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Structural elucidation, bio-inspired synthesis, and biological activities of cyclic diarylpropanes from *Horsfieldia kingii*

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ABSTRACT

Bioactivity-guided phytochemical investigation on 70% aqueous acetone extracts of the twigs and leaves of *Horsfieldia kingii* led to the isolation of two novel cyclic diarylpropanes (**1** and **2**) bearing a 2,3-dihydro-1*H*-indene core, one new diarylpropane (**3**), six known diarylpropanes (**4**–**9**), one flavanol (**10**), and seven lignans (**11**–**17**). Their structures were determined by extensive spectroscopic analysis, electronic circular dichroism calculations, and X-ray diffraction crystallography. Moreover, a biomimetic synthesis of **1** and **2** were accomplished in four steps. The *in vitro* nitric oxide production inhibition tests of these compounds revealed that compounds (±)-**2**, (+)-**2**, (−)-**2**, and **10** were potential with IC_{50} values lower than 10 μM. Compound **2** could inhibit iNOS expression in LPS-induced RAW264.7 cells at a series of non-cytotoxic concentrations (<20 μM). Furthermore, the bioassay results also suggested the primary SARs of 1-phenyl-2,3-dihydro-1*H*-indene based scaffold.

1. Introduction

Horsfieldia is an important genus of *Myristicaceae*, accounting for ~11% of species in the family [1]. Species of *Horsfieldia* have been used as folk medicines to treat kinds of inflammation related diseases, such as pains and infections, for a long history in South Asia [2–5]. Previous studies on the chemical components of *Horsfieldia* have proved the genus to be plenty of flavonoids [6–14] along with less other compounds [3,15–17]. Among the reported flavonoids, diarylpropanes (DAPs) [10–14] or called reduced chalcones usually possess a linear C6–C3–C6 skeleton representing a rare class of flavonoids and taking a comparable percentage. However, compounds isolated from *Horsfieldia* genus were poorly documented with their bioactivity profiles, especially the relative anti-inflammatory activity of the genus for folk use.

H. kingii is an importantly economic and ethnopharmacological plant in South Asia, and has been cultivated in subtropical area of Yunnan. Previous investigations on the non-oil parts of *H. Kingii* resulted in seven DAPs without cytotoxicity against many cancer cell lines [10–12,14]. Given that the folk use of *Horsfieldia* genus depended on its anti-inflammatory effects, and invoked by our continuous interests of exploring the fundamental substances of these ethno-pharmacological resources, the anti-inflammatory activity guided phytochemical investigations were carried out in this work. As a result, three new DAPs, horsfielenides C-E (**1**–**3**) along with 14 known ones (**4**–**17**) were isolated from the active fractions. To our interest, compounds **1** and **2** possess a 2,3-dihydro-1*H*-indene core representing a new type of natural diarylpropane. Herein, the isolation, structural elucidation, bio-inspired synthesis of **1** and **2**, NO production inhibitory activity evaluation of **1**–**17**, and inhibitory effect of **2** on iNOS expression in LPS-induced RAW264.7 cells are reported.

2. Results and discussion

A 70% aqueous acetone extracts of the air-dried and powdered twigs and leaves of *H. kingii* were partitioned between EtOAc and H_2O. The resulting EtOAc portion was then subjected to column chromatography (silica gel) eluting with petroleum ether/acetone to obtain fractions A-D. Fractions C and D with apparent NO production inhibitory activities (Table S1, supplementary material) were further performed on column chromatography (silica gel, MCI

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CHP-20 gel, Sephadex LH-20, and preparative TLC), leading to the isolation of two new cyclic diarylpropanes, horsfielenides C-D (**1**–**2**), a new diarylpropane, horsfielenide E (**3**), and 14 known compounds (**4**–**17**) (Fig. 1).

Horsfielenide C (**1**) was obtained as a brown oil. The molecular formula of **1** was assigned as $C_{15}H_{14}O_3$ by HREIMS (*m*/*z* 242.0949, $[M]^+$, cacld 242.0943) with 9° of unsaturation. The ^1H NMR data (Table 1) suggested a symmetric benzene ring [δ_H 6.94 (2H, d, J = 8.6 Hz, H-2″, 6″), 6.70 (2H, d, J = 8.6 Hz, H-3″, 5″)] and two singlet aromatic protons [δ_H 6.69 (1H, s, H-2′), 6.31 (1H, s, H-5′)]. ^{13}C NMR spectra (Table 1) showed 15 carbon signals, including 12 aromatic carbons (three were substituted with hydroxy groups, δ_C = 156.4, 145.4, and 144.8, respectively), and other three sp^3-hybridized carbons which belonged to one methine (δ_C 51.9) and two methylenes (δ_C 32.2 and 38.4). The ^1H–^1H COSY spectrum disclosed cross signals for two fragments, $CH_2(1)$–$CH_2(2)$–CH(3) and CH(2″)–CH(3″) (Fig. 2). The HMBC correlations from H-1 (δ_H 2.81, 2.70) to C-2' (δ_C 112.3), and from H-2' (δ_H 6.69)/H-5' (δ_H 6.31) to C-3' (δ_C 145.4)/C-4' (δ_C 144.8) indicated that the 3,4-dihydroxyphenyl moiety was linked to C-1. In addition, the HMBC correlations from H-3 (δ_H 4.05) to C-1″ (δ_C 138.5)/C-2″ (δ_C 129.9), and from H-2″ (δ_H 6.94) to C-4″(δ_C 156.4) suggested that the 4-hydroxyphenyl group was placed at C-3. Moreover, the HMBC correlations from H-3 to C-5′ (δ_C 112.6, *d*)/C-6′ (δ_C 139.9, *s*) revealed the C–C linkage of C-3 to C-6′, which altogether permitted compound **1** to be a unique cyclic diarylpropane with a 2,3-dihydro-1*H*-indene core. Compound **1** was detected as a racemic mixture by chiral HPLC (Fig. S11). Being decisive in the absolute configuration determination for natural prodcuts especially the new ones before biological evaluation is necessary [18], ECD calculation was used to establish the absolute configurations of (+)-**1** and (−)-**1**. The tested ECD sprctra of (+)-**1** and (−)-**1** were in good agreement with those computational calculations of 3*S* and 3*R* (Fig. 3), indicating 3*S* and 3*R* configurations for (+)-**1** and (−)-**1**, respectively.

The spectroscopic characterization of horsfielenide D (**2**) implied that it was an analogue of **1**. The presence of OMe [δ_H 3.75 (3H, s, H-7″)] signal in 1D NMR spectra, similar HMBC correlations from H-2′ (δ_H 6.68) to C-3′ (δ_C 145.2)/C-4′ (δ_C 145.0), and H-2″ (δ_H 7.05) to C-4″ (δ_C 159.5), along with HREIMS data (*m*/*z* 256.1100, $[M]^+$, cacld 256.1099, molecular formula: $C_{16}H_{16}O_3$), together proved **2** to be a 4″-methoxy analogue of **1**. Similarly, **2** was resolved to (+)-**2** and (−)-**2** by chiral HPLC (Fig. S22). Further comparing their experimental spectra with those of **1** (Fig. S1), the absolute configurations of (+)-**2** and (−)-**2** were assigned as 3*S* and 3*R*, respectively.

Compound **3**, a colorless oil with a molecular formula of $C_{17}H_{18}O_3$ as deduced by HREIMS (*m*/*z* 270.1253, $[M]^+$, calcd 270.1256), exhibited a typical diarylpropane-type ^{13}C NMR spectra with 12 aromatic carbons and three sp^3-hybridized methylenes (Table 1) [12]. By further analyzing the ^1H–^1H COSY, HSQC, and HMBC spectrum, compound **3** was determined as 1-(3′,4′-methylenedioxyphenyl)-3-(4″-methoxyphenyl)propane, and named horsfielenide E.

Other compounds isolated were elucidated as virolane (**4**) [7], 1-(2′-hydroxy-4′-methoxyphenyl)-3-(3″, 4″-methylenedioxyphenyl)-propan-2-ol (**5**) [19], 1-(2′-hydroxy-4′-methoxyphenyl)-3-(4″-hydroxy-3″-methoxyphenyl)-propane (**6**) [20], horsfielenidine A (**7**) [13], virolanol B (**8**) [21], virolanol C (**9**) [21], (+)-catechin (**10**) [22], (−)-kobusin (**11**) [23], (+)-eudesmin (**12**) [23], (+)-phillygenin (**13**) [24], 3′-desmethylarctigenin (**14**) [25], (−)-hinokinin (**15**) [26], matairesinol (**16**) [27], and 3′,4′-de-*O*-methylenehinokinin (**17**) [28].

Horsfielenides C and D (**1**–**2**) are the first examples of natural cyclic diarylpropanes with 2,3-dihydro-1*H*-indene core. Biogenetically, **1** and **2** were likely derived from chalcone (Scheme 1). To be detailed, reduction of the corresponding chalcone might give three intermediates including ***i*** (totally reduced), ***ii*** (partially reduced), and ***iii*** (partially reduced). Subsequently, diarylpropane ***i*** was likely oxidized to form diarylpropanyl cation ***iv*** [29], which was perhaps also generated by diarylpropanol ***ii*** and diarylpropene ***iii*** under acidic conditions. The key transformation would be the Friedel-Crafts cyclization of ***iv*** to give compounds **1** and **2**.

Based on the hypothetic biosynthesis of **1** and **2**, a total synthetic route was subsequently developed (Scheme 2). Initially, aldehyde **18** was transformed to aldehyde **19** by homologation using the Wittig/hydrolysis sequence [30] in 90% yield. Next, the proposed

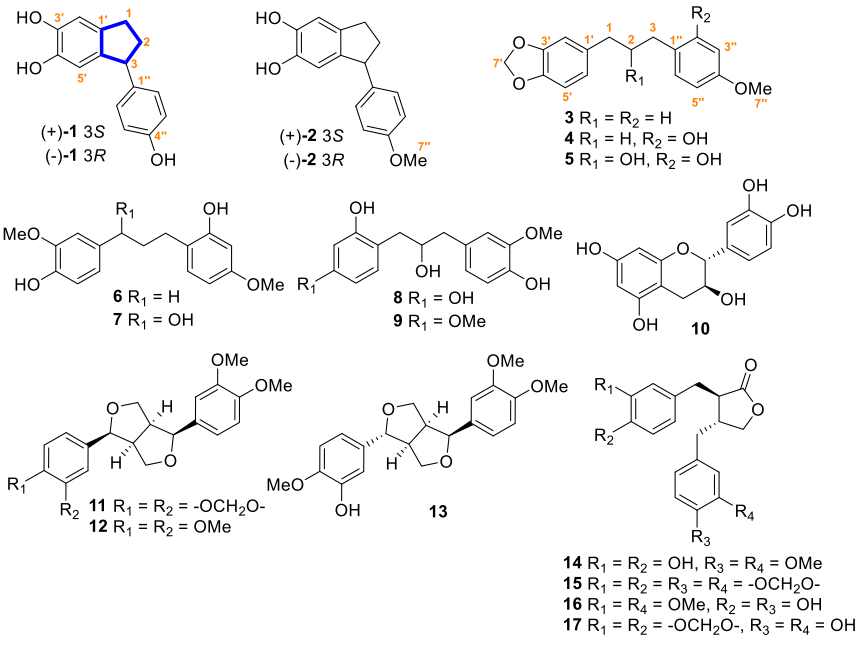


Fig. 1. Structures of compounds **1**–**17** from *H. kingii*.

Table 1
^{1}H and ^{13}C NMR data for **1**–**3** (δ in ppm and J in Hz).

No.	1[a]		2[a]		3[b]	
	δ_H (J in Hz)	δ_C (mult.)	δ_H (J in Hz)	δ_C (mult.)	δ_H (J in Hz)	δ_C (mult.)
1	2.81 m; 2.70 m	32.2 t	2.84 (ddd, 15.0, 8.5, 3.5) 2.75 m	32.2 t	2.58 (t, 7.8)[c]	35.2 t
2	2.40 m 1.84 m	38.4 t	2.46 m 1.89 (dq, 12.4, 8.6)	38.4 t	1.91 m	33.5 t
3	4.05 (t, 8.1)	51.9 d	4.11 (t, 8.1)	51.9 d	2.60 (t, 7.7) [c]	34.5 t
1′	–	136.8 s	–	136.3 s	–	136.3 s
2′	6.69 s	112.3 d	6.68 s	111.9 d	6.71 s	109.0 d
3′	–	145.4 s	–	145.2 s	–	144.7 s
4′	–	144.8 s	–	145.0 s	–	145.6 s
5′	6.31 s	112.6 d	6.29 s	112.5 d	6.75 (d, 7.9)	108.2 d
6′	–	139.9 s	–	139.5 s	6.65 (d, 7.9)	121.2 d
7′	–	–	–	–	5.93 s	100.8 t
1″	–	138.5 s	–	139.4 s	–	134.4 s
2″	6.94 (d, 8.6)	129.9 d	7.05 (d, 8.6)	129.8 d	7.12 (d, 8.6)	129.4 d
3″	6.70 (d, 8.6)	116.2 d	6.82 (d, 8.6)	114.7 d	6.86 (d, 8.5)	113.9 d
4″	–	156.4 s	–	159.5 s	–	157.9 s
5″	6.70 (d, 8.6)	116.2 d	6.82 (d, 8.6)	114.7 d	6.86 (d, 8.5)	113.9 d
6″	6.94 (d, 8.6)	129.9 d	7.05 (d, 8.6)	129.8 d	7.12 (d, 8.6)	129.4 d
7″	-	–	3.75 s	55.6 q	3.81 s	55.4 q

[a] Data were recorded in CD_3OD, ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz).
[b] Data were recorded in CD_3Cl, ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz).
[c] Partial overlapped signals.

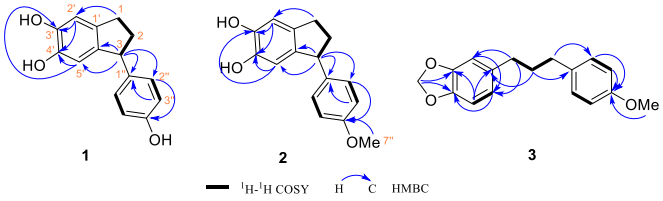


Fig. 2. Key ^{1}H–^{1}H COSY and key HMBC correlations for **1**–**3**.

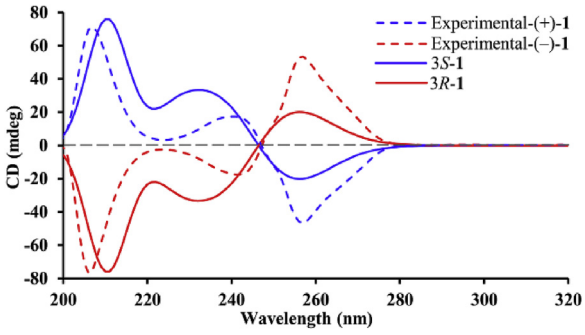
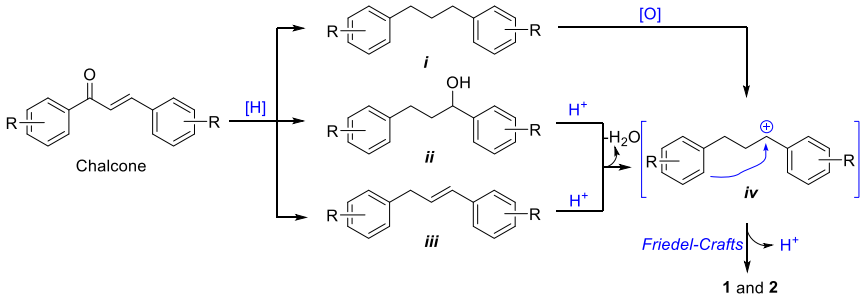


Fig. 3. Experimental and calculated ECD spectra of **1**.

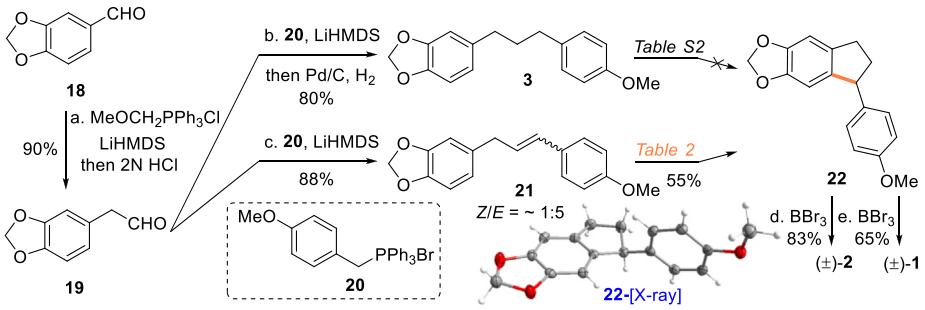
precursor diarylpropane **3** and diarylpropene **21** were obtained by Wittig/catalytic hydrogenation sequence and Wittig reaction in 80% and 88% yield, respectively.

With compounds **3** and **21** in hand, the biomimetic cyclization was explored. Given benzylic C–H bond is sensitive to oxidants, compound **3** was chosen as substrate to investigate the desired cyclization by forming the benzylic cation *in situ* using DDQ [31], Fe(II)/DDQ [32], and Fe(II)/(tBuO)$_2$ [33] (Table S2). As a result, diarylpropane **3** was oxidized by DDQ to form dihydrochalcones **3a**/**3b** and chalcones **3c**/**3d** as inseparable mixtures, respectively (entries 1–3, Table S2). A catalytic amount of $FeCl_2$ (0.2 equiv) significantly accelerated the conversion of substrate **3**, but not the desired cyclization (entry 4, Table S2). Moreover, no reaction was detected using (tBuO)$_2$ as an oxidant (entries 5–6, Table S2). All the observations suggested that the benzylic cation (like diarylpropanic cation ***iv*** in Scheme 1) generated *in situ* by DDQ could not be trapped by either of the aromatic rings of **3** but DDQ itself [34].

To carry on the synthesis, various acid-promoted conditions were screened using diarylpropene **21** as substrate (Table 2). Initial attempts using trifluoromethanesulfonic acid (TfOH) [35] gave desired cyclized product **22** albeit in low yields (<15%, entries 1–3). Other protic acids like sulfuric acid and hydrochloric acid resulted in decomposion of the starting material **21** (data not shown). Silver salts [36] ($AgBF_4$, AgOTf, and $AgPF_6$, entries 4–6) also promoted the



Scheme 1. Plausible biogenetic pathway for **1** and **2**.



Scheme 2. Total synthesis of **1** and **2**. Conditions: a) $MeOCH_2PPh_3Cl$, LiHMDS, THF, −78 °C − RT, 2 h; then 2 N HCl, reflux, 3 h, 90%. b) **20**, LiHMDS, THF, −78 °C − RT, 2 h; then Pd/C, H_2 (balloon), EA/MeOH (5 : 1), RT, 6 h, 80%. c) **20**, LiHMDS, THF, −78 °C − RT, 2 h, 88%. d) BBr_3, DCM, −40 °C, 0.5 h, 83%. e) BBr_3, DCM, 0 °C, 4 h, 65%.

Table 2
Acid-promoted cyclization of **21**.[a]

Entry	Conditions	Time (h)	Product (yield%) [c]
1	TfOH (0.1 equiv), DCM, −20 °C	12	**22** (trace)
2	TfOH (0.1 equiv), DCM, 0 °C - RT	3	**22** (10)
3	TfOH (0.1 equiv), DCM, reflux	3	**22** (15)
4	$AgBF_4$ (0.1 equiv), DCM, sealed, 60 °C	6	**22** (17)
5	AgOTf (0.1 equiv), DCM, sealed, 60 °C	4	**22** (30)
6 [b]	$AgPF_6$ (0.1 equiv), DCM, sealed, 60 °C	4	**22** (10)
7	$AuCl{\cdot}Me_2S$ (0.1 equiv), 1,4-dioxane, sealed, 100 °C	12	**22** (16)
8 [b]	$Cu(OTf)_2$ (0.1 equiv), DCM, RT	12	NR [d]
9	$Cu(OTf)_2$ (0.1 equiv), DCM, 60 °C	16	**22** (33)
10	$Cu(OTf)_2$ (0.2 equiv), DCM, 60 °C	10	**22** (35)
11	$Cu(OTf)_2$ (0.1 equiv), DCM, O_2 (1 atm), 60 °C	12	**22** (45)
12	$Cu(OTf)_2$ (0.1 equiv), DCM, O_2, sealed, 60 °C	8	**22** (55)

[a] All the reactions were performed on 0.1 mmol scale.
[b] the starting materials were recovered.
[c] isolated yield.
[d] no reaction.

cyclization, of which AgOTf could give higher yield of 30%. Moreover, a harsh condition using $AuCl{\cdot}Me_2S$ [37] resulted in low yield of **22** (entry 7). In addition, we found that cyclization could be also catalyzed by $Cu(OTf)_2$ [38] in boiling DCM (60 °C) to give **22** in 33% yield although no reaction was observed at room temperature (entries 8 and 9). The commonly used solvents like DCE, MeCN, toluene, etc. were also screened using $Cu(OTf)_2$ as catalyst, but all the tested solvents gave lower yield than DCM (data not shown). Higher catalyst loading did not increase the yield but accelerated the reaction rate (entry 10). Pleasingly, the satisfactory yield of **22** was obtained by filling reaction system with one atm of oxygen in a sealed tube (entries 11 and 12). Finally, (±)-**1** and (±)-**2** were prepared by removal of dioxymethylene and methyl of **22** using BBr_3 in DCM, which could further support the structural elucidations of **1** and **2** on the basis of X-ray structure of **22** (Scheme 2).

After completion of the synthesis, all isolated compounds (**1**–**17**) and synthetic compound **22** were tested against NO production in RAW264.7 macrophages. As shown in Table 3, compounds **2**, **4**–**8**, and **10** could dose-dependently inhibit NO production in LPS-stimulated RAW264.7 macrophages without cytotoxicity (CC_{50} > 40 μM). To be specified, compounds (±)-**2**, (+)-**2**, and (−)-**2** showed strong inhibitory activities with IC_{50} values of 4.40 ± 0.69, 4.76 ± 0.31, and 6.41 ± 0.21 μM, respectively, which were more potent than that of catechin (**10**, IC_{50} = 8.86 ± 0.35 μM) and positive control L-NMMA (IC_{50} = 13.82 ± 0.81 μM). Interestingly, compound **1** with three free phenolic hydroxy groups (more polar) and compound **22** with no free phenolic hydroxy group (less polar) were both inactive in inhibition of NO production (IC_{50} > 40 μM), indicating that the free phenolic hydroxy groups in 1-phenyl-2,3-dihydro-1*H*-indene scaffold (**1**, **2**, and **22**) might account for firstly and most importantly the permeability of these compounds into cells, and secondly the binding affinity to target proteins. Moreover, the similar IC_{50} values of (±)-**2**, (+)-**2**, and (−)-**2** might be resulted from a non-selective inhibition mode of these compounds towards the target. As it is well known, inducible NO synthase (iNOS) plays an important role in NO amount in inflammation [39]. We docked (+)-**2** and (−)-**2** into iNOS to provide the possibility for validating this non-selective inhibition. As shown in Fig. S2, both (+)-**2** (A) and (−)-**2** (B) could bind to iNOS protein and occupy its active pocket nearby the Heme-Fe by interacting with residues Tyr341, Gly365, Trp366, Glu371, and Heme-Fe itself [39,40]. However, the detailed mechanism deserves to be elucidated in future. Thus, the primary structure-activity relationships (SARs) of this scaffold are concluded based on these observations as: hydroxy groups at C3′/

Table 3
In vitro NO production inhibitory activities of compounds **1**–**17** and **22**.

Compd.	IC_{50} (μM) [a]	Compd.	IC_{50} (μM) [a]
(±)-**1**	> 40	**9**	> 40
(+)-**1**	> 40	**10**	8.86 ± 0.35
(−)-**1**	> 40	**11**	> 40
(±)-**2**	4.40 ± 0.69	**12**	> 40
(+)-**2**	4.76 ± 0.31	**13**	> 40
(−)-**2**	6.41 ± 0.21	**14**	> 40
3	> 40	**15**	> 40
4	28.78 ± 2.12	**16**	> 40
5	30.34 ± 4.78	**17**	> 40
6	30.43 ± 5.22	**22**	> 40
7	24.52 ± 2.13	L-NMMA	13.82 ± 0.81
8	29.16 ± 2.42	–	–

[a] Inhibition of NO production, L-NMMA (NG-Monomethyl-L-arginine, monoacetate salt) was used as positive control.

C4′ and methoxy group at C4″ are favorable; C3 stereocenter is tolerable with both 3*S* and 3*R*.

To further evaluate the anti-inflammatory potency of compound **2**, the inhibitory effect of **2** on iNOS expression in LPS-induced RAW264.7 cells were performed. As a result, **2** showed dose-dependent inhibitory effects on iNOS expression in LPS-induced RAW264.7 macrophages compared to control (Fig. 4), indicating that compound **2** inhibited LPS-induced NO production likely by down-regulating iNOS protein expression.

3. Conclusion

In summary, an ethnopharmacological plant *H. kingii* was investigated on its bioactive components. A total of 17 compounds were isolated from the bioactive fractions of *H. kingii* extracts. Among these compounds, **2**, **4**–**8**, and **10** showed inhibitory effects on NO production in LPS-stimulated RAW264.7 macrophages without cytotoxicity. Moreover, a four-step synthetic route to **1** and **2** was developed based on biogenetic hypothesis. Most importantly, compound **2** was the most potential one (IC_{50} = 4.40 ± 0.69 μM) representing a promising anti-inflammatory lead. Our present findings provide the scientific basis to further support the folk treatments of *Horsfieldia* species.

4. Experimental

4.1. General experimental procedures

Optical rotations were measured with an AUTOPOL VI polarimeter (Rudolph, USA). UV data were obtained on a Shimadzu UV-2401A spectrophotometer (Shimadzu, Kyoto, Japan). An IR Affinity-1S spectrophotometer was used for scanning IR spectroscopy with KBr pellets (Shimadzu, Kyoto, Japan). ECD spectra were taken with a Chirascan instrument (Applied photophysics, England). 1D and 2D NMR spectra were recorded on ADVANCE III 400 MHz, AM-500 MHz, and ADVANCE III 600 MHz spectrometers (Bruker, German). Unless otherwise specified, chemical shifts (δ) were expressed in ppm with reference to solvent signals ($CDCl_3$: δ_C = 77.16 ppm; CD_3OD: δ_C = 49.00 ppm; residual $CHCl_3$ in $CDCl_3$: δ_H = 7.26 ppm; residual CH_3OH in CD_3OD: δ_H = 3.31 ppm). HREIMS (70 eV) were measured on a VG Auto Spec-3000 spectrometer (VG PRIMA, England). Column chromatography was performed with silica gel (100–200 mesh) (Qingdao Marine Chemical, Inc., Qingdao, People's Republic of China), MCI gel CHP 20P (75–150 μm; Mitsubishi Chemical Corporation, Tokyo), Sephadex LH-20 (Amersham Biosciences AB, Uppsala, Sweden), Lichroprep RP-18 (40–63 μm, Merck, Darmstadt, Germany). Fractions were examined by TLC (Si gel GF254) (Qingdao Marine Chemical, Inc., Qingdao, China), and spots were visualized by heating silica gel plates sprayed with 10% H_2SO_4 in EtOH. Preparative TLC (Si gel 60 GF_{254}, Qingdao Marine Chemical, Inc., Qingdao, China). All reactions were carried out under an atmosphere of argon in dry and freshly distilled solvents under anhydrous conditions, unless otherwise noted, monitoring by TLC (Si gel GF_{254}), and spraying phosphomolybdic acid (10% in EtOH) followed by heating.

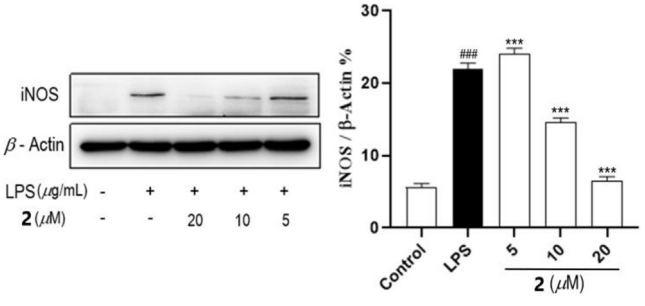


Fig. 4. Effects of compound **2** on LPS-induced iNOS expression in RAW264.7 cells. Cells were pretreated with **2** (5, 10, and 20 μM) for 1 h, then co-incubated with LPS (1 μg/mL) for another 12 h. Values represent the mean ± SD of three independent experiments. ($^{\#}$ *vs* Control, * *vs* LPS, ***/$^{\#\#\#}P < 0.001$).

4.2. Plant material

The twigs and leaves of *H. kingii* were collected from the Guanlei town, Mengla County of the Yunnan Province in China in November 2016. The samples were identified by Mr. Shishun Zhou, a botanist of Xishuangbanna Tropical Botanical Garden, Chinese Academy of Sciences. The voucher specimen (No. 16112110) was deposited in Yunnan Normal Univesity.

4.3. Extraction and isolation

The twigs and leaves (5.0 Kg) of *H. kingii* were extracted for four times (two days for each time) with 70% aqueous acetone (40 L) at room temperature, and then were filtered followed by concentration in vacuum to remove acetone. The residue (~10 L) was extracted with EtOAc (5 L × 6) and the EtOAc layer was concentrated in vacuum to yield EtOAc portions (280 g). The EtOAc portion was separated by column chromatography (silica gel, petroleum ether/acetone, 20:1 to 1:1) to yield fractions A-D based on the TLC analysis. Fraction C (83 g) was subjected to column chromatography on Lichroprep RP-18 (MeOH–H_2O, 50:50 to 95:5) to provide four subfractions C1–C4. After purification by repeated column chromatography (silica gel, $CHCl_3$/acetone, 50:1–10:1 gradient system, and Sephadex LH-20, $CHCl_3$/MeOH, 3:2), subfraction C1 afforded compounds **2** (22 mg), **6** (14 mg), **14** (7 mg), and **16** (17 mg), repectively. Moreover, C2 was then purified by repeated column chromatography of Sephadex LH-20 ($CHCl_3$/MeOH, 3:2) and silica gel ($CHCl_3$/acetone, 30:1 to 10:1) to give compound **4** (25 mg), **13** (18 mg), and compound **16** (12 mg), repectively. Compounds **3** (11 mg), **11** (7 mg), **12** (9 mg), **13** (157 mg), and **15** (16 mg) were separated from C4 by column chromatography of RP-18 (MeOH/H_2O, 50:50 to 100:0), MCI gel (MeOH/H_2O, 80:20 to 100:0), and Sephadex LH-20 ($CHCl_3$/MeOH, 3:2), repectively.

Fraction D (42 g) was subjected to column chromatography of Lichroprep RP-18 (MeOH/H_2O, 30:80 to 95:5) to obtain three subfractions D1-D3. From D1, compound **10** (40 mg) was isolated by column chromatography of Sephadex LH-20 ($CHCl_3$/MeOH, 3:2). D2 was separated by column chromatography of Sephadex LH-20 ($CHCl_3$/MeOH, 3:2), silica gel ($CHCl_3$/acetone, 30:1 to 5:1), and silica gel (petroleum ether/ethyl acetate, 20:1 to 10:1) to yield **7** (8 mg), **8** (13 mg), and **9** (15 mg), respectively. Compounds **1** (17 mg), **5** (22 mg), and **17** (11 mg) were isolated from D3 by Sephadex LH-20 ($CHCl_3$/MeOH, 3:2) and preparative TLC (CH_2Cl_2/acetone, 4:1, for two times).

Compound **1** was separated using a chiral stationary phase [Agilent 1260 HPLC with Ultimate Cellu-Amy-DR (10 × 250 mm) column (MeOH/H_2O 96:4, v/v, 2 mL/min)] respectively to provide (+)-**1** (6.8 mg, t_R = 7.5 min), and (−)-**1** (6.6 mg, t_R = 8.0 min). Similarly, compound **2** was resolved [Agilent 1260 HPLC with Ultimate Cellu-Amy-DR (10 × 250 mm) column (MeOH/H_2O 95:5, v/v, 2 mL/min)] to provide (+)-**2** (10.4 mg, t_R = 9.6 min) and (−)-**2** (10.5 mg, t_R = 10.6 min), respectively.

4.3.1. Horsfielenide C (*1*)

Brown oil; UV (MeOH) λ_{max} (log ε) 202 (3.91), 219 (3.66), 283 (3.22) nm; IR (KBr) ν_{max} 3441, 2972, 1632, 1512, 1237, 836 cm^{-1}; ^1H and ^{13}C NMR: see Table 1; HREIMS $[M]^+$ *m/z* 242.0949 (calcd for

$C_{15}H_{14}O_3$, 242.0943). (+)-Horsfielenide C: $[\alpha]_D^{25}$ +70.9 (*c* 0.15, MeOH). (−)-Horsfielenide C: $[\alpha]_D^{25}$-72.2 (*c* 0.15, MeOH).

4.3.2. Horsfielenide D (**2**)

Brown oil; UV (MeOH) λ_{max} (log ε) 203 (3.81), 221 (3.43), 293 (2.99) nm; IR (KBr) ν_{max} 3429, 2922, 1604, 1510, 1462, 1026, 842 cm^{-1}; ^1H and ^{13}C NMR: see Table 1; HREIMS $[M]^+$ *m/z* 256.1100 (calcd for $C_{16}H_{16}O_3$, 256.1099). (+)-Horsfielenide D: $[\alpha]_D^{25}$+18.6 (*c* 0.20, MeOH). (−)-Horsfielenide D: $[\alpha]_D^{25}$–20.1 (*c* 0.20, MeOH).

4.3.3. Horsfielenide E (**3**)

Colorless oil; UV (MeOH) λ_{max} (log ε) 209 (2.01), 230 (2.21), 285 (1.78) nm; IR (KBr) ν_{max} 2935, 1612, 1513, 1489, 1244, 1039, 937, 810 cm^{-1}; ^1H and ^{13}C NMR: see Table 1; HREIMS $[M]^+$ *m/z* 270.1253 (calcd for $C_{17}H_{18}O_3$, 270.1256).

4.4. Total synthesis of **1** and **2**

4.4.1. Synthesis of aldehyde **19**

To a suspension of (methoxymethyl)triphenylphosphonium chloride (7.2 g, 21.0 mmol) in THF (40 mL) was added dropwise of LiHMDS (1 *M* in THF, 21.0 mL, 21.0 mmol) at 0 °C, the resulting mixture was stirred at 0 °C for 30 min to give a clear red solution before the reaction was moved to −78 °C cold bath. To this mixture, aldehyde **18** (3.0 g, 20.0 mmol) in THF (15 mL) was added, and the resulting mixture was warmed to room temperature and stirred for 2 h. After consumption of the starting materials, the reaction was quenched by adding of 2 *N* HCl (60 mL) at 0 °C. The resulting mixture was heated to reflux for 4 h, then was cooled at 0 °C, and $NaHCO_3$ (~10 g) was added portionwise to the mixture. Ethyl acetate (100 mL) and water (100 mL) was added, the organic layer was washed by water (100 mL × 3) and brine (100 mL × 2), and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layer was dried over Na_2SO_4, and evaporated under vacuum to give crude product which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 10:1) to yield aldehyde **19** (2.95 g, 90%) as a slightly yellow oil. IR (KBr) ν_{max} 2897, 2827, 2725, 1722, 1489, 1246, 1039, 925, 810 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 9.70 (d, *J* = 1.0 Hz, 1H, H-2), 6.80 (d, *J* = 7.9 Hz, 1H, H-5′), 6.69 (s, 1H, H-2′), 6.66 (d, *J* = 7.9 Hz, 1H, H-6′), 5.96 (s, 2H, H-7′), 3.59 (d, *J* = 1.0 Hz, 2H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.4 (C-2), 148.4 (C-4′), 147.2 (C-3′), 125.4 (C-1′), 122.9 (C-6′), 110.0 (C-2′), 108.9 (C-5′), 101.3 (C-7′), 50.3 (C-1). HREIMS *m/z*: $[M]^+$ calcd. for $C_9H_8O_3$ 164.0473, found 164.0473.

4.4.2. Synthesis of horsfielenide E (**3**)

To a suspension of **20** (2.95 g, 6.4 mmol) in THF (20 mL) was added dropwise of LiHMDS (1 *M* in THF, 6.4 mL, 6.4 mmol) at 0 °C, the resulting mixture was stirred at 0 °C for 15 min to give a clear orange solution before the reaction was moved to −78 °C cold bath. To this mixture, aldehyde **19** (1.0 g, 6.1 mmol) in THF (10 mL) was added, and the resulting mixture was warmed to room temperature and stirred for 2 h. After consumption of the starting materials, the reaction was quenched by adding of water (10 mL) at 0 °C. The resulting mixture was portioned by ethyl acetate (50 mL) and water (50 mL) was added, the organic layer was washed by water (50 mL × 3) and brine (50 mL × 2), and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layer was dried over Na_2SO_4, and evaporated under vacuum to give an orange oil which was passed through a short pad of silica gel eluting with petroleum ether/ethyl acetate = 20:1 (200 mL) to yield crude diarylpropene **21** (~1.5 g). This crude product was dissolved in ethyl acetate/MeOH (5:1, 60 mL), Pd/C (150 mg, 5% Pd) was added. The resulting dark suspension was connected to a H_2 balloon, and stirred at room temperature for 6 h. Then the reaction mixture was passed a short pad of Celite® to remove Pd/C, the filter cake was washed by ethyl acetate (10 mL × 3), the filtrates were then combined and evaporated under vacuum to give slightly yellow oil, which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 20:1) to yield **3** (1.3 g, 80%) as a colorless oil. IR (KBr) ν_{max} 2929, 1612, 1513, 1489, 1244, 1039, 939, 810 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.6 Hz, 2H, H-2″, H-6″), 6.84 (d, *J* = 8.6 Hz, 2H, H-3″, H-5″), 6.73 (d, *J* = 7.9 Hz, 1H, H-5′), 6.68 (d, *J* = 1.5 Hz, 1H, H-2′), 6.63 (dd, *J* = 7.9, 1.6 Hz, 1H, H-6′), 5.92 (s, 2H, H-7′), 3.80 (s, 3H, H-7″), 2.57 (dd, *J* = 15.7, 9.1 Hz, 4H, H-1, H-3), 1.89 (m, 2H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9 (C-4″), 147.7 (C-4′), 145.6 (C-3′), 136.4 (C-1′), 134.5 (C-3′), 129.4 (C-2″, C-6″), 121.3 (C-6′), 113.9 (C-3″, C-5″), 109.0 (C-2′), 108.2 (C-5′), 100.8 (C-7′), 55.4 (C-7″), 35.2 (C-1), 34.5 (C-3), 33.6 (C-2). HREIMS *m/z*: $[M]^+$ calcd. for $C_{17}H_{18}O_3$ 270.1256, found 270.1253.

4.4.3. Synthesis of diarylpropene **21**

To a suspension of **20** (2.95 g, 6.4 mmol) in THF (20 mL) was added dropwise of LiHMDS (1 *M* in THF, 6.4 mL, 6.4 mmol) at 0 °C, the resulting mixture was stirred at 0 °C for 15 min to give a clear orange solution before the reaction was moved to −78 °C cold bath. To this mixture, aldehyde **19** (1.0 g, 6.1 mmol) in THF (10 mL) was added, and the resulting mixture was warmed to room temperature and stirred for 2 h. After consumption of the starting materials, the reaction was quenched by adding of water (10 mL) at 0 °C. The resulting mixture was portioned by ethyl acetate (50 mL) and water (50 mL) was added, the organic layer was washed by water (50 mL × 3) and brine (50 mL × 2), and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layer was dried over Na_2SO_4, and evaporated under vacuum to give an orange oil which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 20:1) to yield **21** (1.4 g, 88%) as a slightly yellow oil. IR (KBr) ν_{max} 2895, 1606, 1508, 1487, 1246, 1176, 1037, 929, 804 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) E-isomer displayed δ 7.31 (d, *J* = 8.7 Hz, 2H, H-2″, H-6″), 6.85 (d, *J* = 8.7 Hz, 2H, H-3″, H-5″), 6.77 (d, *J* = 7.9 Hz, 1H, H-5′), 6.75 (d, *J* = 1.2 Hz, 1H, H-2′), 6.71 (d, *J* = 7.8 Hz, 1H, H-6′), 6.40 (d, *J* = 15.7 Hz, 1H, H-3), 6.24–6.14 (m, 1H, H-2), 5.93 (s, 2H, H-7′), 3.81 (s, 3H, H-7″), 3.45 (d, *J* = 6.8 Hz, 2H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) E-isomer displayed δ 159.0 (C-4″), 147.8 (C-4′), 146.0 (C-3′), 134.4 (C-1′), 130.5 (C-3′), 130.4 (C-3), 127.3 (C-2″, C-6″), 127.3 (C-2), 121.5 (C-6′), 114.0 (C-3″, C-5″), 109.3 (C-2′), 108.3 (C-5′), 100.9 (C-7′), 55.4 (C-7″), 39.1 (C-1). HREIMS *m/z*: $[M]^+$ calcd. for $C_{17}H_{16}O_3$ 268.1099, found 268.1100.

4.4.4. Synthesis of cyclic diarylpropane **22**

To an oven-dried tube was charged with diarylpropene **21** (27.0 mg, 0.1 mmol) and dry DCM (4.0 mL) was added $Cu(OTf)_2$ (4.0 mg, 0.01 mmol). The reaction tube was filled with oxygen and sealed. The sealed reaction mixture was stirred at 60 °C for 8 h. Then the mixture was cooled to room temperature and was added saturated brine (5.0 mL) followed by dilution with DCM (10 mL). The organic layer was collected and washed with water (10 mL × 2) and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 80:1) to yield **22** (14.7 mg, 55%) as a white powder which was further crystalized to give colorless needles. mp 143–145 °C [petroleum ether/ethyl acetate (3:2, v/v)]. IR (KBr) ν_{max} 2927, 1632, 1512, 1474, 1248, 1037, 938, 831 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.6 Hz, 2H, H-2″, H-6″), 6.85 (d, *J* = 8.6 Hz, 2H, H-3″, H-5″), 6.74 (s, 1H, H-2′), 6.40 (s, 1H, H-5′), 5.90 (dd, *J* = 11.1, 1.3 Hz, 2H, H-7′), 4.18 (t, *J* = 8.1 Hz, 1H, H-3), 3.80 (s, 3H, H-7″), 2.92 (ddd, *J* = 15.3, 8.5, 3.5 Hz, 1H, H-1a), 2.86–2.78 (m, 1H, H-1b), 2.59–2.51 (m, 1H, H-2a), 2.00 (ddd, *J* = 17.2, 12.5, 8.6 Hz, 1H, H-2b). ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.2 (C-4″), 146.7 (C-3′), 146.6 (C-4′), 140.2 (C-6′), 137.8 (C-1″), 137.1 (C-1′), 129.0 (C-2″, C-6″), 114.0

(C-3″, C-5″), 105.6 (C-5′), 104.9 (C-2′), 101.0 (C-7′), 55.4 (C-7″), 50.7 (C-3), 37.4 (C-2), 31.8 (C-1). HREIMS *m/z*: $[M]^+$ calcd. for $C_{17}H_{16}O_3$ 268.1099, found 268.1097.

4.4.5. Synthesis of horsfielenide D (**2**)

To a solution of **22** (20.0 mg, 0.074 mmol) in DCM (4 mL) was added dropwise of BBr_3 (1 *M* in DCM, 148 μL, 0.15 mmol) at −40 °C, the resulting mixture was stirred at −40 °C for 30 min. The reaction was quenched by adding of water (1 mL) at −40 °C. DCM (10 mL) and water (10 mL) was added, the organic layer was washed by water (10 mL × 3) and brine (10 mL × 2), and the aqueous layer was extracted with DCM (10 mL). The combined organic layer was dried over Na_2SO_4, and evaporated under vacuum to give crude product which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 3:1) to yield compound **2** (15.7 mg, 83%) as a brown oil. IR (KBr) ν_{max} 3420, 2927, 1604, 1510, 1026, 839 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ 7.04 (d, J = 8.5 Hz, 2H, H-2″, H-6″), 6.82 (d, J = 8.6 Hz, 2H, H-3″, H-5″), 6.68 (s, 1H, H-2′), 6.30 (s, 1H, H-5′), 3.75 (s, 3H, H-7″), 2.84 (m, 1H, H-1a), 2.75 (m, 1H, H-1b), 2.45 (m, 1H, H-2a), 1.89 (dq, J = 12.0, 8.6 Hz, 1H, H-2b). ^{13}C NMR (150 MHz, CD_3OD) δ 159.5 (C-4″), 145.2 (C-3′), 144.9 (C-4′), 139.5 (C-6′), 139.4 (C-1″), 136.3 (C-1′), 129.8 (C-2″, C-6″), 114.7 (C-3″, C-5″), 112.5 (C-5′), 111.9 (C-2′), 55.6 (C-7″), 51.9 (C-3), 38.4 (C-2), 32.2 (C-1). HREIMS *m/z*: $[M]^+$ calcd. for $C_{16}H_{16}O_3$ 256.1099, found 256.1100.

4.4.6. Synthesis of horsfielenide C (**1**)

To a solution of **22** (20.0 mg, 0.074 mmol) in DCM (4 mL) was added dropwise of BBr_3 (1 *M* in DCM, 296 μL, 0.30 mmol) at 0 °C, the resulting mixture was stirred at 0 °C for 4 h. The reaction was quenched by adding of water (1 mL) at 0 °C. DCM (10 mL) and water (10 mL) was added, the organic layer was washed by water (10 mL × 3) and brine (10 mL × 2), and the aqueous layer was extracted with DCM (10 mL). The combined organic layer was dried over Na_2SO_4, and evaporated under vacuum to give crude product which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1:2) to yield compound **1** (11.6 mg, 65%) as a brown oil. IR (KBr) ν_{max} 3440, 2927, 1632, 1612, 1510, 1237, 1174, 839 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 6.95 (d, J = 8.5 Hz, 2H, H-2″, H-6″), 6.69 (d, J = 8.6 Hz, 2H, H-3″, H-5″), 6.67 (s, 1H, H-2′), 6.30 (s, 1H, H-5′), 4.08 (t, J = 8.3 Hz, 1H, H-3), 2.83 (ddd, J = 15.0, 8.6, 3.6 Hz, 1H, H-1a), 2.74 (m, 1H, H-1b), 2.44 (dtd, J = 12.0, 7.7, 3.6 Hz, 1H, H-2a), 1.87 (dq, J = 12.4, 8.6 Hz, 1H, H-2b). ^{13}C NMR (100 MHz, CD_3OD) δ 156.6 (C-4″), 145.1 (C-3′), 144.9 (C-4′), 139.7 (C-6′), 138.3 (C-1″), 136.4 (C-1′), 129.8 (C-2″, C-6″), 116.1 (C-3″, C-5″), 112.5 (C-5′), 111.9 (C-2′), 51.9 (C-3), 38.4 (C-2), 32.2 (C-1). HREIMS *m/z*: $[M]^+$ calcd. for $C_{15}H_{14}O_3$ 242.0943, found 242.0949.

4.4.7. X-ray diffraction analysis of **22**

Single crystal of **22** was obtained from petroleum ether/ethyl acetate (3:2, v/v) at ambient temperature. The crystal data were collected on a Bruker APEX DUO diffractometer (100 K, Mo Kα radiation). The full crystallographic data (CCDC 1903590) of **22** were deposited in the Cambridge Crystallographic Data Centre.

4.5. ECD calculation

The methods for ECD calculation were performed according to previous work [41].

4.6. Nitric oxide production inhibition

The NO production inhibitory assay in LPS-stimulated RAW264.7 cells was measured based on the Griess reaction. RAW264.7 cells (8 × 104/well) were seeded onto 96-well plates and treated with 5.0, 10.0, 20.0, and 40.0 μM of tested compounds for 1 h followed by the treatment with LPS (1 μg/mL). The detailed procedures were recorded on the manual of Beyotime's Griess solution kits. The absorbance at 540 nm was measured in a microplate reader (Thermo Fisher Scientific, USA). The purity of all tested compounds was proved on HPLC (Table S4).

4.7. Western blot analysis

RAW264.7 cells were pretreated with compound **2** (5, 10, and 20 μM) for 1 h, and then were co-stimulated with LPS (1 μg/mL) for 12 h in a 5% CO_2 containing incubator at 37 °C. The cells were collected on ice, washed twice with ice-cold PBS, and suspended in 120 μL of the lysis buffer containing 1 mM PMSF and 1:25 complete PI. After incubation of lysates on ice for 0.5 h, the mixtures were subjected to centrifugation (14000 g) at 4 °C for 5 min to give the cytosolic fractions. The nuclear and cytoplasmic protein samples were extracted using Nuclear and Cytoplasmic Protein Extraction kit (Beyotime). The western blot method was according to the literature [42].

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 data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2020.131494.

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