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Dihydrostilbenes and diarylpropanes: Synthesis and in vitro pharmacological evaluation as potent nitric oxide production inhibition agents

Ha Young Jang [a,†], Hyeong Jin Park [a,†], Kongara Damodar [a], Jin-Kyung Kim [b], Jong-Gab Jun [a,*]

[a] Department of Chemistry and Institute of Applied Chemistry, Hallym University, Chuncheon 24252, South Korea
[b] Department of Biomedical Science, College of Natural Science, Catholic University of Daegu, Gyeungsan-Si 38430, South Korea

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ABSTRACT

An efficient synthesis of dihydrostilbenes (**1**–**5**) and diarylpropanes (**6**–**10**) is achieved from the commercially available starting materials and Wittig-Horner reaction, Claisen–Schmidt condensation and hydrogenation as key steps. Later, their nitric oxide (NO) production inhibition effects were evaluated in lipopolysaccharide (LPS)-induced RAW-264.7 macrophages as an indicator of *anti*-inflammatory activity. All the tested compounds significantly decreased NO production in a concentration-dependent manner except compounds **2**, **6** and **8** and did not show notable cytotoxicity except compound **1**. Two compounds i.e., compound **9** (hindsiipropane B) (100%; IC_{50} = 1.84 μM) possessed the most potent NO inhibitory activity which was even stronger than the positive control, L-NMMA (90.1%; IC_{50} = 2.73 μM) followed by compound **4** (75.5%; IC_{50} = 2.98 μM) at 10 μM concentration and this finding was also further correlated by suppressed expression of LPS stimulated inducible NO synthase. Our study revealed that compound **9**, a 1,3-diarylpropane scaffold with 3″,4″-dimethoxyphenyl and 3′,4′-dihydroxy-2′-methoxyphenyl motifs could be considered as potential compound or lead compound for further development of NO production-targeted *anti*-inflammatory agents.

Inflammation is a cellular defense mechanism of the host organism that protects cells from pathogens.[1] Swelling, redness of the area, pain, and sometimes loss of function are the symptoms of inflammation.[2] The mechanism of inflammation can be chiefly categorized as arachidonic acid (AA)-dependent and AA-independent pathways.[2] In the first one, phospholipase A2 (PLA2), cyclooxygenase (COX-1, -2, -3) and lipoxygenase (5-LOX, 8-, 12-, 15-) enzyme families and proinflammatory prostaglandins (PGs) produced via the COX pathway, and leukotrienes (LTs) produced via the LOX pathway are involved. The second mechanism of inflammation involves nitric oxide synthase (endothelial-NOS, neuronal-NOS and inducible-NOS), nuclear factor-*k*B (NF-*k*B), and peroxisome proliferator activated receptor (PPAR).

NOS produces nitric oxide (NO) from L-arginine, a small and transient free-radical species with multifaceted role in human physiology and pathophysiology.[3] The role of NO in the pathogenesis of inflammation generally depends upon its concentration.[4] Physiologically vital amounts of NO produced by inducible-NOS (iNOS) in response to inflammatory stimuli help in mounting an effective defense against pathogens, whereas, excess NO production by iNOS can cause inflammation, asthma, diabetes, stroke, cancer and neurodegenerative disorders.[5] Hence, pharmacological interference with the NO production cascade is claimed as a promising strategy of many of the therapeutic intervention in inflammatory diseases.

Stilbenoids (stilbenes, dihydrostilbenes, phenanthrenes and their oligomers) are portrayed by a 1,2-diphenylethane scaffold and biosynthetically they are closely related to the flavonoids. Particularly, dihydrostilbenes (1,2-diarylethanes or bibenzyls) are important subclass of phytochemicals in view of their noteworthy pharmacological effects such as *anti*-inflammatory,[6] antifungal,[7] antibacterial,[8] antioxidant,[9] and anticancer.[10] Some compounds also exhibit tubulin polymerization inhibition activity.[10]

1,3-Diarylpropanes, homologues to dihydrostilbenes and a subclass of flavonoids (C6–C3–C6 unit) are also an important secondary metabolites of plants and exhibit diverse biological activities *viz.* antifungal,[11] *anti*-inflammatory,[12] anticancer,[13] antiadipogenic,[14] antitubercular,[13a] and antimalarial,[15] to name a few. 1,3-Diarylpropanes attached with anthranilic acid were also investigated as β-amyloid aggregation inhibitors in Alzheimer's

* Corresponding author. Tel.: +82 33 248 2075; fax: +82 33 256 3421.
E-mail address: jgjun@hallym.ac.kr (J.-G. Jun).
† Contributed equally to this work.

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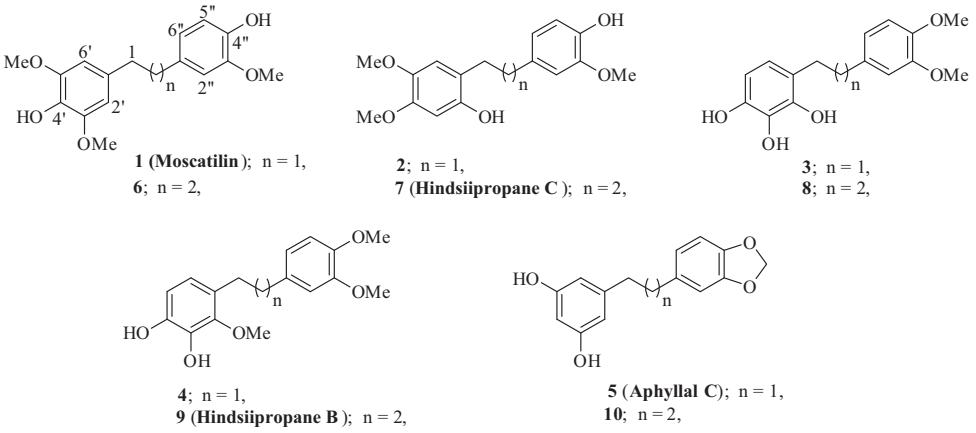
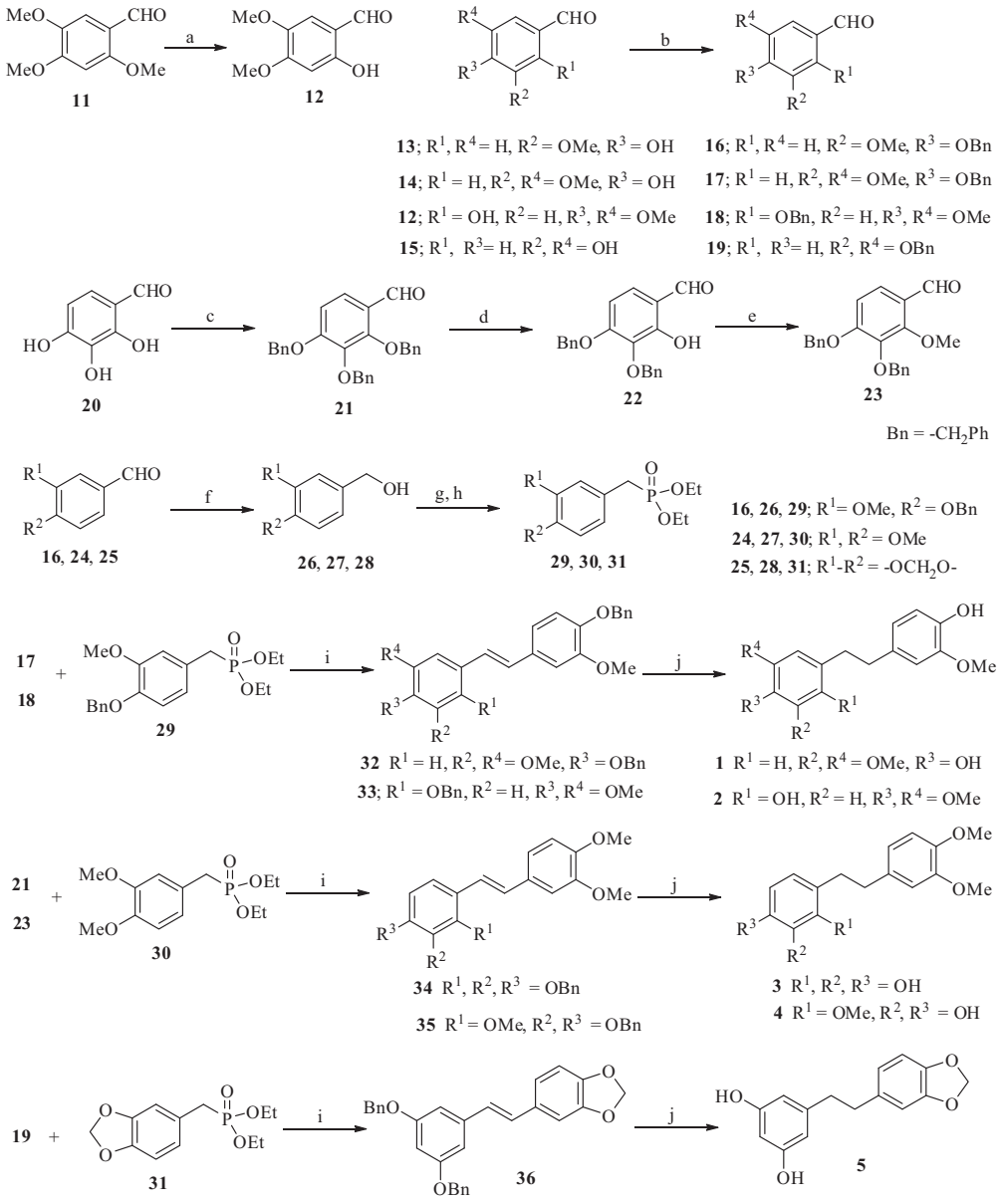
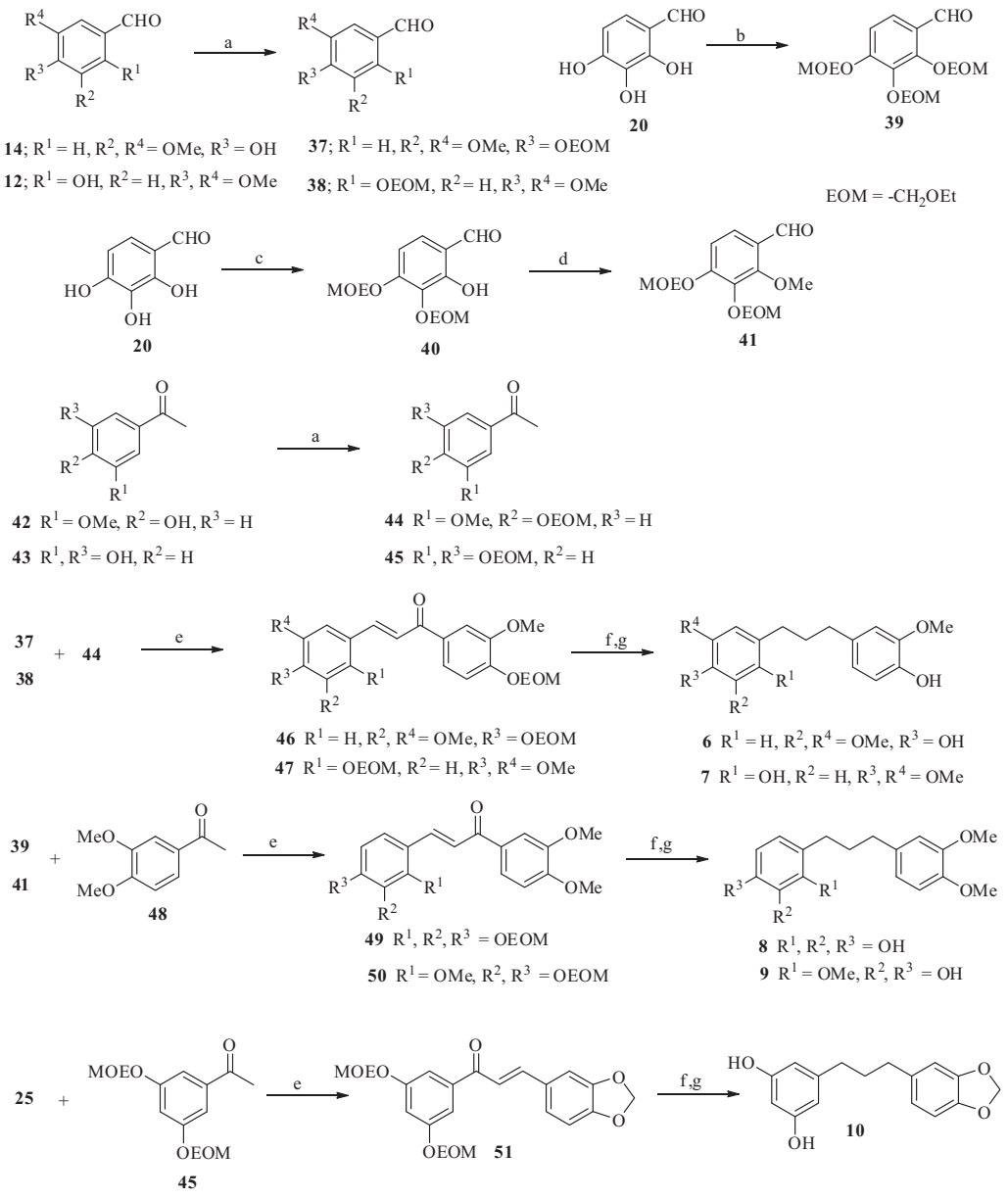


Figure 1. Structures of dihydrostilbenes (**1**–**5**) and diarylpropanes (**6**–**10**).



Scheme 1. Reagents and conditions. (a) 1.0 M BCl_3 (in CH_2Cl_2), CH_2Cl_2, −78 °C-rt, 3 h, 98%; (b) benzyl bromide, K_2CO_3, acetone, 0–40 °C, 12 h, 81–90%; (c) benzyl bromide, Cs_2CO_3, DMF, 0–80 °C, 21 h, 91%; (d) $MgBr_2{\cdot}Et_2O$, ether, rt, 14 h, 71%; (e) MeI, K_2CO_3, DMF, rt, 3 h, 98%; (f) $NaBH_4$, MeOH, 0 °C-rt, 30 min, 91–98%; g) phosphorus tribromide, CH_2Cl_2, 0 °C, 1 h; (h) triethyl phosphite, xylene, reflux, 10 h, 89–96% (over 2 steps); (i) NaH, THF, 0 °C-rt, 12 h, 75–92%; (j) triethylsilane (excess), 10% Pd/C, MeOH, rt, 20 min, 75–96%.



Scheme 2. Reagents and conditions. (a) chloromethyl ethyl ether, K_2CO_3, tetrabutylammonium iodide, DMF, rt, 12 h, 41–86%; (b) chloromethyl ethyl ether, NaH, DMF, 0–40 °C, 12 h, 85%; (c) chloromethyl ethyl ether, *N*,*N*-diisopropylethylamine, CH_2Cl_2, 40 °C, 12 h, 63%; (d) methyl iodide, NaH, DMF, rt, 3 h, 89%; (e) KOH, MeOH/H_2O (2/1), rt, 8 h, 76–94%; (f) 6 N HCl, MeOH, rt, 1 h; (g) H_2 (balloon), Pd/C, acetic acid, rt, 48 h, 43–62% (over 2 steps).

disease.[16] Owing to their wide range of bioactivities, dihydrostilbenes and 1,3-diarylpropanes have become of great interest to many research groups in chemistry, biomedicine as well as those in agricultural and food chemistry.

In continuation of our work[17] on the synthesis of bioactive natural products and their analogues as potential NO inhibitors, herein we report an efficient synthesis and in vitro *anti*-inflammatory activity evaluation of dihydrostilbenes (**1**–**5**) and 1,3-diarylpropanes (**6**–**10**) (Fig. 1). In this, **1** (moscatilin) and **5** (aphyllal C) are natural dihydrostilbenes, isolated from *Dendrobium moscatum* and *Dendrobium aphyllum*, respectively.[18] In **6**–**10**, compounds **6**, **7** (hindsiipropane C) and **9** (hindsiipropane B) are natural 1,3-diarylpropanes in which **6** isolated from *Phacellaria compressa* Benth and the last two (**7** & **9**) isolated from *Celastrus hindsii*, respectively.[19] Remaining compounds **2**–**4**, **8** and **10** are synthetic compounds.

First, our efforts for the synthesis of dihydrostilbenes (**1**–**5**) commenced with the selective demethylation of 2,4,5-trimethoxybenzaldehyde (**11**) using boron trichloride (Scheme 1). The resulting aldehyde **12** along with vanillin (**13**), syringaldehyde (**14**) and 3,5-dihydroxybenzaldehyde (**15**) were protected using benzyl bromide and K_2CO_3 in acetone to furnish aldehydes **16**–**19**, respectively. 2,3,4-Trihydroxybenzaldehyde (**20**) was treated with benzyl bromide and Cs_2CO_3 in *N*,*N*-dimethylformamide (DMF) and the resulting 2,3,4-tris(benzyloxy)benzaldehyde (**21**) was underwent selective debenzylation using magnesium bromide diethyl etherate ($MgBr_2{\cdot}Et_2O$) to yield substituted salicylaldehyde **22** which upon methylation gave the aldehyde **23**. Next, aldehyde **16**, 3 4-dimethoxybenzaldehyde (**24**) and piperonal (**25**) were reduced with sodium borohydride ($NaBH_4$) and the resulting benzyl alcohols **26**–**28** were converted into corresponding Wittig-Horner reagents **29**–**31**, respectively by a two-step synthetic sequence. Next, Wittig-Horner reaction[20] between **29** and **31** and aldehydes **17**, **18**, **21**, **23** and **19** was executed with sodium hydride (NaH) as a base and the corresponding stilbenes **32**–**36** were obtained in good to high yields, respectively. Finally, debenzylation

Table 1
Anti-inflammatory activities of dihydrostilbenes (**1**–**5**) and diarylpropanes (**6**–**10**)

Compound	NO production (% inhibition)	
	1 μM	10 μM
Medium(MED)	1.2 ± 0.7 (98.8)***	1.2 ± 0.7 (98.8)***
LPS	100.0 ± 7.4 (0.0)	100.0 ± 7.4 (0.0)
1	92.6 ± 19.6 (7.4)	**21.6 ± 5.2 (78.4)****
2	64.8 ± 2.7 (35.2)	70.5 ± 3.9 (29.5)
3	57.3 ± 6.8 (42.7)	53.0 ± 1.4 (47.0)
4	75.7 ± 9.7 (24.3)	**24.5 ± 5.8 (75.5)****
5	83.0 ± 22.3 (17.0)	71.7 ± 11.6 (28.3)
6	72.8 ± 8.1 (27.2)	78.2 ± 3.4 (21.8)
7	61.8 ± 8.4 (38.2)	43.5 ± 1.1 (56.5)
8	70.4 ± 20.5 (29.6)	71.4 ± 12.0 (28.6)
9	63.1 ± 8.6 (36.9)	**0.0 ± 0.0 (100.0)****
10	59.2 ± 2.1 (40.8)	46.4 ± 8.3 (53.6)
L-NMMA	85.0 ± 4.4 (15.0)	9.9 ± 2.7 (90.1)***

The results are reported as mean value ± SEM for $n = 3$. Statistical significance is based on the difference when compared with LPS-treated groups (***$P < 0.001$).
% Inhibition is based on LPS as shown in parenthesis.

and olefinic bond reduction of stilbenes **32**–**36** were achieved in one step using excess triethylsilane (12–15 equiv) and Pd/C system[21] in a very short reaction time (20 min) to furnish the desired dihydrostilbenes **1**–**5** in good yields, respectively.

Next, we envisioned that the synthesis 1,3-diarylpropanes **6**–**10** could be achieved from their corresponding chalcone derivatives. Accordingly, the synthesis began with ethoxymethyl- (EOM-) protection of phenolic aldehydes **12** and **14** using chloromethyl ethyl ether (EOM-Cl), K_2CO_3 and catalytic tetrabutylammonium iodide (TBAI) in anhydrous DMF (Scheme 2).

Selective protection of aldehyde **20** was achieved with *N*,*N*-diisopropylethylamine (DIPEA) to give di-EOM protected aldehyde **40**, which upon methylation yielded compound **41**, however, protection of **20** using NaH instead of DIPEA as base produced all-protected **39** without selectivity. 3-Methoxy-4-hydroxyacetophenone (**42**) and 3,5-dihydroxyacetophene (**43**) were also protected with EOM-group by treating with EOM-Cl, K_2CO_3 and TBAI system. Next, Claisen–Schmidt condensation between acetophenones **44**, **48**, **45** and aldehydes **37**, **38**, **39**, **41**, **25** in the presence of KOH as base in MeOH/H_2O (2/1) at room temperature afforded the EOM-protected chalcones **46**–**51**, respectively. Finally, deprotection of EOM- group using 6 N HCl followed by complete enone group reduction of **46**–**51** under hydrogen atmosphere furnished the desired 1,3-diarylpropanes **6**–**10**, respectively. The structures of the final compounds **1**–**10** were settled from their spectral (^{1}H & ^{13}CNMR and MS) data.

In order to evaluate the anti-inflammatory effects of the prepared dihydrostilbenes (**1**–**5**) and 1,3-diarylpropanes (**6**–**10**), we measured the amount of nitric oxide (NO) which is one of the essential mediators on inflammation induced by lipopolysaccharide (LPS) in macrophage-derived RAW 264.7 cells.[22] In fact, it is difficult to quantify NO intrinsically in view of its short half-life and existence of other scavenging molecules. Hence, measurement of its accumulated stable degradation products nitrite (NO_2^-) and nitrate (NO_3^-) is preferred and the Griess reagent is employed for this combined (nitrite + nitrate) measurement.

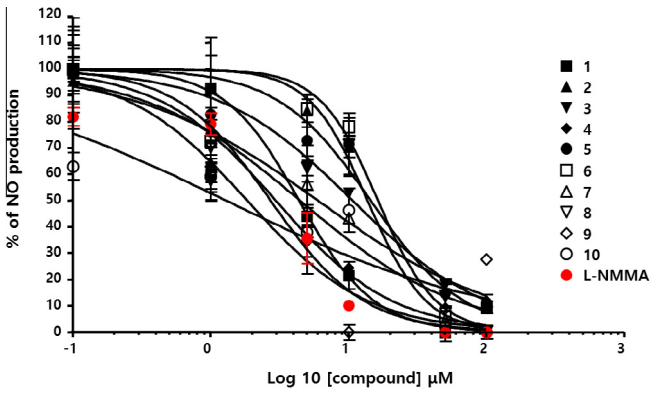


Figure 2. Inhibition of iNOS mediated NO production by compounds **1**–**10**.

Anti-inflammatory activity: Effects of compounds **1**–**10** on NO generation by induced macrophages was monitored (Table 1). Lipopolysaccharide (LPS) treated RAW 264.7 has been used to stimulate the production of NO through the activation of iNOS and N^G-monomethyl-L-arginine acetate (L-NMMA)[23] was employed as positive control. Though, NO inhibition activity conducted at 0.1, 1, 5, 10, 50 and 100 μM concentrations, significant activity changes were observed at 1–10 μM. At 50 and 100 μM concentrations, all compounds exhibited same level activity (more than 80% NO inhibition by each compound) (Fig. 2). Hence, we discussed the activity at 1 and 10 μM concentrations only. At these concentrations, all the tested compounds decreased NO production in a concentration-dependent manner except compounds **2**, **6** and **8**. The percentage of NO production inhibition ranged from 100.0% to 21.8% and from 42.7% to 7.4% at the highest (10 μM) and lowest (1 μM) concentrations, respectively. Of the 10 compounds (**1**–**10**) prepared in the present study, 3 compounds i.e., **9** (hindsiipropane B) (100.0%), followed by **1** (78.4%) and **4** (75.5%) showed the strongest inhibitory activities at 10 μM (Table 1 and Fig. 2).

Next, the activated RAW 264.7 cell viability was carried out at 1–100 μM concentrations to ensure that cell death was not responsible for the decreased NO expression in compound (**1**–**10**)-treated group by the MTT cell viability assay (Table 2). Except compound **1** (moscatilin), all the compounds did not had significant cytotoxicity at 10 μM concentration which leading to effective inhibition of NO production. At 50 μM concentration also similar results observed, whereas at 100 μM concentration, in addition to compound **1**, compounds **8**–**10** also displayed cytotoxicity. IC_{50} values of compounds **1**–**10** were evaluated by using GraphPad Prism 4.0 software and showed 4.40, 13.77, 6.02, 2.98, 14.53, 16.4, 4.46, 10.72, 1.84 and 1.30 μM, respectively (Table 2). Although compound **1** had good inhibition of NO production (78.4%) at 10 μM concentration with an IC_{50} value of 4.40 μM, its inhibitory effect seems to be more likely related to its cytotoxic effect towards the RAW 264.7 cells (only 52.9% cell viability at 10 μM). These results indicate that **9** (hindsiipropane B) possessed the most potent NO inhibition activity with an IC_{50} value of 1.84 μM which is even better than the positive control L-NMMA (IC_{50} 2.73). Next, compound **4** had a little weaker activity than L-NMMA with an IC_{50} value of 2.98 μM. This findings were also in accordance with the previous literature reports,[24] wherein, compound **1** and analogues of compound **5** were reported as poor NO inhibitors. To understand the underlying molecular mechanisms by which compounds **1**–**10** reduces LPS-induced NO production, we further studied the effect of **1**–**10** on iNOS protein expression in RAW 264.7 cells using Western blot analysis. As shown in Figure 3, the results were consistent with the findings related to NO production (Table 1 and Fig. 2), the protein expression of iNOS induced by LPS in RAW 264.7 cells was dramatically suppressed by compound **9** (hindsiipropane B) treatment. This indicates that the reduced expression of iNOS due to these compounds exposure was responsible for the inhibition of NO production.

From the aforementioned pharmacological results, some structural features that might have influenced the NO inhibitory activity can be drawn from the comparison of the chemical structures of the compounds **1**–**10**. (i) Compounds (**9** and **4**) bearing 3″,4″-dimethoxyphenyl and 3′,4′-dihydroxy-2′-methoxyphenyl moieties, were fruitful to show potent NO inhibition with no

Table 2
Proliferation effect of dihydrostilbenes (**1**–**5**) and diarylpropanes (**6**–**10**)

Compound	Proliferation effect[a]				IC_{50} (μM)
	1 μM	10 μM	50 μM	100 μM	
Medium(MED)	100.0 ± 4.8	100.0 ± 4.8	100.0 ± 7.9	100.0 ± 7.9	
1	143.4 ± 6.0**	52.9 ± 4.5**	47.0 ± 0.8***	59.6 ± 8.4*	4.40
2	119.9 ± 4.2	123.6 ± 13.8	128.3 ± 17.6	132.9 ± 25.1	13.77
3	113.9 ± 17.8	114.4 ± 3.7	128.2 ± 9.7	133.2 ± 8.0	6.02
4	105.7 ± 3.8	99.9 ± 4.3	94.8 ± 10.2	81.9 ± 3.0	**2.98**
5	96.8 ± 4.4	90.8 ± 1.8	82.7 ± 1.6	78.9 ± 2.4	14.53
6	98.4 ± 2.9	98.7 ± 1.9	88.7 ± 1.5	82.0 ± 4.8	16.40
7	135.2 ± 8.5**	112.6 ± 6.6	88.4 ± 3.9	80.9 ± 3.1	4.46
8	110.5 ± 1.8	130.3 ± 7.2	86.4 ± 1.6	73.2 ± 2.1*	10.72
9	117.9 ± 4.6	103.1 ± 7.7	86.3 ± 3.1	61.9 ± 3.1**	**1.84**
10	115.9 ± 1.2	102.2 ± 8.3	86.7 ± 2.4	70.4 ± 2.7*	1.30
L-NMMA	100.1 ± 3.1	100.3 ± 2.1	113.3 ± 5.4	97.2 ± 7.2	2.73

[a] The results are reported as mean value ± SEM for $n = 3$ (*$P < 0.05$, **$P < 0.01$ ***$P < 0.001$).

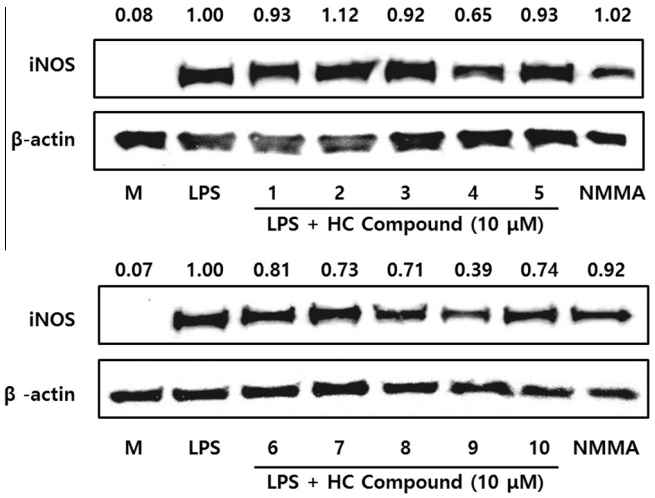


Figure 3. Effects of compounds **1**–**10** on iNOS expression (Western blot).

cytotoxicity; (ii) two aryl moieties linked by a three carbon chain (compound **9**) is more effective than two (compound **4**). Therefore, **9** (hindsiipropane B) could be considered as potential compound or lead compound for development of NO production-targeted anti-inflammatory agents.

In conclusion, we have described an efficient synthesis of dihydrostilbenes (**1**–**5**) and diarylpropanes (**6**–**10**) from the commercially available starting materials and Wittig-Horner reaction, Claisen–Schmidt condensation and hydrogenation as key steps. Next, their NO production inhibition effects were evaluated in LPS-induced RAW-264.7 macrophages as an indicator anti-inflammatory activity. Except compounds **2**, **6** and **8**, all the tested compounds significantly decreased NO production in a concentration-dependent manner and did not had marked cytotoxicity except compound **1**. In this study, two compounds i.e., compound **9** (hindsiipropane B) (100%; $IC_{50} = 1.84$ μM) possessed the most potent NO inhibitory activity which was even stronger than the positive control, L-NMMA (90.1%; $IC_{50} = 2.73$ μM) followed by compound **4** (75.5%; $IC_{50} = 2.98$ μM) which was slightly lower than L-NMMA. This finding was further correlated with the suppressed expression of iNOS induced by LPS. Our study suggested that compound **9**, holding a 1,3-diarylpropane scaffold with 3″,4″-dimethoxyphenyl and 3′,4′-dihydroxy-2′-methoxyphenyl motifs could be considered as potential compound or lead compound for further development of a NO production-targeted anti-inflammatory agents.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2016.10.034.

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