 1600 and 1510 (aromatic C=C stretching), 1235 (aromatic C−O stretching), 1041 (saturated C−O stretching), 964 (C_{sp2}-H_{trans} bending); **^{1}H NMR (500 MHz, $CDCl_3$)** δ, ppm: 7.44 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 2.0 Hz, 1H), 7.05 (dd, J = 8.5, 2.0 Hz, 1H), 6.95 (s, 2H), 6.91 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 8.5 Hz, 1H), 4.08 (q, J = 7.0 Hz, 2H), 3.97 (s, 3H), 3.92 (s, 3H), 1.45 (t, J = 7.0 Hz, 3H);**^{13}C NMR (125 MHz, $CDCl_3$)** δ, ppm: 158.46, 149.10, 148.60, 130.86, 130.19, 127.46, 126.48, 126.30, 119.50, 114.69, 113.47, 111.26, 108.57, 63.50, 55.96, 55.87, 14.87.**ESI-MS:** 270.32 ($[M+H]^+$).

*4.1.6. General procedure for synthesis of compounds, **SB 4b, SB 6b, SB 8b, SB 8e***

Compound **SB 8b** was synthesized from **SB 8a** via poly *O*-dealkylation. **SB 8a** (1.50 g, 4.8 mmol) and N,N-dimethylaniline (30 mL) were stirred at 100 °C. Anhydrous $AlCl_3$ (3.0 equiv.) was slowly added into the mixture and heated at 180 °C for 5 h. Then, the resultant mixture was quenched with ice water followed by the step-wise addition of 37% HCl until the colour of the mixture turned to brownish-orange colour. The mixture was then extracted by using ethyl acetate and then the excess solvent was evaporated off. The crude product was washed with chloroform to yield the desired compound **SB 8b** as off-white solid. **SB 4b**, **SB 6b**, **SB 8e** were synthesized from **SB 4a**, **SB 6a**, **SB 8a** according to the describe method.

*4.1.6.1. (E)-3-(4-Hydroxystyryl)benzene-1,2-diol (trans-2,3,4′-trihydoxystilbene) (**SB 4b**)*. Off-white solid, yield: 65%, m.p. 216–218 °C.**IR (cm^{-1}):** 3265 (O−H stretching), 1595 and 1506 (aromatic C=C stretching), 1224 (aromatic C−O stretching), 965 (C_{sp2}-H_{trans} bending); **^{1}H NMR (500 MHz, DMSO-d_6)** δ, ppm: 7.36 (d, J = 8.0 Hz, 2H), 7.20 (d, J_{trans} = 16.5 Hz, 1H), 7.05–6.99 (m, 2H), 6.76 (d, J = 8.0 Hz, 2H), 6.67–6.60 (m, 2H); **^{13}C NMR (125 MHz, DMSO-d_6)** δ, ppm: 157.37, 145.86, 143.33, 129.27, 128.13, 127.98, 125.35, 121.01, 119.5, 116.85, 116.03, 114.22.**ESI-MS:** 228.24 ($[M+H]^+$).

*4.1.6.2. (E)-2-(4-Hydroxystyryl)benzene-1,4-diol (trans-2,5,4′-trihydoxystilbene) (**SB 6b**)*. Off-white solid, yield: 56%, m.p. 215–216 °C.**IR (cm^{-1}):** 3280 (O−H stretching), 1599 and 1509 (aromatic C=C stretching), 1222 (aromatic C−O stretching), 964 (C_{sp2}-H_{trans} bending); **^{1}H NMR (500 MHz, DMSO-d_6)** δ, ppm: 9.55 (s, 1H), 8.95 (s, 1H), 8.72 (s, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.13 (d, J_{trans} = 16.5 Hz, 1H), 6.96 (d, J_{trans} = 16.0 Hz, 1H), 6.90 (d, J = 3.0 Hz, 1H), 6.76 (d, J = 8.5 Hz, 2H), 6.65 (d, J = 8.5 Hz, 1H), 6.49 (dd, J = 8.5, 2.5 Hz, 1H); **^{13}C NMR (125 MHz, DMSO-d_6)** δ, ppm: 157.42, 150.41, 147.89, 129.21, 128.02, 127.89, 125.10, 120.99, 116.91, 116.02, 115.54, 111.94. **ESI-MS:** 228.24 ($[M+H]^+$).

*4.1.6.3. (E)-4-(4-Hydroxystyryl)benzene-1,2-diol (trans-3,4,4′-trihydoxystilbene) (**SB 8b**)*. Off-white solid, yield: 67%, m.p. 241–243 °C (lit. 242–243 °C [34]). **IR (cm^{-1}):** 3338 (O−H stretching), 1596 and 1519 (aromatic C=C stretching), 1228 (aromatic C−O stretching), 961 (C_{sp2}-H_{trans} bending); **^{1}H NMR (500 MHz, DMSO-d_6)** δ, ppm: 9.49 (s, 1H), 9.01 (s, 1H), 8.91 (s, 1H), 7.35 (d, J = 8.5 Hz, 2H), 6.93 (d, J = 2.0 Hz, 1H), 6.80 (m, 3H), 6.74 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 8.0 Hz, 1H);**^{13}C NMR (125 MHz, DMSO-d_6)** δ, ppm: 157.18, 145.82, 145.47, 129.64, 129.06, 127.80, 126.04, 125.55, 118.5, 116.17, 115.94, 113.41. **ESI-MS:** 228.24 ($[M+H]^+$).

*4.1.6.4. (E)-4,4′-(Ethene-1,2-diyl)benzene-1,2-diol) (trans-3,4,3′,4′-tetrahydoxystilbene) (**SB 8e**)*. Purple solid, yield: 70%, m.p. 208–210 °C (lit. 211–212 °C [35]). **IR (cm^{-1}):** 3309 (O−H stretching), 1603 and 1513 (aromatic C=C stretching), 1273 (aromatic C−O stretching), 958 (C_{sp2}-H_{trans} bending); **^{1}H NMR (500 MHz, DMSO-d_6)** δ, ppm: 9.00 (s, 1H), 8.88 (s, 1H), 6.92 (s, 2H), 6.79 (d, J = 8.0 Hz, 2H), 6.80 (m, 4H);**^{13}C NMR (125 MHz, DMSO-d_6)** δ, ppm: 145.82, 145.44, 129.61, 125.9, 118.49, 116.14, 113.39. **ESI-MS:** 244.24 ($[M+H]^+$).

4.2. In vitro aortic rings assay

4.2.1. Materials

Acetylcholine (Ach) and phenylephrine (PE) were acquired from Acros Organics (Belgium). Both the Ach and PE were diluted with distilled water into 0.1 mM as stock solutions. The synthesized stibenoid derivatives, **SB 1-8e** were dissolved in 1% of Tween 80 and no precipitation was observed. All the chemicals were stored in freezer (Pensonic, PFZ-230) at −20 °C for future use.

4.2.2. Animals

Sprague Dawley (SD) rats of 8–12 weeks old (around 180–240 g) were acclimated in the animal transit house for 12-h light-dark cycles with the access to water and food pellet. Animals were cared according to the laid down rules by Animal Research and Service Centre (ARASC), Universiti Sains Malaysia. The experiments were conducted based on the Guideline of Universiti Sains Malaysia Institutional Animal Care and Use Committee (USM IACUC) with animal ethics approval: USM/IACUC/2019/(120)(1026).

4.2.3. Aortic rings preparation and validity confirmation

Krebs-Henseleit (K-H) solution was freshly prepared by dissolving 118.0 mM NaCl, 4.7 mM KCl, 25.0 mM $NaHCO_3$, 2.5 mM $CaCl_2$, 11.0 mM D-glucose, 1.2 mM KH_2PO_4 and 1.2 mM $MgSO_4$ in distilled water at pH 7.4. Then, SD rat was sacrificed by overdose inhalation of CO_2 for two minutes. The thoracic aorta was isolated immediately and placed in the petri dish containing the K-H solution continuously aerated with carbogen (5% CO_2 and 95% O_2) with the temperature maintained at 37 °C. After the removal of the adipose tissue, and the aorta was trimmed into 3–4 mm ring segments. The aortic ring was mounted in the 37 °C maintained and carbogen supplied organ bath filled with 10 mL of K-H solution by using two needle hooks with one side of the needle hook connected to force-electricity transducer (GRASS Force-Displacement Transducer FT03C Isometric Measurement), and the other side was fixed on the L-shaped braces. The mounted aortic rings were left for equilibrating for 45 min. The K-H solution of the organ bath was changed at 15-minutes intervals. The resting tension was readjusted to 1.0 g if necessary. Once stabilized, the contractile and relaxing integrity of the aortic rings were examined using PE (1 μM) and Ach (1 μM), respectively. At least 60% of vascular response was achieved to confirm the validity of the aortic rings. Aortic rings were rinsed three times with the K-H solution at 15-minute intervals prior to the PE pre-contraction procedure [29,36]. The vascular response towards each synthesized stilbenoid derivative was evaluated in four replicates (n = 4).

4.2.4. Vascular reactivity study

The endothelium-intact aortic rings were used to examine the vascular responds of the synthesized stilbenoid derivatives **SB1-8e**. PE (1 μM) was added into the organ bath for pre-contraction and left for at least 30 min until the plateau stage. Subsequently, 100 μl of the stilbenoid derivative (8 mg/ml) was added into the organ bath respectively and left for 20 min, the final concentration of each compound in the organ bath was 0.08 mg/ml. The vascular response was detected by the force-electricity transducer and amplified by the Quad Bridge Amp (AD instrument, Australia) with the digital signal was converted by powerLab 26T (AD instrument, Australia). The maximum relaxation (R_{max}) of each stilbenoid derivatives was recorded. The data were expressed as mean ± S.E.M.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2020.104239.

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