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Synthesis and structure–immunosuppressive activity relationships of bakuchiol and its derivatives

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Abstract—A series of derivatives of bakuchiol were synthesized and tested in vitro for their cytotoxicity, and inhibition of T cell proliferation and B cell proliferation. The data obtained provided preliminary structure–activity relationships of the compounds as immunosuppressive activity.

1. Introduction

Bakuchiol is a prenylated phenolic monoterpene isolated from the seeds of *Psoralea corylifolia* L. (Leguminoesae) which has been used to treat a wide variety of diseases and conditions in both Chinese and Indian folkloric medicine.[1] Bakuchiol is one of the active compounds reported to exert anti-oxidative, anti-microbacterial activity, inhibit iNO expression, and inhibit mitochondrial lipid peroxidation.[2] Also, bakuchiol has been demonstrated to possess anti-inflammatory activity since it is able to control leukocytic functions such as eicosanoid production, migration, and degranulation in the inflammatory site and it is a weak inhibitor of secretory and intracellular phospholipase A_2 (PLA_2) but dose-dependently reduces the formation of LTB_4 and TXB_2 by human neutrophils and platelet microsomes, respectively.[3–5] In addition, it can inhibit COX-1 (cyclooxygenase), COX-2, and 5-lipoxygenase.[6] It also inhibits the expression of the inducible nitric oxide synthase gene via the inactivation of nuclear transcription factor-kappaB in RAW 264.7 macrophages.[7] On the other hand, it has been reported that cyclobakuchiols exhibited higher anti-inflammatory potency than bakuchiol.[4,5] These findings prompted us to synthesize the derivatives of bakuchiol and investigate the structure–activity relationships of bakuchiol and its analogues as immunosuppressive activity (Fig. 1).

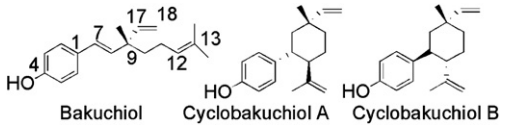

Figure 1. Bakuchiol and cyclobakuchiols.

A series of bakuchiol derivatives modified at C-12, 13, a second series modified at C-9, and a third series with modified aryl groups were prepared and tested in vitro for their cytotoxicity on murine splenocytes, and inhibition activity on concanavalin A (ConA) induced T cell proliferation and on lipopolysaccharide (LPS) induced B cell proliferation.[8–11] Through the examination of the T/B lymphocyte proliferative reaction, we could understand the in vitro immunosuppression function of the compounds.

2. Results and discussion

2.1. Chemistry

In prior studies, the diastereomeric mixture of cyclobakuchiols **A** and **B**, extracted from *Psoralea glandulosa*, could increase the anti-inflammatory activity in compar-

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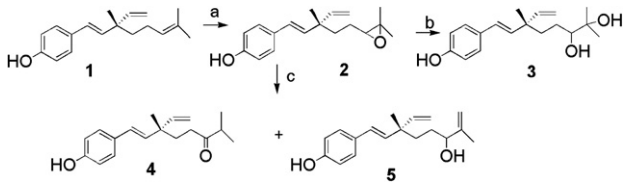
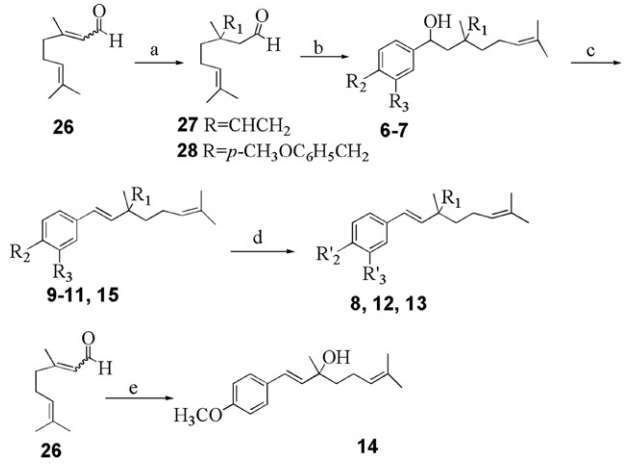


Scheme 1. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, rt, 3 h, 78%; (b) 70% H_2SO_4, dioxane: H_2O = 1:1, rt, 1 min, 99%; c. *p*-TsOH, CH_2Cl_2, rt, 0.5 h, 64% (5), 20% (4).

ison with its biogenetic precursor, bakuchiol. Therefore, we initially focused our attention on the modification of the side chain. First, $\Delta^{12,13}$ double bond is investigated and the synthesis of the derivatives was illustrated in Scheme 1. Key intermediate **2** was prepared by epoxidation of bakuchiol (**1**) with *m*-chloroperbenzoic acid[12] followed by ring opening with 70% H_2SO_4 in dioxane and water (1:1) to give **3**. Alternatively, the epoxy ring of **2** could undergo rearrangement in the presence of *p*-TsOH to give compounds **4** and **5**.[13]

Then, in order to probe the effect of chiral quaternary center (C-9), $\Delta^{7,8}$ double bond, and $\Delta^{17,18}$ double bond, we designed the following synthetic approach to get (±)bakuchiol and its derivatives (Scheme 2). Key intermediate **27** was prepared by 1,4-addition procedure with citral (**26**) and vinylmagnesium bromide. Treatment of **27** with *p*-methoxyphenylmagnesium bromide furnished the alcohol **6**, with (3-fluoro-4-methoxyphenyl)magnesium bromide furnished the alcohol **7**, and with (3,4-dimethoxyphenyl)magnesium bromide followed by dehydration furnished **11**. Compounds **9** and **10** were obtained by dehydration with **6** and **7**, respectively. Compounds **9**, **10**, and **11** were demethylated with MeMgI to produce **8**, **12**, and **13**, respectively.[14] Compound **15** was obtained by 1,4-addition procedure with citral (**26**) and *p*-methoxybenzylmagnesium chloride followed by dehydration and demethylation. Citral (**26**) could convert to compound **14** in one step by an 1,2-addition procedure, which probably underwent a rearrangement progress.



Scheme 2. Reagents and conditions: (a) CuI, R_1MgBr, THF, −40 °C, 2–4 h, 40–60%; (b) ArMgBr THF, 0 °C, 91%; (c) $POCl_3$, Py., 140 °C, 1 h, 95%; (d) MeMgI, 180 °C, 10 min, 91%; (e) *p*-$CH_3OC_6H_4MgBr$, THF, 0 °C–rt, 4 h, 95%.

Next, we began the modification of aromatic ring while keeping the side chain fixed. In the first approach, compound **16** was prepared by methylation of bakuchiol (**1**). In the second approach, we introduced a variety of groups at *ortho*-position of the phenol. The selective *ortho*-formylation product **17** was obtained by the reported procedures starting from bakuchiol (**1**)[15] which reacted with $C_6H_5CH_2P^+Ph_3Br^-$ to afford **18** and with *p*-$CH_3OC_6H_5CH_2P^+Ph_3Br^-$ to afford **20**. Alternatively, compound **17** was treated with $NaBH_4$ in methanol to give **19**. On the other hand, nitration of bakuchiol (**1**) with nitric acid gave **21** which was reacted with Zn–Fe to yield **22**. Treatment of **22** with acetic anhydride furnished **23**, with urea gave **24**, and with carbon disulfide gave **25**.[16] Synthetic methods are shown in Scheme 3.

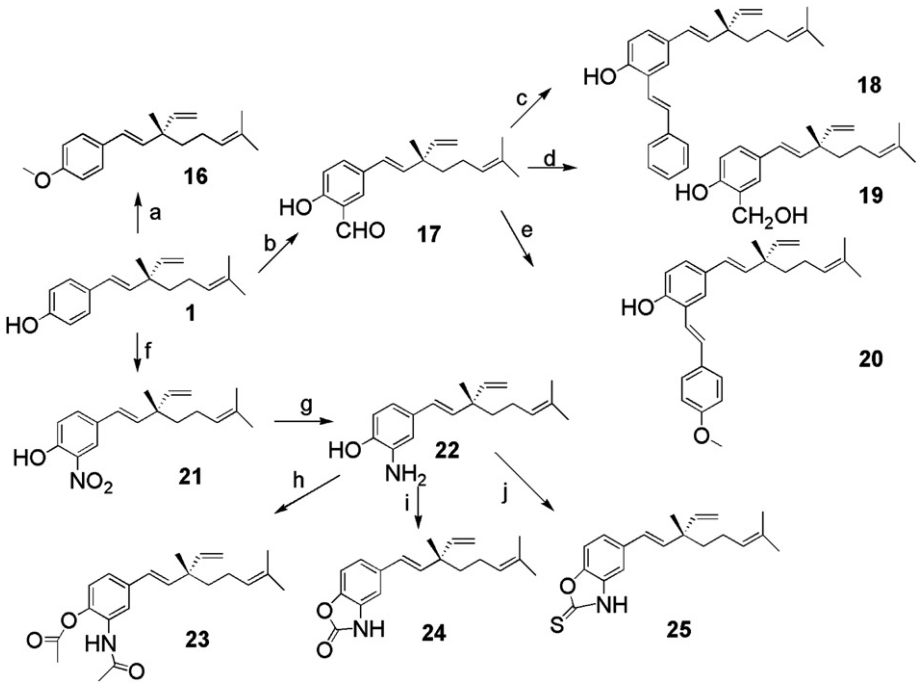
2.2. Biological activity

All of the compounds were tested in MTT assay for their cytotoxicity, T cell and B cell functional assays for evaluating their immunosuppressive activity in vitro. The pharmacological results of these compounds are summarized in Tables 1–3.

The effect of $\Delta^{12,13}$ modifications showed that all the C-12,13 derivatives (**2**, **3**, **4**, **5**) exhibited higher bioactivity than bakuchiol on the Con A induced T cell proliferation. In the inhibition of LPS induced B cell proliferation, **2**, **3** exhibited lower bioactivity and **4**, **5** exhibited slightly higher bioactivity at the concentration of 1 μM, however, all the compounds (**2**, **3**, **4**, **5**) exhibited higher bioactivity at the concentration of 10 μM compared to bakuchiol (**1**). The entire $\Delta^{12,13}$ series also showed an increase in cytotoxicity compared to bakuchiol (**1**), especially for compound **3** which exhibited cytotoxicity at a lower concentration (10 μM). In this series, compound **2** was the most active analogue.

To our disappointment, the C-9, $\Delta^{7,8}$ double bond, and $\Delta^{17,18}$ double bond were not good sites to modify since the derivatives did not show obviously improved activity while exhibiting higher cytotoxicity. (±)bakuchiol (**8**) exhibited slightly improved inhibitory activity both on ConA-induced T cell proliferation and on LPS-induced B cell proliferation meanwhile increased the cytotoxicity compared to bakuchiol (**1**). The C-7,8 modifications (**6, 7**) and C-17,18 modifications (**14, 15**) showed lower inhibitory activity on ConA-induced T cell proliferation and almost the same or slightly improved inhibitory activity on LPS-induced B cell proliferation compared to (±)bakuchiol (**8**). For the extraordinary cytotoxicity of compound **10**, we presumed that it was because the compound itself at the higher concentration (10 and 100 μM) would absorb the photons which influenced the OD value. Compound **9** showed no significant inhibitory activity on ConA-induced T cell proliferation and there was no dose-dependent relationship.

On the basis of the pharmacological results of aryl substitutions, several structure–activity relationship conclusions were summarized as follows:



Scheme 3. Reagents and conditions: (a) CH_3I, K_2CO_3, acetone, 5 h, 90%; (b) $(CH_2O)n$, $MgCl_2$, Et_3N, THF, reflux, 62%; (c) 50% NaOH, $C_6H_5CH_2P^+Ph_3Br^-$, CH_2Cl_2, rt, 85% (recovered starting material); (d) $NaBH_4$, CH_3OH, rt, 96%; (e) 50% NaOH, *p*-$CH_3OC_6H_5CH_2P^+Ph_3Br^-$, CH_2Cl_2, rt, 85% (recovered starting material); (f) HNO_3, CH_3COOH: cyclohexane = 1:3, 40–50 °C, 70%; (g) Zn–Fe, CH_2Cl_2, 5% HCl, 40 °C, 93%; (h) $(CH_3CO)_2O$, Py., rt, 99%; (i) NH_2CONH_2, Py., reflux, 99%; (j) KOH, CS_2, CH_3OH, H_2O, 97%.

Table 1. Effect of Compounds **1**–**5** on murine lymphocyte proliferation induced by Concanavalin A (ConA) (5 mg/mL) or lipopolysaccharide (LPS) (10 mg/mL)

Compound	Concentration (M)	Cytotoxicity	Inhibitory rate (%)	
			ConA-induced T cell proliferation[a]	LPS-induced B cell proliferation
1	10^{-6}	−	−14	−21
	10^{-5}	−	−27	−39
	10^{-4}	−	−18	−32
2	10^{-6}	−	−30	−14
	10^{-5}	−	−93	−89
	10^{-4}	+	−100	−99
3	10^{-6}	−	−30	−16
	10^{-5}	+	−89	−83
	10^{-4}	+	−100	−99
4	10^{-6}	−	−15	−25
	10^{-5}	+	−47	−45
	10^{-4}	+	−100	−100
5	10^{-6}	−	−22	−22
	10^{-5}	−	−75	−63
	10^{-4}	+	−100	−99

[a] Student's *t*-test was used to determine significance. Once the OD value was reduced and $P < 0.05$ was considered significant.

1. Protecting the phenol with methyl (**16**) could slightly improve the inhibitory activity.
2. Introducing conjugated groups to the *ortho*-position of the phenol (**17**, **18**) led to higher immunosuppressive activity, except the nitro compound (**21**), which relatively increased the cytotoxicity and their (**17**, **18**) inhibitory activity on LPS-induced B cell proliferation was more potent than on ConA-induced T cell proliferation. It was noteworthy that **20** slightly strengthened the T lymphocyte proliferation.
3. Introducing electron-donating groups (**19**, **22**) did not cause obvious change of the inhibitory effect but improved the cytotoxicity. If held in the phenol and the amino (**23**, **24**), it could decrease the cytotoxicity but the thiazole compound **25** exhibited considerable cytotoxicity.

3. Conclusions

In summary, a series of derivatives of bakuchiol were synthesized and assessed in vitro for their cytotoxicity of lym-

Table 2. Effect of compounds **6–15** on murine lymphocyte proliferation induced by Concanavalin A (ConA) (5 mg/mL) or lipopolysaccharide (LPS) (10 mg/mL)

Compound	R_1	$R_2(R_2')$	$R_3(R_3')$	Concentration (M)	Cytotoxicity[a]	Inhibitory rate (%)	
						ConA-induced T cell proliferation	LPS-induced B cell proliferation
6	CH_2CH	OCH_3	H	10^{-6}	–	−9	−21
				10^{-5}	–	−8	−38
				10^{-4}	+	−93	−99
7	CH_2CH	OCH_3	F	10^{-6}	–	−20	−36
				10^{-5}	–	−11	−40
				10^{-4}	–	−100	−100
8	CH_2CH	OH	H	10^{-6}	–	−19	−26
				10^{-5}	–	−45	−42
				10^{-4}	+	−100	−99
9	CH_2CH	OCH_3	H	10^{-6}	–	−13	−29
				10^{-5}	–	−10	−35
				10^{-4}	–	+2	−26
10	CH_2CH	OCH_3	F	10^{-6}	+	−17	−33
				10^{-5}	–	−20	−38
				10^{-4}	–	1	−9
11	CH_2CH	OCH_3	$R_3=R_2$	10^{-6}	–	−26	−29
				10^{-5}	–	−22	−51
				10^{-4}	+	−100	−99
12	CH_2CH	OH	F	10^{-6}	–	−8	−30
				10^{-5}	–	−46	−48
				10^{-4}	+	−100	−100
13	CH_2CH	OH (OCH_3)	OCH_3 (OH)	10^{-6}	–	−10	−33
				10^{-5}	+	−100	−100
				10^{-4}	+	−100	−99
14	OH	OCH_3	H	10^{-6}	–	−24	−31
				10^{-5}	–	−24	−45
				10^{-4}	+	−97	−98
15	$CH_2C_6H_4OCH_3$-*p*	OCH_3	H	10^{-6}	–	−2	−18
				10^{-5}	–	−2	−32
				10^{-4}	+	−100	−100

[a] Student's *t*-test was used to determine significance. Once the OD value was reduced and $P < 0.05$ was considered significant.

phocyte, inhibitory activity on Con A-induced T cell proliferation and LPS-induced B cell proliferation in comparison with bakuchiol. In the current study, it was found that C-12,13 was a potential site to be modified that could improve the inhibitory activity and the introduction of conjugated groups to the *ortho*-position of the phenol was probably a good way to improve the immunosuppressive activity. The chiral quaternary center (C-9) was essential since (±)bakuchiol could increase the cytotoxicity.

4. Experimental

4.1. Chemistry

NMR: Bruker 400 MHz instrument; TMS as internal standard; δ in ppm, J in Hz. EI-MS, HR-EI-MS: Finnigan LCQ-DECA instrument. Column chromatography (CC): silica gel (200–300 mesh; Qingdao Marine Chemical, China). TLC: GF 254 silica gel plates (Yantai Marine Chemical Co. Ltd, China); detection by spraying with 5% H_2SO_4 soln. followed by heating. HPLC: Agilent 1100 series. Solvents were distilled from the appropriate drying agents before use.

4.1.1. Preparation of 12,13-epoxybakuchiol (2). Bakuchiol (5.0 mmol) was dissolved in 30 ml CH_2Cl_2 at 0 °C and *m*-CPBA (*m*-chloroperbenzoic acid, 5.5 mmol) in 60 ml CH_2Cl_2 was added slowly. After being stirred for 3 h at 25 °C, aqueous saturated $NaHSO_3$ solution was added and stirred for an additional 0.5 h. The reaction mixture was extracted with CH_2Cl_2 and the organic layer was washed with water, dried, and evaporated. The product was purified by column chromatography using hexane–EtOAc as eluent to give **2** (78%).

Compound **2**: ^{1}H NMR (400 MHz, CD_3COCD_3) δ 1.19 (6H, s), 1.22 (3H, s), 1.58 (4H, m), 2.64 (1H, t,

Table 3. Effect of compounds **16–25** on murine lymphocyte proliferation induced by Concanavalin A (ConA) (5 mg/mL) or lipopolysaccharide (LPS) (10 mg/mL)

Compound	Concentration (M)	Cytotoxicity[a]	Inhibitory rate (%)	
			ConA-induced T cell proliferation	LPS-induced B cell proliferation
16	10^{-6}	–	−16	−33
	10^{-5}	–	0	−22
	10^{-4}	–	−74	−69
17	10^{-6}	–	−21	−41
	10^{-5}	–	−79	−90
	10^{-4}	+	−100	−100
18	10^{-6}	–	−13	−24
	10^{-5}	–	−34	−57
	10^{-4}	+	−100	−100
19	10^{-6}	–	−22	−25
	10^{-5}	+	−23	−34
	10^{-4}	+	−100	−100
20	10^{-6}	–	16	3
	10^{-5}	–	24	−8
	10^{-4}	+	−100	−100
21	10^{-6}	–	−10	−22
	10^{-5}	+	−16	−27
	10^{-4}	+	−9	−9
22	10^{-6}	–	−23	−36
	10^{-5}	+	−40	48
	10^{-4}	+	−100	−100
23	10^{-6}	–	−14	−21
	10^{-5}	–	−46	−52
	10^{-4}	+	−100	−100
24	10^{-6}	–	−16	−21
	10^{-5}	–	−14	−16
	10^{-4}	–	−19	−16
25	10^{-6}	–	−19	−30
	10^{-5}	+	−33	−43
	10^{-4}	+	−99	−100

[a] Student's *t*-test was used to determine significance. Once the OD value was reduced and $P < 0.05$ was considered significant.

J = 6.0 Hz), 5.01 (1H, m), 5.05 (1H, m), 5.92 (1H, m), 6.09 (1H, d, J = 16.2 Hz), 6.30 (1H, d, J = 16.2 Hz), 6.78 (2H, d, J = 8.5 Hz), 7.27 (2H, d, J = 8.5 Hz); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 18.6, 23.3, 23.4, 24.7, 38.0, 42.5, 57.9, 64.2, 112.0, 115.8, 127.7, 127.8, 129.9, 134.7, 146.5, 157.3; EI-MS *m*/*z* 272 (M^+); HR-EI-MS *m*/*z* calcd $C_{18}H_{24}O_2$: 272.1776, found: 272.1779.

4.1.2. Preparation of 12,13-diolbakuchiol (3). Compound **2** (1.0 mmol) was dissolved in the mixture of dioxane and water (1:1, 15 ml) at 25 °C and 2–3 drops of 70% H_2SO_4 were added. After 1 min, the reaction mixture was quenched by aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated. The product was purified by column chromatography using hexane–EtOAc as eluent to give **3** (99%).

Compound **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (6H, s), 1.13 (3H, s), 1.23 (1H, m), 1.40 (1H, m), 1.54 (1H, m), 1.86 (1H, m), 3.18 (1H, dd, J = 5.0, 12.0 Hz), 4.95 (1H, d, J = 10.8 Hz), 4.96 (1H, d, J = 17.6 Hz), 5.86 (1H, dd, J = 10.8, 17.6 Hz), 6.05 (1H, d, J = 15.9 Hz), 6.23 (1H, d, J = 15.9 Hz), 6.72 (2H, d, J = 8.5 Hz), 7.20 (2H, d, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 24.8, 25.6, 26.9, 39.2, 42.7; 72.5, 79.4, 111.6, 115.8, 127.3, 127.7, 130.1, 135.3, 147.0, 157.2; EI-MS *m*/*z* 290 (M^+); HR-EI-MS *m*/*z* calcd $C_{18}H_{26}O_3$: 290.1882. Found: 290.1880.

4.1.3. Preparation of 12-oxobakuchiol (4) and Δ,[14] 12-hydroxybakuchiol (5). *p*-TsOH (0.1 mmol) was added to a solution of compound **2** (1 mmol) in CH_2Cl_2 at room temperature and the resulting solution was stirred for 0.5 h. The reaction mixture was quenched by aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated. The product was purified by column chromatography using hexane–EtOAc as eluent to give **4** (20%) and **5** (64%).

Compound **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, s), 1.08 (3H, s), 1.17 (3H, s), 1.79 (2H, t, J = 7.8 Hz), 2.45 (2H, t, J = 7.8 Hz), 2.60 (1H, m), 5.02 (1H, dd, J = 1.2, 17.5 Hz), 5.06 (1H, dd, J = 1.2, 10.8 Hz), 5.83 (1H, dd, J = 10.8, 17.5 Hz), 5.98 (1H, d, J = 16.2 Hz),

6.25 (1H, d, J = 16.2 Hz), 6.79 (2H, d, J = 8.6 Hz), 7.23 (2H, d, J = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 23.4, 34.1, 35.8, 41.0, 42.0, 112.5, 11.4, 127.1, 127.3, 130.2, 134.6, 145.1, 155.1, 215.8; IRν_{max} (KBr): 3382.6, 2968.0, 1695.1, 972.0, 813.8 cm^{-1}; EI-MS m/z 272 (M^+); HR-EI-MS m/z calcd $C_{18}H_{24}O_2$: 272.1777. Found: 272.1767.

Compound **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (3H, s), 1.56 (2H, m), 1.70 (3H, s), 1.77 (2H, m), 4.06 (1H, m), 4.95 (4H, m), 5.73 (1H, br s), 5.85 (1H, dd, J = 10.8, 17.6 Hz), 6.01 (1H, d, J = 16.2 Hz), 6.23 (1H, d, J = 16.2 Hz), 6.76 (2H, d, J = 8.4 Hz), 7.21 (2H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 23.4, 26.9, 29.5, 36.7, 42.1, 111.6, 112.1, 115.4, 126.7, 127.3, 130.4, 135.3, 145.7, 147.0, 154.9; EI-MS m/z 272 (M^+); HPLC 98.2% (the ratio of diastereoisomeric mixture is almost 1:1).

4.1.4. The procedures for preparation of compounds 6–15. A solution of Grignard reagent (2 equiv) in an inert argon atmosphere was added to a suspension of cuprous iodide (0.5 equiv) in THF and cooled to −40 °C. After stirring for 15 min at −40 °C, a solution of citral (1 equiv) in THF was added to the reaction mixture and the mixture was stirred for an additional 2 h at −40 °C. After quenching with an aqueous saturated NH_4Cl solution, the mixture was diluted with Et_2O and successively washed twice with water and once with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by column chromatography using hexane–EtOAc as eluent.

Subsequently, another Grignard reagent was added to the aldehyde obtained above in dry THF with cooling (0 °C) and stirring. After stirring for another hour, the reaction mixture was allowed to stand overnight at room temperature. The contents were cooled to 0 °C, decomposed with cooled solution of ammonium chloride, and worked up in the usual manner. The product was purified by column chromatography using hexane–EtOAc as eluent to give the alcohol as diastereoisomeric mixtures.

The mixture of alcohols was dissolved in dry pyridine and phosphoryl chloride was added dropwise with stirring. The mixture was heated under reflux at 140 °C (bath) for 1 h, cooled, diluted with light petroleum, and washed with dilute hydrochloric acid, saturated sodium hydrogen carbonate, and water. The light petroleum layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by column chromatography using light petroleum as eluent.

The product obtained above was added to a solution of methylmagnesium iodide in anhydrous ether. All the solvent was evaporated off under vacuum, and the residue, under argon, was heated at 180 °C for 10–20 min. After cooling the mixture to rt, ether and dilute hydrochloric acid were added. The mixture was shaken and the ether layer was washed with water, dried, and evaporated. The product was purified by column chromatography using hexane–EtOAc as eluent.

Compound **6**: (2 steps, overall yield: 54%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (3H, s), 1.38 (2H, m), 1.59 (3H, m), 1.67 (3H, m), 1.84 (4H, m), 3.78 (3H, s), 4.76 (1H, m), 5.08 (3H, m), 5.89 (1H, m), 6.87 (2H, m), 7.25 (2H, m). EI-MS m/z 288 (M^+); HR-EI-MS m/z calcd $C_{19}H_{28}O_2$: 288.2089. Found: 288.2077.

Compound **7**: (2 steps, overall yield: 51%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, m), 1.34 (2H, m), 1.58 (3H, m), 1.67 (3H, m), 1.85 (4H, m), 3.88 (3H, m), 4.75 (1H, m), 5.08 (3H, m), 5.89 (1H, m), 6.90 (1H, m), 7.01 (1H, m), 7.07(1H, m). EI-MS m/z 306 (M^+); HR-EI-MS m/z calcd $C_{19}H_{27}FO_2$: 306.1995, Found: 306.1981.

Compound **8**: (Yield: 88–92%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, s), 1.50 (2H, m), 1.59 (3H, s), 1.68 (3H, s), 1.96 (2H, m), 5.02 (1H, d, J = 17.5 Hz), 5.04 (1H, d, J = 10.8 Hz), 5.12 (1H, t, J = 7.5 Hz), 5.89 (1H, dd, J = 10.8, 17.5 Hz), 6.06 (1H, d, J = 16.2 Hz), 6.26 (1H, d, J = 16.2 Hz), 6.78 (2H, d, J = 8.5 Hz), 7.25 (2H, d, J = 8.5 Hz). EI-MS: 256 (M^+); HR-EI-MS m/z calcd $C_{18}H_{24}O$: 256.1827; found: 256.1829.

Compound **9**: (Yield: 90–96%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, s), 1.50 (2H, m), 1.58 (3H, s), 1.67 (3H, s), 1.93 (2H, m), 3.80 (3H, s), 5.01 (1H, d, J = 17.8 Hz), 5.03 (1H, d, J = 10.5 Hz), 5.10 (1H, t, J = 7.4 Hz), 5.88 (1H, dd, J = 10.4, 17.8 Hz), 6.06 (1H, d, J = 16.6 Hz), 6.26 (1H, d, J = 16.6 Hz), 6.84 (2H, d, J = 8.6 Hz), 7.29 (2H, d, J = 8.6 Hz). EI-MS m/z 270 (M^+); HR-EI-MS m/z calcd $C_{19}H_{26}O$: 270.1984. Found: 270.1985.

Compound **10**: (Yield: 90–96%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, s), 1.49 (2H, m), 1.58 (3H, s), 1.67 (3H, s), 1.93 (2H, m), 3.88 (3H, s), 5.03 (2H, m), 5.10 (1H, t, J = 7.1 Hz), 5.87 (1H, dd, J = 10.8, 17.5 Hz), 6.06 (1H, d, J = 16.2 Hz), 6.21 (1H, d, J = 16.2 Hz), 6.88 (1H, t, J = 8.5 Hz), 7.02 (1H, d, J = 9.4 Hz), 7.12 (1H, dd, J = 2.1, 12.5 Hz); EI-MS m/z 288 (M^+); HR-EI-MS m/z calcd $C_{19}H_{25}FO$: 288.1890. Found: 288.1881.

Compound **11**: (2 steps, overall yield: 86%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, s), 1.49 (2H, m), 1.58 (3H, s), 1.67 (3H, s), 1.94 (2H, m), 3.88 (3H, s), 3.91 (3H, s), 5.04 (2H, m), 5.11 (1H, t, J = 7.1 Hz), 5.87 (1H, dd, J = 10.8, 17.3 Hz), 6.06 (1H, d, J = 16.2 Hz), 6.27 (1H, d, J = 16.2 Hz), 6.81 (1H, d, J = 8.7 Hz), 6.88 (1H, d, J = 8.7 Hz), 6.92 (1H, s); EI-MS m/z 300 (M^+); HR-EI-MS m/z calcd $C_{20}H_{28}O_2$: 300.2089. Found: 300.2097.

Compound **12**: (Yield: 88–92%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, s), 1.48 (2H, m), 1.58 (3H, s), 1.67 (3H, s), 1.93 (2H, m), 5.05 (3H, m), 5.86 (1H, dd, J = 10.7, 17.5 Hz), 6.06 (1H, d, J = 16.1 Hz), 6.21 (1H, d, J = 16.1 Hz), 6.92 (1H, t, J = 8.6 Hz), 7.02 (1H, d, J = 9.4 Hz), 7.12 (1H, dd, J = 1.9, 12.0 Hz). EI-MS

m/z 274 (M^+); HR-EI-MS *m/z* calcd $C_{18}H_{23}FO$: 274.1733. Found: 274.1732.

Compound **13**: (Yield: 88–92%) ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (1.5H, s), 1.20 (1.5H, s), 1.49 (2H, m), 1.58 (3H, s), 1.67 (3H, s), 1.94 (2H, m), 3.86 (1.5H, s), 3.89 (1.5H, s), 5.02 (2H, m), 5.10 (1H, m), 5.87 (1H, m), 6.04 (1H, m), 6.23 (1H, m), 6.79 (1H, m), 6.86 (1H, m), 7.01 (1H, s). EI-MS *m/z* 286 (M^+); HR-EI-MS *m/z* calcd $C_{19}H_{26}O_2$: 286.1933. Found: 286.1928.

Compound **14**: (Yield: 95%) ^1H NMR (400 MHz, $CDCl_3$) δ 1.37(3H, s), 1.59 (3H, s), 1.65 (2H, m), 1.68 (3H, s), 2.07 (2H, m), 3.81 (3H, s), 5.14 (1H, m), 6.14 (1H, d, J = 16.2 Hz), 6.53 (1H, d, J = 16.2 Hz), 6.86 (1H, d, J = 8.7 Hz), 7.32 (1H, d, J = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 23.0, 25.7, 28.3, 42.6, 55.3, 73.4, 113.9, 124.3, 126.5, 127.5, 129.8, 132.0, 134.5, 159.0; EI-MS *m/z* 260 (M^+); HR-EI-MS *m/z* calcd $C_{17}H_{24}O_2$: 260.1776. Found: 260.1774.

Compound **15**: (3 steps, overall yield: 36%) ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (3H, s), 1.41 (2H, m),1.57 (3H, s), 1.66 (3H, s), 1.94 (2H, m), 2.62 (1H, s), 2.63 (1H, s), 3.78 (3H, s), 3.81 (3H, s), 5.09 (1H, m), 6.00 (1H, d, J = 16.2 Hz), 6.11 (1H, d, J = 16.2 Hz), 6.78 (1H, d, J = 8.8 Hz), 6.85 (1H, d, J = 8.7 Hz) 7.03 (1H, d, J = 8.8 Hz),7.28 (1H, d, J = 8.7 Hz); EI-MS *m/z* 364 (M^+); HR-EI-MS *m/z* calcd $C_{25}H_{32}O_2$: 364.2402. Found: 364.2406.

4.1.5. Preparation of methyl ether of bakuchiol (16). Bakuchiol (2 mmol) was dissolved in acetone (5 ml) and anhydrous K_2CO_3 (3 mmol) was added followed by 2 mmol of MeI. The mixture was allowed to reflux for 8 h. The reaction mixture was cooled, filtered, and evaporated. The product was purified by column chromatography using hexane–EtOAc as eluent to give **16** (90%).

The NMR spectra data of compound**16** are the same as those with that of compound **9**.

4.1.6. Preparation of 3-formylbakuchiol (17). A mixture of bakuchiol (10 mmol), $MgCl_2$ (20 mmol), Et_3N (20 mmol) and paraformaldehyde (30 mmol) under argon and in THF (15 ml) was heated under reflux for 3 h. The reaction mixture was cooled to room temperature and ether was added. The resulting organic phase was washed successively with 1 N HCl and water, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by column chromatography using hexane–EtOAc as eluent to give **17** (62%).

Compound **17**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, s), 1.51 (2H, m), 1.58 (3H, s), 1.67 (3H, s), 1.95 (2H, m), 5.06 (3H, m), 5.88 (1H, dd, J = 10.6, 17.5 Hz), 6.12 (1H, d, J = 16.2 Hz), 6.28 (1H, d, J = 16.2 Hz), 6.94 (1H, d, J = 8.6 Hz), 7.50 (1H, d, J = 2.0 Hz), 7.56 (1H, dd, J = 2.0, 8.6 Hz), 9.89 (1H, s), 10.93 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 23.2, 25.7, 41.2, 42.6, 112.2, 117.7, 120.4, 124.6, 125.2, 130.2, 131.0, 131.4, 134.5, 137.4, 145.5, 160.6, 196.6; IR ν_{max} (KBr) 2966.0, 2921.7, 1660.4, 1484.9, 970.0, 914.1 cm^{-1}; EI-MS *m/z* 284 (M^+); HR-EI-MS *m/z* calcd $C_{19}H_{24}O_2$: 284.1777. Found: 284.1776.

4.1.7. Preparation of 3-(*E*)-styrylbakuchiol (18) and 3-methoxystyrylbakuchiol (20). Compound 17 (1 mmol) and the Wittig salt (1.2 mmol) were dissolved in CH_2Cl_2 (10 ml) followed by adding 50% NaOH (7 mmol) dropwise. After 3 h, the reaction mixture was quenched by aqueous saturated NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated. The product was purified by column chromatography using hexane–EtOAc as eluent.

Compound **18**: (Yield: 85%) ^1H NMR (400 MHz, CD_3COCD_3) δ 1.15 (3H, s), 1.45 (2H, m), 1.51 (3H, s), 1.59 (3H, s), 1.92 (2H, m), 4.98 (2H, m), 5.07 (1H, m), 5.88 (1H, dd, J = 10.2, 18.0 Hz), 6.12 (1H, d, J = 16.5 Hz), 6.26 (1H, d, J = 16.5 Hz), 6.84 (1H, d, J = 8.2 Hz), 7.14 (1H, dd, J = 2.0, 8.2 Hz), 7.18 (1H, m), 7.23 (1H, d, J = 16.4 Hz), 7.30 (2H, t, J = 7.6 Hz), 7.45 (1H, d, J = 16.4 Hz), 7.52 (2H, d, J = 7.1 Hz), 7.62 (1H, d, J = 2.0 Hz); IR ν_{max} (KBr): 3253.4, 2969.9, 2927.5, 1498.4, 966.2, 507.2 cm^{-1}; EI-MS *m/z* 358 (M^+); HR-EI-MS *m/z* calcd $C_{26}H_{30}O$: 358.2297. Found: 358.2292.

Compound **20**: (Yield: 85%) ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, s), 1.51 (2H, m), 1.59 (3H, s), 1.68 (3H, s), 1.97 (2H, m), 3.84 (3H, s), 5.04 (2H, m), 5.12 (1H, m), 5.89 (1H, dd, J = 10.6, 17.3 Hz), 6.10 (1H, d, J = 16.2 Hz), 6.28 (1H, d, J = 16.2 Hz), 6.75 (1H, d, J = 8.2 Hz), 6.90 (2H, d, J = 2.0, 8.6 Hz), 7.07 (1H, d, J = 16.2 Hz), 7.15 (1H, dd, J = 2.2, 8.2 Hz), 7.20 (1H, d, J = 16.2 Hz), 7.48 (3H, m); EI-MS *m/z* 388 (M^+); HR-EI-MS *m/z* calcd $C_{27}H_{32}O_2$: 388.2403. Found: 388.2404.

4.1.8. Preparation of 3-hydroxymethylbakuchiol (19). Compound **17** (1 mmol) was dissolved in CH_3OH (10 ml) and $NaBH_4$ was added. After 0.5 h, the reaction mixture was poured into 20 ml water and extracted with Et_2O. The organic layer was washed with brine, dried, and evaporated. The product was purified by column chromatography using hexane–EtOAc as eluent to give **19** (96%).

Compound **19**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, s), 1.48 (2H, m), 1.58 (3H, s), 1.67 (3H, s), 1.95 (2H, m), 2.27 (1H, t, J = 4.5), 4.86 (2H, d, J = 4.5 Hz), 5.02 (2H, m), 5.09 (1H, m), 5.86 (1H, dd, J = 10.8, 17.2 Hz), 6.04 (1H, d, J = 16.1 Hz), 6.22 (1H, d, J = 16.1 Hz), 6.83 (1H, d, J = 8.1 Hz), 7.06 (1H, s), 7.21 (1H, dd, J = 8.1 Hz); EI-MS *m/z* 286 (M^+); HR-EI-MS *m/z* calcd $C_{19}H_{26}O_2$: 286.1933. Found: 286.1941.

4.1.9. Preparation of 3-nitrobakuchiol (21). The mixture of HNO_3 and HOAc (12:24 mmol) was added to the solution of bakuchiol (10 mmol) in HOAc and cyclohexane (1:3, 50 ml) with heating (48 °C) and stirring. 10 min later, the reaction mixture was poured into water and extracted with Et_2O. The organic layer was washed with brine, dried, and evaporated. The product was purified by column chromatography using hexane–EtOAc as eluent to give **21** (70%).

Compound **21**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, s), 1.51 (2H, m), 1.58 (3H, s), 1.67 (3H, s), 1.92 (2H, m), 5.05 (3H, m), 5.86 (1H, dd, J = 10.6, 17.5 Hz), 6.17 (1H, d, J = 16.2 Hz), 6.26 (1H, d, J = 16.2 Hz), 7.10 (1H, d, J = 8.9 Hz), 7.62 (1H, dd, J = 2.2, 8.9 Hz), 8.03 (1H, d, J = 2.2 Hz), 10.54 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 22.9, 23.0, 25.5, 40.9, 42.6, 112.6, 120.1, 121.9, 124.6, 131.0, 131.7, 133.6, 135.1, 139.4, 145.3, 154.2; EI-MS *m*/*z* 301 (M^+); HR-EI-MS *m*/*z* calcd $C_{18}H_{23}NO_3$: 301.1677, Found: 301.1685.

4.1.10. Preparation of 3-aminobakuchiol (22). Five percentage of HCl (1 ml) and Fe–Zn (3:3 mmol) were added to the solution of compound **21** in CH_2Cl_2 (10 ml) with heating (40 °C) and stirring. 1 h later, the reaction mixture was cooled, filtered. The filtrate was extracted with CH_2Cl_2 and washed with aqueous saturated $NaHCO_3$ solution. The organic layer was dried and evaporated. The product was purified by column chromatography using hexane–EtOAc as eluent to give **22** (93%).

Compound **22**: ^{1}H NMR (400 MHz, $CDCl_3$+D_2O) δ 1.17 (3H, s), 1.47 (2H, m), 1.57 (3H, s), 1.67 (3H, s), 1.93 (2H, m), 4.78 (1H, br s), 5.01 (2H, m), 5.10 (1H, m), 5.86 (1H, dd, J = 10.8, 17.5 Hz), 6.00 (1H, d, J = 16.2 Hz), 6.17 (1H, d, J = 16.2 Hz), 6.64 (1H, d, J = 8.0 Hz), 6.68 (1H, dd, J = 1.8, 8.0 Hz), 6.81 (1H, d, J = 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 23.0, 23.1, 25.5, 41.1, 42.3, 111.9, 114.4, 115.3, 118.1, 124.9, 126.9, 131.4, 131.6, 134.3, 135.7, 143.6, 146.2; EI-MS *m*/*z* 271 (M^+); HR-EI-MS *m*/*z* calcd $C_{18}H_{25}NO$: 271.1937. Found: 271.1950.

4.1.11. Preparation of 3-acetamido-4-acetylbakuchiol (23). Compound **22** was acetylated by the conventional manner, using the Ac_2O/pyridine, to give the product **23** (99%).

Compound **23**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, s), 1.48 (2H, m), 1.58 (3H, s), 1.67 (3H, s), 1.93 (2H, m), 2.19 (3H, s), 2.36 (3H, s), 5.01 (2H, m), 5.09 (1H, t, J = 7.2 Hz), 5.86 (1H, dd, J = 10.8, 17.4 Hz), 6.17 (1H, d, J = 16.4 Hz), 6.29 (1H, d, J = 16.4 Hz), 7.05 (1H, d, J = 8.3 Hz),7.13 (1H, d, J = 8.3 Hz), 8.16 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 21.1, 23.2, 24.7, 25.7, 41.1, 42.7, 112.2, 120.5, 121.9, 122.2, 124.6, 126.3, 129.6, 131.4, 136.5, 138.8, 139.3, 145.5, 168.1, 168.7; EI-MS *m*/*z* 355 (M^+); HR-EI-MS *m*/*z* calcd $C_{22}H_{29}NO_3$: 355.2148. Found: 355.2159.

4.1.12. Preparation of 3,4-benzo[*d*]oxazole-2′-onebakuchiol (24). A solution of compound **22** (0.5 mmol) and urea (0.5 mmol) in dry pyridine (0.5 ml) was refluxed for 10–12 h and poured into ice-cold water. The resulting mixture was extracted with EtOAc and washed with brine. The organic layer was dried and evaporated. The product was purified by column chromatography using hexane–EtOAc as eluent to give **24** (99%).

Compound **24**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, s), 1.54 (2H, m), 1.58 (3H, s), 1.67 (3H, s), 1.95 (2H, m), 5.06 (3H, m), 5.87 (1H, dd, J = 10.8, 17.4 Hz), 6.14 (1H, d, J = 16.4 Hz), 6.30 (1H, d, J = 16.4 Hz), 7.08 (1H, dd, J = 1.7, 8.3 Hz), 7.12 (2H, m), 9.00 (1H, br s); IR ν_{max} (KBr): 3216.7, 2923.6, 1778.1, 1463.7, 968.1, 709.7 cm^{-1}; EI-MS *m*/*z* 297 (M^+); HR-EI-MS *m*/*z* calcd $C_{19}H_{23}NO_2$: 297.1729. Found: 297.1733.

4.1.13. Preparation of 3,4-benzo[*d*]oxazole-2′-thionebakuchiol (25). A solution of compound **22** (0.5 mmol), KOH (0.5 mmol), and CS_2 (0.5 mmol) in methanol (1 ml) and water (0.15 ml) was refluxed for 3 h. The reaction mixture was poured into water, extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated. The product was purified by column chromatography using hexane–EtOAc as eluent to give **19** (97%).

Compound **25**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, s), 1.51 (2H, m), 1.58 (3H, s), 1.67 (3H, s), 1.95 (2H, m), 5.06 (3H, m), 5.87 (1H, dd, J = 10.8, 17.5 Hz), 6.18 (1H, d, J = 16.3 Hz), 6.32 (1H, d, J = 16.3 Hz), 7.18 (1H, d, J = 1.5 Hz), 7.22(1H, dd, J = 1.5, 8.5 Hz), 7.26 (1H, d, J = 8.5 Hz), 10.6 (1H, br s); IR ν_{max} (KBr): 3178.2, 2966.0, 1459.9, 933.4, 628.7 cm^{-1}; EI-MS *m*/*z* 313 (M^+); HR-EI-MS *m*/*z* calcd $C_{19}H_{23}NOS$: 313.1501. Found: 313.1518.

4.2. Biological assays

4.2.1. Reagents. Concanavalin A (Con A), lipopolysaccharide (LPS, *Escherichia coli* 055:B5), 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide (MTT), and 3,3′,5,5′-tetramethylbenzidine (TMB) were Sigma (St. Louis, MO, USA) products. RPMI (Roswell Park Memorial Institute) 1640 medium was purchased from GibcoBRL, Life Technologies (USA). Fetal bovine serum (FBS) was purchased from HyClone Laboratories (Utah, USA). [^{3}H]thymidine (1 mCi/ml) was purchased from the Shanghai Institute of Atomic Energy.

4.2.2. Animal. BALB/c mice, used at 6 to 8 weeks of age, were purchased from Shanghai Experimental Animal Center and were housed in a controlled environment (12-h light/12-h dark photoperiod, 22 ± 1 °C, 55% ± 5% relative humidity). All husbandry and experimental contact made with the mice maintained specific pathogen-free conditions. All mice were allowed to acclimatize in our facility for 1 week before any experiments were started. All experiments were carried out according to the NIH Guide for Care and Use of Laboratory Animals and were approved by the Bioethics Committee of the Shanghai Institute of Materia Medica.

4.2.3. Preparation of spleen cell suspensions. Mice were sacrificed and their spleens were removed aseptically. A single spleen cell suspension was prepared and cell debris and clumps were removed. Erythrocytes were lysed with Tris-buffered ammonium chloride (0.155 M NH_4Cl, 16.5 mM Tris, pH 7.2) as previously described,[8–11] with slight modifications. Mononuclear cells were washed and resuspended in RPMI-1640 medium supplemented with 10% FBS, penicillin (100 U/ml), and streptomycin (100 mg/ml).

4.2.4. MTT assay. Cytotoxicity was assessed by the MTT assay as previously described,[8–11] with slight modifications. Briefly, spleen cells were cultured in triplicate for 48 h with compounds. The cells with media alone were used as controls. MTT (5 mg/ml) reagent was added 4 h before the end of culture, and then cells were lysed with 10% sodium dodecyl sulfate (SDS), 50% *N*,*N*-dimethyl formamide, pH 7.2. OD values were read at 570 nm 6 h later and the cell death percent was calculated. Five mice were analyzed for each data point.

4.2.5. Mitogen-induced proliferation assay. Spleen cells were cultured in triplicate for 48 h with 5 mg/ml of Concanavalin A (Con A) or 10 mg/ml of lipopolysaccharide (LPS) plus compounds. Cells were pulsed with 0.5 μCi/well of [^{3}H]thymidine for 8 h and harvested onto glass fiber filters. The incorporated radioactivity was then counted using a Beta Scintillation Counter (MicroBeta Trilux, PerkinElmer Life Sciences). Five mice were analyzed for each data point.

References and notes

1. Sun, N. J.; Woo, S. H.; Cassady, J. M.; Snapka, R. M. *J. Nat. Prod.* **1998**, *61*, 362, and references cited therein.
2. Park, E. J.; Zhao, Y. Z.; Kim, Y. C.; Sohn, D. H. *Planta Med.* **2005**, *71*, 508, and references cited therein.
3. Backhouse, C. N.; Delporte, C. L.; Negrete, R. E., et al. *J. Ethnopharmacol.* **2001**, *78*, 27.
4. Ferrandiz, M.; Gil, B.; Sanz, M. J., et al. *J. Pharm. Pharmacol.* **1996**, *48*, 975.
5. Backhouse, C. N.; Delporte, C. L.; Negrete, R. E., et al. *Phytochemistry* **1995**, *40*, 325.
6. Jia, Q.; Hong, M. F. U.S. patent 0,251,749, 2006.
7. Pae, H. O.; Cho, H.; Oh, G. S., et al. *Int. Immunopharmacol.* **2001**, *1*, 1849.
8. Yang, Z. S.; Zhou, W. L.; Sui, Y., et al. *J. Med. Chem.* **2005**, *48*, 4608.
9. Yao, G. M.; Ding, Y.; Zuo, J. P., et al. *J. Nat. Prod.* **2005**, *68*, 392.
10. Yang, Z. S.; Wang, J. X.; Zhou, Y., et al. *Bioorg. Med. Chem.* **2006**, *14*, 8043.
11. Zhang, Y. N.; Zhong, X. G.; Zheng, Z. P., et al. *Bioorg. Med. Chem.* **2007**, *15*, 988.
12. Ryu, S. Y.; Choi, S. U.; Lee, C. O.; Zee, O. P. *Arch. Pharm. Res.* **1992**, *15*, 356.
13. Kita, Y.; Furukawa, A.; Futamura, J.; Ueda, K.; Sawama, Y.; Hamamoto, H.; Fujioka, H. *J. Org. Chem.* **2001**, *66*, 8779.
14. This work will be detailed in a recent report.
15. Hansen, T. V. *Org. Synth.* **2005**, *82*, 64; Hansen, T. V.; Skattebol, L. *Tetrahedron Lett.* **2005**, *46*, 3357.
16. Varma, R. S.; Verma, K. K. *Indian J. Chem.* **1988**, *27B*, 698.