

4-Hydroxy-2'-Nitrodiphenyl Ether Analogues as Novel Tyrosinase Inhibitors

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Tyrosinase ubiquitously existing from microorganisms to animals and plants is known to be the most critical and rate limiting enzyme during melanin biosynthesis. In order to develop new tyrosinase inhibitor we have synthesized 14 diphenyl ether compounds possessing hydroxyl, bromo, and nitro groups in the structure. Among the compounds prepared, **18** and **19** have shown much stronger inhibition of tyrosinase monophenolase function than arbutin used as a positive control. Both compounds **18** and **19** possess *para*-hydroxyphenyl moiety in their structure, which might reinforce the importance of *p*-hydroxyphenyl group in the tyrosinase inhibitory process. In the DPPH radical scavenging activity test, none of the compounds even **18** and **19** showed significant antioxidant activity. The results suggest that elaborate adjustment of diphenyl ether analogues with proper substituents have potential to be developed as new skin whitening agents working on the tyrosinase function.

Key Words: Tyrosinase inhibitor, Hydroxynitrodiphenyl ether, DPPH, Melanogenesis, Skin whitening

Introduction

Tyrosinase also known as polyphenol oxidase (PPO) is a multifunctional copper containing glycoprotein which induces the browning of fruits, vegetables and mammalian melanogenesis. Since the discovery of tyrosinase by Bourquelot and Bertrand in 1895 from the mushroom *Russula nigricans*, a number of studies have been made on targeting tyrosinase.^{1,2} Tyrosinase ubiquitously existing from microorganisms to animals and plants is known to be the most critical and rate limiting enzyme during melanin biosynthesis.³ It catalyzes first two steps in the melanin biosynthesis, the *ortho*-hydroxylation of tyrosine (monophenol type) to DOPA (*o*-diphenol type) and oxidation of DOPA to dopaquinone (*o*-quinone type). This resulting quinone can be subsequently transformed into melanin pigments through a series of enzymatic and non-enzymatic reactions.⁴⁻⁶ The inhibition of tyrosinase is most common approach to achieve skin depigmentation as this enzyme catalyzes the rate limiting steps of the melanin biosynthesis.⁷

To date numbers of tyrosinase inhibitors are developed from synthesis and natural resources. Most of them are phenol/catechol derivatives, structurally similar to tyrosine or DOPA, which acts as alternative substrates of tyrosinase.⁸ Tyrosinase inhibitors are often constructed from one of two distinct substructures such as 4-substituted resorcinol moiety and catechols.⁹ Depending on their chemical structures, compounds with electron donor groups in their molecule may act as substrates and those with powerful electron acceptor groups may act as competitive inhibitors of tyrosinase.¹⁰ The 4-substituted resorcinol group has ability to bind into binuclear active site of the enzyme and inhibit its function. Catechol structure, with two OH groups at *o*-positions, may behave as a chelator with the copper ions in the tyrosinase.¹¹

Kojic acid¹² and arbutin¹³ are widely known hypopigmenting

agents (Figure 1). Recently, bibenzyl analogues are reported to have potent anti-tyrosinase activity with almost 20-fold strength than kojic acid.¹⁴ Polyhydroxydiphenyl ether isolated from endophytic fungus has antioxidant activity,¹⁵ which has potential to be effective on tyrosinase function.

Hydroxydiphenyl ethers are useful intermediates in organic synthesis and are found in a large number of biologically active compounds.¹⁶ Many reports, recently, have demonstrated that the diphenyl ether scaffolds are found in a number of natural products and biologically important molecules. These compounds have shown diverse pharmacological activities, such as antimetabolic, immunosuppressive and antibiotic activity, and are used in the control of weeds.¹⁷ Diarylbromophenols isolated from marine red alga showed potent DPPH scavenging activity. Free radicals attack biological molecules leading to many diseases associated with cell injury.¹⁸ Although diverse biological spectrum of hydroxydiphenyl ethers has been reported, little attention has been paid to the anti-tyrosinase activity of the

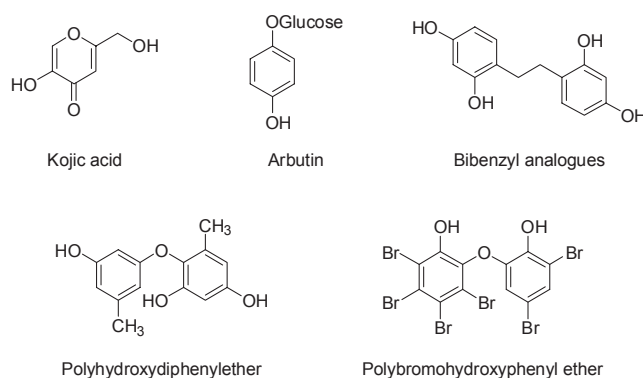


Figure 1. Tyrosinase inhibitors and biological active components from marine resources.

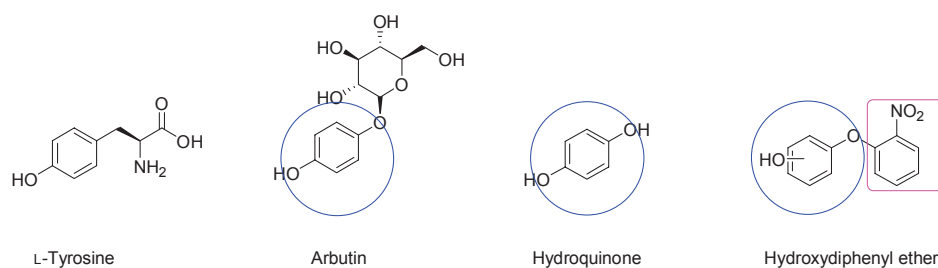


Figure 2. Structural similarity of hydroxynitrodiphenyl ether with L-tyrosine, arbutin, and hydroquinone.

compounds. In an effort to find potent anti-tyrosinase agent, we carried out our study to find a lead compound with hydroxyphenyl ether nucleus. For this purpose we considered the *para*-hydroxyphenyl part of L-tyrosine, arbutin and hydroquinone as common structure. Finally, we chose nitrophenyl as a one aryl ether part in the structure, which controls the electrostatic property of the diphenyl ether (Figure 2).

Experimental Section

General. Most of the chemicals and reagents used were obtained from Aldrich Chemical Co. and some were from other companies like Junsei, Acros Organics, Tokyo Chemicals. Melting points were measured without correction in open capillaries with Barnstead Electrothermal melting point apparatus, Manual MEL-TEMP (Model No: 1202D). Chromatographic separations were monitored by thin-layer chromatography (TLC) using commercially available pre-coated Merck Kieselgel 60 F₂₅₄ plate (0.25 mm) and detected by visualizing under UV at 254 and 365 nm. Silica gel column chromatography (SGC) was carried out with Merck Kieselgel 60 (0.040 - 0.063 mm). All solvents used for chromatography were directly used without distillation. NMR spectra were recorded on Varian AS 400 (¹H NMR at 400 MHz and ¹³C NMR at 100 MHz) with tetramethylsilane (TMS) as an internal standard. Chemical shift (δ) values are expressed in ppm and coupling constant (*J*) values in hertz (Hz). GC mass data were recorded using Agilent-5975C MSD (U.S.A) and Shimadzu GCMS-QP2010 (Japan).

General procedure A. To the round bottom flask containing proper phenol compound (1.0 eq.), were added sodium hydride (1.6 eq.) and copper (I) chloride (3.0 eq.). *N,N*-dimethylformamide (10 - 20 mL) was injected under nitrogen at room temperature followed by 5 min. stirring. After the addition of bromonitrobenzene, the reaction mixture was refluxed for 3 h under nitrogen condition. Reaction mixture was cooled to rt and diluted with ethyl acetate (EtOAc). The organic layer was washed with 1.0 M HCl, water, brine and dried with anhydrous Na₂SO₄. Solvent was removed under reduced pressure and purified by silica gel column chromatography to yield the product.

General procedure B. To the solution of diphenyl ether intermediate in 1,2-dichloroethane was added dropwise boron tribromide (BBr₃) solution under nitrogen atmosphere at rt and stirred for 30 h at rt. After addition of diethyl ether, the reaction mixture was further stirred for 15 min at rt. Ethyl acetate was added to the mixture and the organic layer was washed with H₂O

and brine successively, and dried over anhydrous Na₂SO₄. Solvent was removed under reduced pressure and residue was purified.

2-Hydroxy-2'-nitrodiphenyl ether (3): Following the general procedure B (rt, 30 h), compound **1** (104 mg, 0.43 mmol) was demethylated using BBr₃ (215 mg, 0.86 mmol) in 1,2-dichloroethane (3 mL). Purification by silica gel column chromatography (EtOAc : *n*-hexane = 1 : 8) afforded compound **3** (21 mg, 46.3%) as an oil. *R*_f = 0.42 (EtOAc : *n*-hexane = 1 : 3); ¹H NMR (400 MHz, CDCl₃) δ 6.90 (ddd, 1H, *J* = 1.6, 7.6, 8.4 Hz, H-5), 7.05 (dd, 1H, *J* = 1.2, 8.0 Hz, H-3), 7.08 (dd, 2H, *J* = 1.6, 8.0 Hz, H-6, 6'), 7.15 (ddd, 1H, *J* = 1.6, 7.6, 8.4 Hz, H-4), 7.20 (td, 1H, *J* = 1.2, 8.4 Hz, H-4'), 7.50 (ddd, 1H, *J* = 1.6, 8.0, 9.2 Hz, H-5'), 7.92 (dd, 1H, *J* = 1.6, 8.0 Hz, H-3'); ¹³C NMR (100 MHz, CDCl₃) 117.6, 119.0, 120.8, 120.9, 123.6, 126.0, 126.9, 134.6, 140.9, 142.2, 148.2, 150.6 ppm; EI-MS (*m/z*) 231.0 [M]⁺.

4'-Bromo-2-hydroxy-2'-nitrodiphenyl ether (4): Following the general procedure B (rt, 30 h), compound **2** (151 mg, 0.47 mmol) was demethylated using BBr₃ (240 mg, 0.94 mmol) in 1,2-dichloroethane (3 mL). Purification by silica gel column chromatography (EtOAc : *n*-hexane = 1 : 8) compound **4** (48 mg, 33.0%) as a gray semi-solid. *R*_f = 0.46 (EtOAc : *n*-hexane = 1 : 3); ¹H NMR (400 MHz, CDCl₃) δ 6.18 (s, 1H, OH-2), 6.91 (td, 1H, *J* = 1.2, 8.8 Hz, H-5), 7.01 (d, 2H, *J* = 9.2 Hz, H-3, 6), 7.07 (dd, 1H, *J* = 1.6, 8.4 Hz, H-6'), 7.15 (ddd, 1H, *J* = 1.2, 8.4, 9.2 Hz, H-4), 7.45 (dd, 1H, *J* = 1.6, 9.2 Hz, H-5'), 7.91 (d, 1H, *J* = 2.8, Hz, H-3'); ¹³C NMR (100 MHz, CDCl₃) 117.8, 120.2, 120.8, 121.1, 125.9, 127.2, 128.7, 134.6, 140.8, 142.0, 148.0, 149.4 ppm; EI-MS (*m/z*) 265.0 [M+H-NO₂]⁺.

3-Methoxy-2'-nitrodiphenyl ether (5): Following the general procedure A, guaiacol (1.0 g, 8.06 mmol) was coupled with 2-bromo-nitrobenzene (1.63 g, 8.06 mmol) using sodium hydride (0.320 g, 13.30 mmol) and copper (I) chloride (2.43 g, 24.62 mmol) in DMF. The crude product was purified by silica gel column chromatography (EtOAc : *n*-hexane = 1 : 8) to yield compound **5** (341 mg, 17.3%) as a light yellow crystalline solid. *R*_f = 0.51 (EtOAc : *n*-hexane = 1 : 3); mp 54 - 56 °C; ¹H NMR (400 MHz, CDCl₃) δ 3.79 (s, 3H, OCH₃-3), 6.61 (dd, 1H, *J* = 2.4, 4.0 Hz, H-2), 6.62 (d, 1H, *J* = 8.8 Hz, H-6), 6.73 (dd, 1H, *J* = 1.6, 8.4 Hz, H-4), 7.05 (dd, 1H, *J* = 0.8, 8.4 Hz, H-6'), 7.20 (td, 1H, *J* = 1.2, 8.4 Hz, H-5), 7.26 (t, 1H, *J* = 8.4 Hz, H-4'), 7.50 (ddd, 1H, *J* = 1.6, 8.4, 8.8 Hz, H-5'), 7.95 (dd, 1H, *J* = 1.6, 8.0 Hz, H-3'); ¹³C NMR (100 MHz, CDCl₃) 55.7, 105.5, 110.5, 111.4, 120.9, 123.5, 125.9, 130.7, 134.3, 141.5, 150.7, 157.1, 161.3 ppm; EI-MS (*m/z*) 245.0 [M]⁺.

3-Hydroxy-2'-nitrodiphenyl ether (6), 6-bromo-3-hydroxy-2'-nitrodiphenyl ether (7) and 4-bromo-3-hydroxy-2'-nitrodiphenyl ether (8): Following the general procedure B (rt, 27 h), compound **5** (78 mg, 0.32 mmol) in 1,2-dichloroethane (4 mL), was demethylated using BBr_3 (160 mg, 0.64 mmol). Purification by silica gel column chromatography (EtOAc : *n*-hexane = 1 : 7) afforded compounds **6** (43 mg, 58.1%) as a gray semi-solid, **7** (11 mg, 11.1%) as a dark brown solid and **8** (7 mg, 7.0%) as a viscous liquid. **Compound 6:** $R_f = 0.34$ (EtOAc : *n*-hexane = 1 : 3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.23 (brs, 1H, OH-3), 6.53 (t, 1H, $J = 2.0$ Hz, H-2), 6.59 (dd, 1H, $J = 2.0, 8.4$ Hz, H-4), 6.64 (dd, 1H, $J = 2.4, 8.4$ Hz, H-6), 7.06 (d, 1H, $J = 8.4$ Hz, H-6'), 7.20 (t, 2H, $J = 8.4$ Hz, H-5, 4'), 7.51 (td, 1H, $J = 1.6, 8.4$ Hz, H-5'), 7.94 (dd, 1H, $J = 1.6, 8.0$ Hz, H-3'); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 106.8, 111.4, 111.8, 121.2, 123.7, 125.9, 131.0, 134.5, 141.6, 150.54, 157.2, 157.3 ppm; EI-MS (m/z) 231.1 $[\text{M}]^+$. **Compound 7:** $R_f = 0.35$ (EtOAc : *n*-hexane = 1 : 3); mp 82 - 84 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.64 (brs, 1H, OH-3), 6.53 (dd, 1H, $J = 2.4, 8.0$ Hz, H-4), 6.69 (d, 1H, $J = 2.8$ Hz, H-2), 7.09 (d, 1H, $J = 8.4$ Hz, H-6'), 7.26 (t, 1H, $J = 7.2$ Hz, H-4'), 7.42 (d, 1H, $J = 8.8$ Hz, H-5), 7.55 (td, 1H, $J = 1.2, 8.4$ Hz, H-5'), 7.97 (dd, 1H, $J = 2.8, 8.0$ Hz, H-3'); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 105.2, 106.8, 112.4, 121.8, 124.4, 126.1, 132.9, 134.6, 141.9, 149.8, 153.6, 157.2 ppm; EI-MS (m/z) 308.9 $[\text{M}]^+$, 310.9 $[\text{M}+2]^+$; Relative peak intensity = 1:1. **Compound 8:** $R_f = 0.21$ (EtOAc : *n*-hexane = 1 : 3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.44 (brs, 1H, OH-3), 6.53 (d, 1H, $J = 2.8$ Hz, H-2), 6.60 (dd, 1H, $J = 2.8, 8.4$ Hz, H-6), 6.90 (dd, 1H, $J = 1.6, 8.0$ Hz, H-6'), 7.21 (ddd, 1H, $J = 1.2, 7.2, 8.4$ Hz, H-4'), 7.45 (d, 1H, $J = 8.4$ Hz, H-5), 7.51 (ddd, 1H, $J = 1.6, 7.6, 8.4$ Hz, H-5'), 7.98 (dd, 1H, $J = 1.6, 8.0$ Hz, H-3'); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 105.5, 108.8, 114.0, 119.9, 123.8, 126.2, 134.6, 134.7, 140.8, 150.1, 153.1, 156.6 ppm; EI-MS (m/z) 309.0 $[\text{M}]^+$, 311.0 $[\text{M}+2]^+$; Relative peak intensity = 1:1.

4'-Bromo-3-methoxy-2'-nitrodiphenyl ether (9): Following the general procedure A, 3-methoxy phenol (0.7 g, 5.64 mmol) was coupled with 2,5-dibromonitrobenzene (1.9 g, 5.64 mmol) using sodium hydride (0.24 g, 9.31 mmol) and copper (I) chloride (1.7 g, 17.24 mmol) in DMF (15 mL). The crude product was purified by silica gel column chromatography (EtOAc : *n*-hexane = 1 : 10) to yield compound **9** (665 mg, 36.34%) as an orange colored crystalline solid. $R_f = 0.27$ (EtOAc : *n*-hexane = 1 : 5); mp 44 - 46 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 3.79 (s, 3H, OCH_3 -3), 6.59 (dd, 1H, $J = 2.4, 2.4$ Hz, H-2), 6.60 (dd, 1H, $J = 2.4, 2.4$ Hz, H-6), 6.75 (dt, 1H, $J = 1.2, 8.4$ Hz, H-4), 7.00 (d, 1H, $J = 8.8$ Hz, H-6'), 7.27 (t, 1H, $J = 8.8$ Hz, H-5), 7.46 (dd, 1H, $J = 2.8, 8.8$ Hz, H-5'), 7.95 (d, 1H, $J = 2.8$ Hz, H-3'); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 55.7, 105.6, 110.8, 111.3, 122.0, 125.8, 128.5, 130.8, 134.3, 140.8, 149.5, 156.7, 161.4 ppm; EI-MS (m/z) 323.0 $[\text{M}]^+$, 325.0 $[\text{M}+2]^+$; Relative peak intensity = 1:1.

4',6-Dibromo-3-hydroxy-2'-nitrodiphenyl ether (10) and 4'-bromo-3-hydroxy-2'-nitrodiphenyl ether (11): Following the general procedure B (rt, 28 h), compound **9** (134 mg, 0.43 mmol) in 1,2-dichloroethane (4 mL), was demethylated using BBr_3 (220 mg, 0.87 mmol). Purification by silica gel column chromatography (EtOAc : *n*-hexane = 1 : 10) afforded compound **10** (25 mg, 15.0%) as a greenish yellow crystalline solid

and compound **11** (58 mg, 44.2%) as a dark brown oil. **Compound 10:** $R_f = 0.33$ (EtOAc : *n*-hexane = 1 : 3); mp 72 - 74 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.63 (brs, 1H, OH-3), 6.52 (dd, 1H, $J = 2.4, 8.8$ Hz, H-4), 6.69 (d, 1H, $J = 2.4$ Hz, H-2), 7.04 (d, 1H, $J = 9.2$ Hz, H-6'), 7.44 (d, 1H, $J = 8.4$ Hz, H-5), 7.51 (dd, 1H, $J = 2.0, 8.8$ Hz, H-5'), 7.96 (d, 1H, $J = 1.6$ Hz, H-3'); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 105.6, 106.9, 112.4, 122.9, 126.0, 129.4, 133.0, 134.6, 141.8, 148.6, 153.7, 156.8 ppm; EI-MS (m/z) 342.9 $[\text{M}-\text{NO}_2]^+$. **Compound 11:** $R_f = 0.30$ (EtOAc : *n*-hexane = 1 : 3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.24 (brs, 1H, OH-3), 6.53 (t, 1H, $J = 2.4$ Hz, H-2), 6.58 (dd, 1H, $J = 2.4, 8.0$ Hz, H-4), 6.66 (dd, 1H, $J = 2.4, 8.0$ Hz, H-6), 7.01 (d, 1H, $J = 8.8$ Hz, H-6'), 7.21 (t, 1H, $J = 8.0$ Hz, H-5), 7.47 (dd, 1H, $J = 2.8, 8.8$ Hz, H-5'), 7.94 (d, 1H, $J = 2.8$ Hz, H-3'); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 106.8, 111.4, 112.2, 122.2, 125.8, 128.7, 131.1, 134.5, 141.5, 149.3, 156.8, 157.3 ppm; EI-MS (m/z) 309.0 $[\text{M}]^+$, 311.0 $[\text{M}+2]^+$; Relative peak intensity = 1:1.

3,5-Dimethoxy-2'-nitrodiphenyl ether (12): Following the general procedure A, 3-methoxy phenol (0.7 g, 4.54 mmol) was coupled with 2-bromo-nitrobenzene (0.91 g, 4.54 mmol) using sodium hydride (0.18 g, 7.50 mmol) and copper (I) chloride (1.37 g, 13.87 mmol) in DMF (15 mL). The crude product was purified by silica gel column chromatography (EtOAc : *n*-hexane = 1 : 8) to provide compound **12** (195 mg, 11.68%) as a brown colored oil. $R_f = 0.31$ (EtOAc : *n*-hexane = 1 : 5); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 3.74 (s, 6H, OCH_3 -3,5), 6.18 (d, 2H, $J = 2.0$ Hz, H-2, 6), 6.26 (t, 1H, $J = 2.0$ Hz, H-4), 7.07 (dd, 1H, $J = 1.2, 8.4$ Hz, H-6'), 7.18 (ddd, 1H, $J = 1.2, 7.6, 8.0$ Hz, H-4'), 7.49 (ddd, 1H, $J = 1.2, 7.2, 8.8$ Hz, H-5'), 7.93 (dd, 1H, $J = 1.6, 8.4$ Hz, H-3'); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 55.7, 96.9, 97.9, 121.2, 123.6, 125.9, 134.4, 141.6, 150.5, 157.8, 162.0 ppm; EI-MS (m/z) 275.1 $[\text{M}]^+$.

3,5-Dihydroxy-2'-nitrodiphenyl ether (13), 4-bromo-3,5-dihydroxy-2'-nitrodiphenyl ether (14) and 6-bromo-3,5-dihydroxy-2'-nitrodiphenyl ether (15): Following the general procedure B (rt, 14 h), compound **12** (103 mg, 0.37 mmol) was demethylated using BBr_3 (94 mg, 0.37 mmol) in 1,2-dichloroethane (4 mL). Purification by silica gel column chromatography (EtOAc : *n*-hexane = 1 : 4) afforded compound **13** (12 mg, 13.2%) as a greenish brown solid, compound **14** (10 mg, 8.2%) as a dark brown solid and compound **15** (22 mg, 18.1%) as an oil. **Compound 13:** $R_f = 0.44$ (EtOAc : *n*-hexane = 1 : 1); mp 154-156 °C; $^1\text{H NMR}$ (400 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 6.05 (d, 2H, $J = 2.0$ Hz, H-2, 6), 6.14 (t, 1H, $J = 2.0$ Hz, H-4), 7.09 (dd, 1H, $J = 1.2, 8.4$ Hz, H-6'), 7.17 (td, 1H, $J = 1.2, 8.0$ Hz, H-4'), 7.50 (ddd, 1H, $J = 1.6, 7.6, 8.8$ Hz, H-5'), 7.92 (dd, 1H, $J = 2.0, 8.0$ Hz, H-3'); $^{13}\text{C NMR}$ (100 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) 98.6, 99.3, 121.1, 123.2, 125.7, 134.4, 141.3, 150.7, 157.6, 159.0 ppm; EI-MS (m/z) 247.0 $[\text{M}]^+$. **Compound 14:** $R_f = 0.50$ (EtOAc : *n*-hexane = 1 : 1); mp 82 - 84 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.58 (brs, 2H, OH-3, 5), 6.29 (s, 2H, H-2, 6), 7.13 (dd, 1H, $J = 1.2, 8.4$ Hz, H-6'), 7.28 (td, 1H, $J = 1.2, 7.6$ Hz, H-4'), 7.57 (ddd, 1H, $J = 2.8, 8.8, 9.6$ Hz, H-5'), 7.97 (dd, 1H, $J = 1.2, 8.0$ Hz, H-3'); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 94.4, 98.9, 122.3, 124.6, 126.1, 134.6, 142.0, 149.4, 154.0, 157.7 ppm; EI-MS (m/z) 325.0 $[\text{M}]^+$, 327.0 $[\text{M}+2]^+$; Relative peak intensity = 1:1. **Compound 15:** $R_f = 0.45$ (EtOAc/*n*-Hexane, 1:1); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.01 (d, 1H, $J = 2.8$ Hz,

H-4), 6.39 (d, 1H, $J = 2.8$ Hz, H-2), 6.99 (dd, 1H, $J = 1.2, 8.4$ Hz, H-6'), 7.23 (td, 1H, $J = 1.2, 8.4$ Hz, H-4'), 7.53 (ddd, 1H, $J = 1.6, 7.2, 8.4$ Hz, H-5'), 7.98 (dd, 1H, $J = 1.6, 8.0$ Hz, H-3'); ^{13}C NMR (100 MHz, CDCl_3) 94.3, 100.0, 100.5, 120.6, 124.2, 126.2, 134.7, 141.0, 149.7, 153.7, 154.8, 157.0 ppm; EI-MS (m/z) 325.0 $[\text{M}]^+$, 327.0 $[\text{M}+2]^+$; Relative peak intensity = 1:1.

4'-Bromo-4-methoxy-2'-nitrodiphenyl ether (16): Following the general procedure A, 4-methoxyphenol (1.2 g, 9.67 mmol) was coupled with 2,5-dibromonitrobenzene (2.72 g, 9.67 mmol) using sodium hydride (0.38 g, 15.97 mmol) and copper (I) chloride (2.92 g, 29.55 mmol) in DMF (20 mL). The crude product was purified by silica gel column chromatography (EtOAc : *n*-hexane = 1 : 8) to yield compound **16** (475 mg, 15.2%) as an orange colored semisolid. $R_f = 0.57$ (EtOAc : *n*-hexane = 1 : 3); ^1H NMR (400 MHz, CDCl_3) δ 3.81 (s, 3H, OCH_3 -4), 6.87, 6.91 (d, 2H, $J = 9.2$ Hz, H-3, 5), 7.0 (d, 2H, $J = 9.2$ Hz, H-2, 6), 7.23 (d, 1H, $J = 8.4$ Hz, H-6'), 7.40, 7.68 (dd, 1H, $J = 2.0, 8.4$ Hz, H-5'), 7.92, 8.23 (d, 1H, $J = 2.0$ Hz, H-3'); ^{13}C NMR (100 MHz, CDCl_3) 55.9, 115.5, 121.3, 125.4, 131.7, 133.9, 135.7, 140.8, 148.4, 150.9, 157.2 ppm; EI-MS (m/z) 323.0 $[\text{M}]^+$, 325.0 $[\text{M}+2]^+$; Relative peak intensity = 1:1.

4-Methoxy-2'-nitrodiphenyl ether (17): Following the general procedure A, 4-methoxyphenol (3.00 g, 24.16 mmol) was coupled with 1-bromo-2-nitrobenzene (4.88 g, 24.16 mmol) using sodium hydride (0.96 g, 39.92 mmol) and copper (I) chloride (7.31 g, 73.84 mmol) in DMF (30 mL). The crude product was purified by silica gel column chromatography (EtOAc : *n*-hexane = 1 : 8) to yield compound **17** (2.45 g, 41.35%) as a light yellow solid. $R_f = 0.51$ (EtOAc : *n*-hexane = 1 : 3); mp 74-76 °C; ^1H NMR (400 MHz, CDCl_3) δ 3.81 (s, 3H, OCH_3 -4), 6.89-6.93 (m, 3H, H-3, 5, 6'), 7.01 (dd, 2H, $J = 2.8, 9.2$ Hz, H-2, 6), 7.12 (ddd, 1H, $J = 1.2, 7.6, 8.4$ Hz, H-4'), 7.44 (ddd, 1H, $J = 1.6, 7.6, 8.4$ Hz, H-5'), 7.91 (dd, 1H, $J = 1.6, 8.0$ Hz, H-3'); ^{13}C NMR (100 MHz, CDCl_3) 55.9, 115.3, 119.1, 121.3, 122.4, 125.9, 134.2, 140.9, 148.8, 152.2, 157.0 ppm; EI-MS (m/z) 245.0 $[\text{M}]^+$.

4'-Bromo-4-hydroxy-2'-nitrodiphenyl ether (18): Following the general procedure B (rt, 14 h), compound **16** (120 mg, 0.37 mmol) in 1,2-dichloroethane (3 mL), was demethylated using BBr_3 (140 mg, 0.55 mmol). Purification by silica gel column chromatography (EtOAc : *n*-hexane = 1 : 5) provided compound **18** (48 mg, 42.0%) as a brown solid. $R_f = 0.28$ (EtOAc : *n*-hexane = 1 : 3); mp 94-96 °C; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 6.82 (dd, 2H, $J = 2.8, 8.8$ Hz, H-3, 5), 6.84 (d, 1H, $J = 8.0$ Hz, H-6'), 6.89 (dd, 2H, $J = 2.8, 8.8$ Hz, H-2, 6), 7.37 (dd, 1H, $J = 2.0, 9.2$ Hz, H-5'), 7.87 (d, 1H, $J = 2.4$ Hz, H-3'); ^{13}C NMR (100 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) 116.9, 120.0, 121.5, 125.6, 127.1, 134.3, 140.5, 147.6, 151.2, 154.4 ppm; EI-MS (m/z) 265.0 $[\text{M}+\text{H}-\text{NO}_2]^+$.

4-Hydroxy-2'-nitrodiphenyl ether (19): Following the general procedure B (rt, 18 h), compound **17** (75 mg, 0.30 mmol) was demethylated using BBr_3 (152 mg, 0.60 mmol) in 1,2-dichloroethane (3 mL). Purification by silica gel column chromatography (EtOAc : *n*-hexane = 1 : 5) yielded compound **19** (58 mg, 82.25%) as a dark green solid. $R_f = 0.28$ (EtOAc : *n*-hexane = 1 : 3); mp 102-104 °C; ^1H NMR (400 MHz, CDCl_3) δ 5.59 (brs, 1H, OH -1), 6.86 (dd, 2H, $J = 2.8, 8.8$ Hz, H-3, 5), 6.92 (dd, 1H, $J = 1.2, 8.4$ Hz, H-6'), 6.95 (dd, 2H, $J = 2.4, 8.8$

Hz, H-2, 6), 7.13 (ddd, 1H, $J = 1.2, 7.6, 8.4$ Hz, H-4'), 7.46 (ddd, 1H, $J = 1.6, 7.6, 8.4$ Hz, H-5'), 7.92 (dd, 1H, $J = 1.6, 8.0$ Hz, H-3'); ^{13}C NMR (100 MHz, CDCl_3) 116.9, 119.1, 121.5, 122.5, 125.9, 134.4, 140.7, 148.7, 152.2, 153.0 ppm; EI-MS (m/z) 231.0 $[\text{M}]^+$.

1-Methoxy-3,5-bis-(2-nitro-phenoxy)benzene (20) and 5-Hydroxy-3-methoxy-2'-nitrodiphenyl ether (21): Following the general procedure A, 3,5-dihydroxyanisole (255 mg, 1.82 mmol) was coupled with 1-bromo-2-nitrobenzene (920 mg, 4.55 mmol) using sodium hydride (73 mg, 3.01 mmol) and copper (I) chloride (552 mg, 5.57 mmol) in DMF. The crude product was purified by silica gel column chromatography (EtOAc : *n*-hexane = 1 : 10) to yield: compound **20** (35 mg, 5.1%) as an amber colored solid and compound **21** (26 mg, 5.5%) as a dark brown oil. **Compound 20** $R_f = 0.28$ (EtOAc : *n*-hexane = 1 : 3); mp 120-122 °C; ^1H NMR (400 MHz, CDCl_3) δ 3.76 (s, 3H, OCH_3 -1), 6.26 (t, 1H, $J = 2.0$ Hz, H-4), 6.38 (d, 2H, $J = 2.0$ Hz, H-2, 6), 7.12 (d, 2H, $J = 8.4$ Hz, H-6, 6'), 7.24 (td, 2H, $J = 1.2, 8.4$ Hz, H-4, 4'), 7.58 (ddd, 2H, $J = 1.2, 7.6, 8.8$ Hz, H-5, 5'), 7.95 (dd, 2H, $J = 1.6, 8.0$ Hz, H-3, 3'); ^{13}C NMR (100 MHz, CDCl_3) 55.6, 101.0, 101.8, 121.7, 124.3, 126.0, 134.6, 141.7, 149.8, 158.3, 162.3 ppm; EI-MS (m/z) 382.1 $[\text{M}]^+$. **Compound 21**: $R_f = 0.20$ (EtOAc : *n*-hexane = 1 : 3); ^1H NMR (400 MHz, CDCl_3) δ 3.74 (s, 3H, OCH_3 -3), 6.11 (t, 1H, $J = 2.0$ Hz, H-6), 6.17 (t, 1H, $J = 2.0$ Hz, H-4), 6.22 (t, 1H, $J = 2.0$ Hz, H-2), 7.09 (d, 1H, $J = 8.4$ Hz, H-6'), 7.20 (td, 1H, $J = 1.2, 8.0$ Hz, H-4'), 7.51 (ddd, 1H, $J = 1.6, 7.6, 8.4$ Hz, H-5'), 7.95 (dd, 1H, $J = 1.6, 8.0$ Hz, H-3'); ^{13}C NMR (100 MHz, CDCl_3) 55.8, 97.9, 98.1, 99.2, 121.4, 123.8, 125.9, 134.5, 141.6, 150.3, 157.9, 158.0, 162.1 ppm; EI-MS (m/z) 261.1 $[\text{M}]^+$.

1-Hydroxy-3,5-bis-(2-nitro-phenoxy)benzene (22): Following the general procedure B (rt, 5 h), compound **20** (34 mg, 0.09 mmol) was demethylated using BBr_3 (23 mg, 0.09 mmol) in 1,2-dichloroethane (3 mL). Purification by silica gel column chromatography (EtOAc : *n*-hexane = 1 : 4) afforded compound **22** (21 mg, 63.4%) as a brown solid. $R_f = 0.54$ (EtOAc : *n*-hexane = 1 : 1); mp 102-104 °C; ^1H NMR (400 MHz, CDCl_3) δ 5.67 (brs, 1H, OH -1), 6.25 (t, 1H, $J = 1.2$ Hz, H-4), 6.30 (d, 2H, $J = 2.4$ Hz, H-2, 6), 7.13 (d, 2H, $J = 8.0$ Hz, H-6, 6'), 7.25 (t, 2H, $J = 8.0$ Hz, H-4, 4'), 7.56 (ddd, 2H, $J = 1.2, 7.6, 8.4$ Hz, H-5, 5'), 7.94 (dd, 2H, $J = 1.2, 8.0$ Hz, H-3, 3'); ^{13}C NMR (100 MHz, CDCl_3) 101.7, 102.3, 122.0, 124.4, 126.0, 134.7, 141.7, 149.7, 158.3, 158.4 ppm; EI-MS (m/z) 368.1 $[\text{M}]^+$.

Mushroom tyrosinase inhibition assay *in vitro*.²⁰ All samples were dissolved in DMSO in a test tube and diluted with 800 μL of 0.1 M phosphate buffer (pH 6.5) μL . To this sample solution (50 μL), 50 μL of mushroom tyrosinase (2000 U/mL) and 100 μL of 1.5 mM L-tyrosine were also added sequentially. The assay mixture was incubated at 37 °C for 10 min. The amount of dopachrome produced was measured against a blank solution at 490 nm using a spectrophotometer. Percentage inhibition of tyrosinase was calculated by using the following formula.

$$\text{Tyrosinase inhibition (10\%)} = 100 - \left(\frac{b - b'}{a - a'} \times 100 \right)$$

Where *a* and *b* represent absorbance of blank and sample solution respectively. Similarly, *a'* and *b'* represent absorbance in the absence of tyrosinase. Each result is the mean of three concurrent readings. Arbutin was used as a positive control.

DPPH radical scavenging assay.²¹ All compounds used were dissolved in ethanol (Sigma, USA). In order to determine the capacity to scavenge the stable free radical, 1,1-diphenyl-2-picryl-hydrazyl (DPPH) (Sigma, USA), 50 μ L of each compound solution was added to each well in 96-well plate containing 50 μ L of 200 μ M DPPH stock solution. After incubation for 30 min with shaking at room temperature, the absorbance was read at 517 nm using a microplate reader (VERSAmax, Molecular Devices). The percent DPPH scavenging activity was expressed as follow:

$$\text{DPPH scavenging activity (\%)} = \frac{(Ac - Ab) - (As - Ab)}{(Ac - Ab)} \times 100$$

Where *Ac* was the absorbance of the DPPH solution without compound, *As* was that of the DPPH solution with compound, and *Ab* was that of the blank. At least three different experiments for each compound were performed in triplicate. Vitamin C was used as a positive control. For compounds showing more than 30% of DPPH scavenging activity from screening test with 100 μ M concentration in final,

Results and Discussion

Target compound synthesis. All hydroxydiphenyl ether analogues were prepared by the Ullmann-type ether formation reaction, in which an aryl bromide reacts with phenol under basic conditions in the presence of copper (I) salt to form the intermediate diphenyl ethers.¹⁹ Synthetic methods applied for the target compounds were depicted in Scheme 1. Guaiacol was coupled with 2-bromonitrobenzene or 2,5-dibromonitrobenzene by Ullmann-type reaction in the presence of copper (I) chloride to obtain compound **1** and **2**. Sodium hydride and *N,N*-dimethylformamide (DMF) were used as a base and solvent, respectively. Demethylation of compound **1** and **2** was carried out in the presence of BBr₃ (2.0 eq.) to afford compound **3** (46%) and **4** (33%) respectively (Scheme 1). Coupling of 3-methoxyphenol and 2-bromonitrobenzene afforded compound **5** (17%). In the ¹H NMR spectrum, methyl protons of methoxy group of compound **5** showed a singlet peak at δ 3.79. Demethylation of **5** under BBr₃ condition at RT afforded compounds **6** (58%), **7** (11%) and **8** (7%) together from same reaction mixture.

Using the similar procedure the 3-methoxyphenol treated with 2,5-dibromonitrobenzene to obtain compound **9** (36%). Subsequent demethylation of **9** with BBr₃ (2.0 eq.) at rt (28 h) afforded compound **10** (15%) and **11** (44%).

Coupling reaction of 3,5-dimethoxyphenol and 2-bromonitrobenzene provided compound **12** (12%). In the ¹H NMR spectrum, six protons of two methoxy groups of **12** showed a singlet peak at δ 3.74. Doublet peak (*J* = 2.0 Hz) of H-2 and H-6 at δ 6.18 and triplet (*J* = 2.0 Hz) of H-4 at δ 6.26 were also helped to determine the structure. Demethylation of compound **12** under BBr₃ (1.0 eq.) at rt (24 h) afforded compound **13** (13%),

14 (8%) and **15** (18%) at the same time. In the case of compound **14**, ¹H NMR spectrum showed a singlet peak of H-2 and H-6 at δ 6.29 while compound **15** showed two doublet peaks of H-2 and H-6 at δ 6.39 (*J* = 2.0 Hz) and δ 6.01 ppm (*J* = 2.0 Hz), respectively.

Coupling reaction of 4-methoxyphenol with 2-bromonitrobenzene or 2,5-dibromonitrobenzene afforded compound **16** (15%) and **17** (41%) respectively. After demethylation under BBr₃ condition (1.5 eq) at rt (14 h), compound **16** and **17** yielded compound **18** (42%) and **19** (82%) respectively without brominated compounds. All the spectroscopic data were consistent with the expected structures.

Ullmann-type reaction of 3,5-dihydroxyanisole with 2-bromonitrobenzene produced compounds **20** (5%) and **21** (6%) separately in the same reaction mixture. Then compound **22** (63%) was obtained by demethylation of compound **20** under BBr₃ condition (Scheme 2).

Pharmacological activity test.

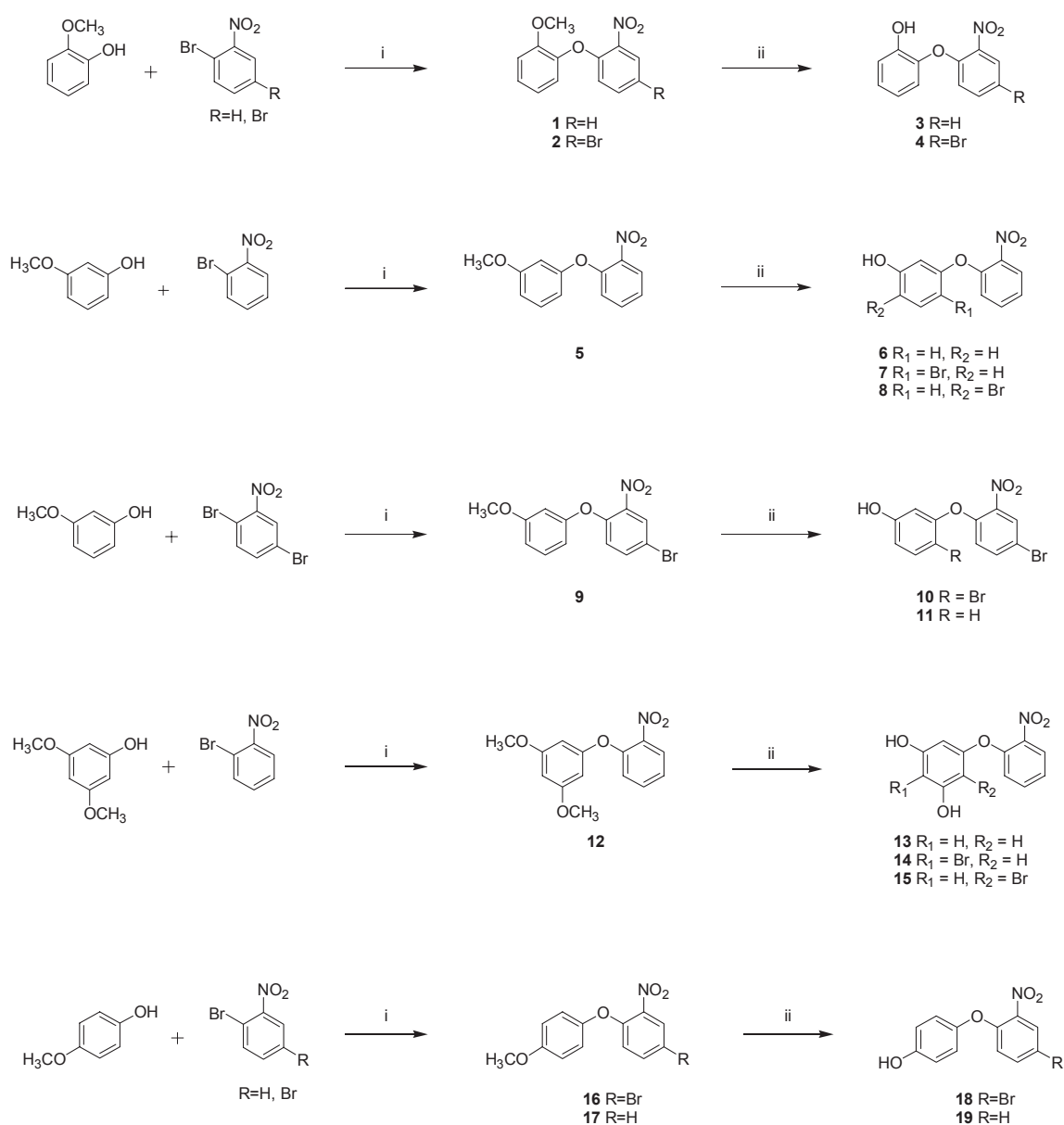
Mushroom tyrosinase inhibitory activity:²⁰ All the compounds were evaluated for monophenolase inhibitory activity of tyrosinase using L-tyrosine as a substrate. The percentage inhibition is presented in Table 1 and 2. Compound **4** showed comparable tyrosinase inhibitory activities to those of arbutin used as a reference within the test concentration range (Table 1). Most other compounds were less active than reference. But, surprisingly, compound **18** and **19** were much stronger inhibitor against tyrosinase function than arbutin (Table 2). Both compounds had *para*-hydroxyphenyl moiety in their structure. It might be due to their structural resemblance to L-tyrosine, a substrate for tyrosinase during early stage of melanogenesis. These results might reinforce the importance of *p*-hydroxyphenyl group in the tyrosinase inhibitory process, which is consistent with the reported information.

DPPH radical scavenging activity: Diphenyl ethers may exert antioxidant property, due to their ability to donate an electron or chelate metals. Since our compounds also have phenolic hydroxyl group and thus may perform antioxidant activity, we intended to test for anti-oxidative activity possibly to prevent or delay pigmentation resulting from auto-oxidation. The anti-oxidative activity of selected compounds was tested by measuring their ability to convert DPPH (1,1-diphenyl-2-picryl hydrazyl) free radical to DPPH-H (1,1-diphenyl-2-picryl hydrazine).

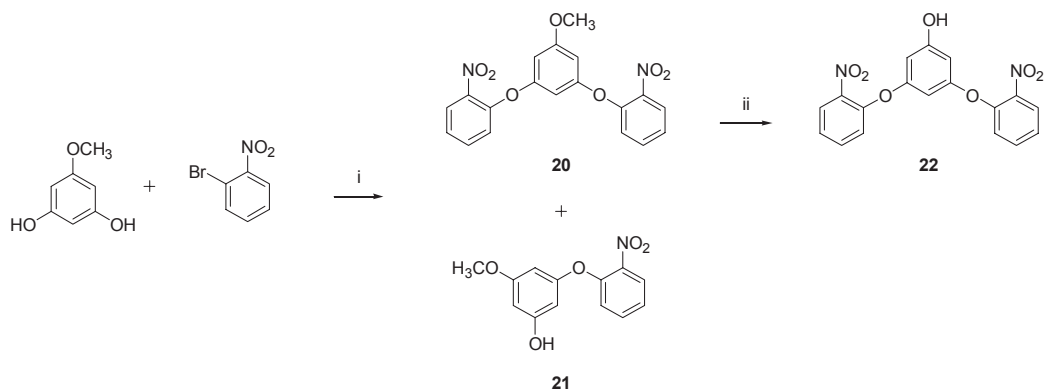
Most compounds are inactive to the antioxidant function with DPPH. (Table 3) Unexpectedly, compounds **18** and **19** were also lack of scavenging activity. This result showed the discrepancy between the antityrosinase activity and DPPH radical scavenging activity among the compounds tested. Compounds **13**, **14** and **15** possessing resorcinol moiety in the structure exhibited moderate antioxidant activity but lower than ascorbic acid used as positive control. Because of low potency of the compounds EC₅₀ of the compounds were not determined. This information implies that elaborate calibration of the resorcinol portion of diphenyl ether can increase the antioxidant ability of the parent compounds.

Conclusions

We have synthesized 14 diphenyl ether compounds possess-



Scheme 1. Synthesis of compounds. *Reagents and conditions:* (i) CuCl, NaH, DMF, reflux; (ii) BBr₃, ClCH₂CH₂Cl, rt



Scheme 2. Synthesis of compounds. *Reagents and conditions:* (i) CuCl, NaH, DMF, reflux; (ii) BBr₃, ClCH₂CH₂Cl, rt

Table 1. Tyrosinase inhibitory activity (%) of compounds

Group	Dose ($\mu\text{g/mL}$)		
	10	20	40
3	4.97 \pm 0.48	8.02 \pm 0.71	9.04 \pm 0.13
4	23.72 \pm 1.99	40.58 \pm 1.53	60.93 \pm 1.94
6	4.95 \pm 0.38	6.88 \pm 0.50	7.91 \pm 0.27
7	23.07 \pm 2.49	41.17 \pm 1.75	61.92 \pm 1.56
8	11.42 \pm 1.57	12.47 \pm 0.64	16.80 \pm 0.50
10	25.38 \pm 2.27	38.2 \pm 1.18	46.92 \pm 0.58
11	5.32 \pm 0.21	9.12 \pm 0.83	14.52 \pm 0.44
13	3.47 \pm 0.64	7.04 \pm 0.59	7.73 \pm 0.22
14	0.60 \pm 0.29	6.32 \pm 1.26	8.23 \pm 0.11
15	6.58 \pm 0.94	17.39 \pm 1.85	24.58 \pm 0.46
21	0	0	0
22	6.68 \pm 0.24	17.53 \pm 2.40	27.28 \pm 1.00
Arbutin	49.25 \pm 0.75	68.63 \pm 1.09	81.46 \pm 1.57

Values represent means \pm S.D. (n = 3).

Table 2. Tyrosinase inhibitory activity (%) of compound **18** and **19**

Compound	Dose ($\mu\text{g/mL}$)		
	1	5	10
18	42.60 \pm 0.90	57.84 \pm 1.61	71.27 \pm 2.20
19	26.21 \pm 2.0	73.77 \pm 1.25	82.67 \pm 0.39
Arbutin	NA ^a	NA	49.25 \pm 0.75

Values represent means \pm S.D. (n = 3). ^aNot analyzed.

Table 3. DPPH scavenging activities of compounds

Compound	DPPH scavenging activity (%) ^a	EC ₅₀ (μM) ^b
Vitamin C	93.90	26.22 \pm 1.45
3	0	NA ^c
4	7.28	NA ^c
6	3.00	NA ^c
7	8.08	NA ^c
8	0	NA ^c
10	7.57	NA ^c
11	0.86	NA ^c
13	28.79	NA ^c
14	45.10	NA ^c
15	17.01	NA ^c
18	11.68	NA ^c
19	3.68	NA ^c
21	7.54	NA ^c
22	4.97	NA ^c

^aThe percent DPPH scavenging activity was obtained with 100 μM concentration of test compounds. ^bConcentration for scavenging 50% of DPPH free radical was expressed in mean value \pm standard deviation obtained in triplicate. ^cNot analyzed.

ing hydroxyl, bromo, and nitro groups in the structure. Compounds **18** and **19** have shown much stronger inhibition of tyrosinase monophenolase function than arbutin used as a positive control. Both compounds possess *para*-hydroxyphenyl moiety in their structure, which might reinforce the importance of *p*-hydroxyphenyl group in the tyrosinase inhibitory process. In the DPPH radical scavenging activity test, none of the compounds even **18** and **19** showed significant antioxidant activity. The result obtained suggests that elaborate adjustment of diphenyl ether analogues with proper substituents may have potential to be developed as new skin whitening agents working on the tyrosinase function.

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