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Synthesis of 7-*O*-(2-Amino)ethyl Flavones and Their Antioxidant Activities

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It is becoming apparent that inadvertent overproduction of reactive oxygen species may result in oxidative tissue injury.[1] Reactive oxygen species have been implicated in a variety of diseases including cardiovascular disease,[2] ischemia,[3] Alzheimer's disease[4] and chronic gut inflammation.[5] Fortunately, plants contain a wide variety of free radical scavenging molecules such as flavonoids, anthocyanins, cartenoids, dietary glutathione and vitamins.[6] The diverse biological properties of flavonoids are suggested mainly due to their antioxidant activity by scavenging oxygen radicals and inhibiting lipid peroxidation.[7] However, the antioxidant activity of the flavonoids varies considerably depending on their backbone structures as well as their substituents.[8]

Luteolin (**1**) is one of the naturally occurring, common flavones which possesses potent antioxidant activities (Figure 1).[9] However, the *in vivo* biological activities of luteolin depend on many parameters, including bioavailability. Low solubility of luteolin in oil results in its poor permeation across cell membranes. Thus, a luteolin and its phospholipid complex was prepared with the aim to improve the lipophilic properties while retaining its DPPH radical scavenging activity.[10] Based on studies examining structure-activity relationships, the lower solubility of flavonoids in aqueous solution can also limit their bioavailability *in vivo*.[11,12] To enhance water solubility over the parent compounds and thereby improving hydrophilic character, complexation of luteolin with cyclodextrins,[13] and synthesis of sodium salt[12] and ammonium salts[14] of flavones have been reported along with investigation of their antioxidant properties. We also recently reported the synthesis of glucose-containing flavones (*e.g.* **2**) in an attempt to improve the physicochemical properties including water solubility.[15] The attachment of a glucose group to luteolin increased superoxide anion scavenging activities, but diminished lipid peroxidation inhibitory activities. We assumed that the reduced inhibition of lipid peroxidation was caused by the increased hydrophilic character. In this work, we describe the synthesis of 7-*O*-aminoethyl flavones **3a-3h** and their antioxidant activities. We introduced amino groups to the structure of luteolin to increase water solubility with formation of hydrochloride salts. It was also thought that the alkyl groups in aminoalkyl flavones can also improve the lipophilic character

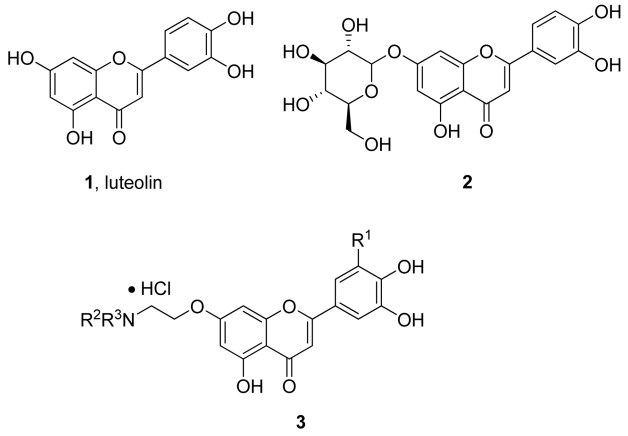

Figure 1. Structures of of luteolin (**1**), 6-*O*-glucosyl-luteolin (**2**), and target compounds (**3**).

by increasing alkyl chains and thereby enhance lipid peroxidation inhibitory activities. Aminoethyl was attached at the C-7 position of **1** *via* an ether bond because we previously found that modification at this position did not substantially influence antioxidant activity.[16] The B-ring of luteolin was also varied by the introduction of two or three hydroxyl groups to examine the influence on antioxidant activity.

The synthesis of 7-*O*-aminoethyl flavones **3a-3h** were accomplished by the procedures shown in Scheme 1. 1-(2-Hydroxy-4,6-bis(methoxymethoxy)phenyl)ethanone (**4**)[17] was condensed with *O*-benzyl-protected aldehydes (**5a**, **5b**) in the presence of NaH in DMF to provide the chalcones **6a** and **6b**.[18] Oxidative cyclization of the chalcones to form flavone ring was accomplished by treatment with PIDA/KOH in methanol to afford **7a** and **7b**.[19] The MOM-protecting group in **7a** and **7b** was removed using 10% HCl in methanol to afford **8a** and **8b**. The selective alkylation of 7-hydroxyl in **8a** and **8b** was performed using commercially available aminoethyl chlorides in the presence of K_2CO_3 in acetone to give **9a-9h**.[20] Finally, the benzyl-protecting groups in **9a-9h** were removed by hydrogenolysis with $Pd(OH)_2$ and cyclohexene in EtOH and then transformed to **3a-3h** as hydrochloride salts by treating with HCl gas in ethanol at 0 °C.

It has been reported that the low solubility of flavones both in oil and aqueous solution can limit their bioavailabilities *in vivo.* In the present study, the aminoethyl moiety

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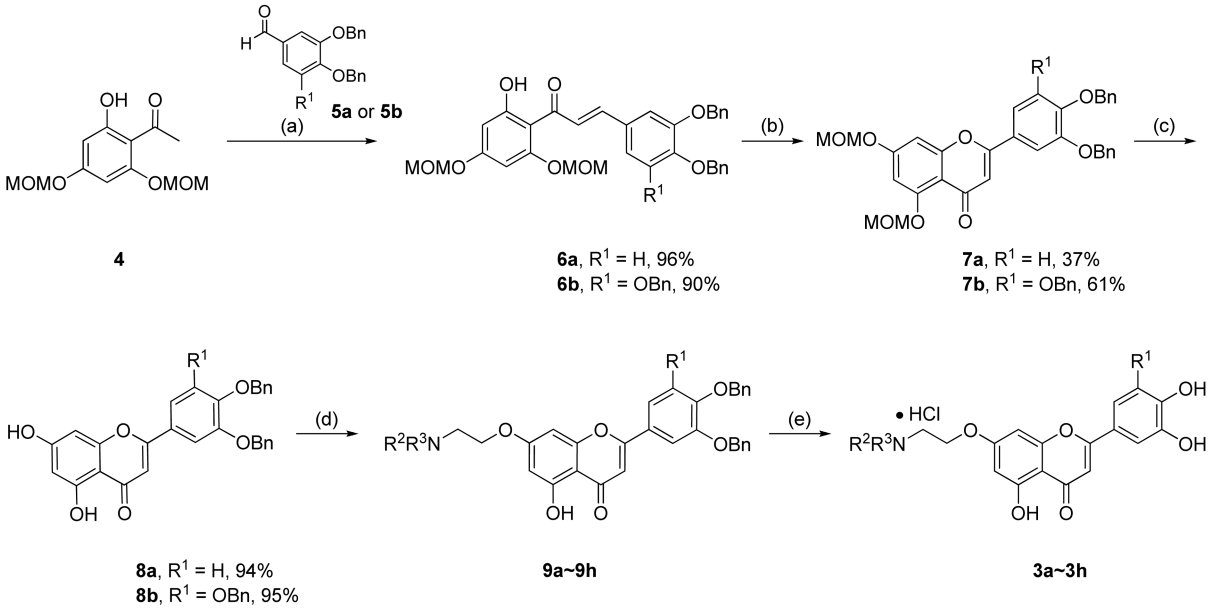
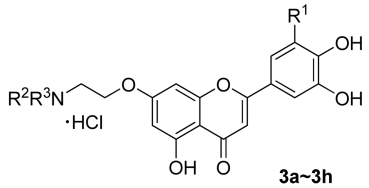


Scheme 1. *Reagents and conditions:* (a) NaH, DMF, 0 °C ~ rt; (b) PIDA, KOH, MeOH, 0 °C ~ rt; (c) 10% HCl, MeOH, 60 °C; (d) $R^2R^3NCH_2CH_2Cl$, K_2CO_3, acetone, reflux; (e) (i) $Pd(OH)_2$/C, EtOH/cyclohexene (1/1), reflux; (ii) HCl (gas), EtOH.

was introduced to the 7-position of luteolin *via* an ether bond to improve its physicochemical properties and enhance antioxidant activity. An additional hydroxyl group was also introduced in the 5'-position of the B-ring in luteolin to examine its influence on antioxidant activities. The antioxidant activities of the synthesized flavones **3a-3h** were

Table 1. Yields and antioxidant activities of aminoethyl flavones **3a-3h**



Entry	R^1	R^2R^3N-	Overall yields (%) from **8a** or **8b**	DPPH radicals[a]	O_2^- radicals[b]	Lipid peroxidation[c]
				IC_{50} (μM)[d]		
3a	H		46	25.90 ± 0.48	3.10 ± 0.81	38.76 ± 2.42
3b	H		35	27.41 ± 3.24	3.45 ± 0.19	18.79 ± 4.07
3c	H		41	52.74 ± 5.34	3.07 ± 0.30	18.01 ± 2.50
3d	H		30	28.82 ± 2.31	3.22 ± 0.26	18.34 ± 1.99
3e	OH		38	19.51 ± 1.12	26.03 ± 12.89	15.11 ± 2.31
3f	OH		43	26.34 ± 0.52	30.12 ± 7.38	19.27 ± 1.61
3g	OH		48	41.89 ± 5.55	19.65 ± 3.58	19.52 ± 1.10
3h	OH		45	36.31 ± 5.55	17.56 ± 9.18	20.80 ± 1.34
1, luteolin				16.18 ± 1.85	8.66 ± 0.10	24.66 ± 4.75
2				17.28 ± 0.27	3.28 ± 0.20	40.41 ± 5.75
Ascorbic acid				40.99 ± 6.19	> 50	-
trolox				-	-	71.44 ± 5.54

[a]DPPH radical scavenging activity. [b]Scavenging activity of superoxide anion radicals generated in the xanthine/xanthine oxidase system. [c]Iron-dependent lipid peroxidation inhibition activity using rat liver homogenate. [d]IC_{50} values (defined as concentrations that inhibited activity by 50%) were calculated using GraphPad Prism using data obtained from at least three independent experiments and expressed as the means ± SD.

evaluated by examining their effects on DPPH and superoxide anion radical scavenging and inhibition of lipid peroxidation (Table 1).[15] Ascorbic acid and trolox were used as positive controls in our assay systems. The antioxidant activity data of the parent compound, luteolin (**1**) and 7-*O*-glucosyl-luteolin (**2**) were also included as positive controls to assess whether antioxidant activities were maintained or increased by these aminoethyl flavones. As shown in Table 1, the synthesized compounds showed varied DPPH radical scavenging activities (IC_{50} = 19.51-52.74 μM) that were similar to or 2~3-fold less potent than those of the parent compounds **1** and **2** (IC_{50} = 16.18 and 17.28 μM, respectively). The superoxide anion radical scavenging activities of **3a-3h** were examined using a xanthine/xanthine oxidase system.[21] Compounds **3a-3d** exhibited potent superoxide anion scavenging activities (IC_{50} = 3.07-3.45 μM) and their potencies were higher than that of **1** (IC_{50} = 8.66 μM) and similar to that of **2** (IC_{50} = 3.28 μM). Interestingly, these activities were 2-3 times lower in compounds **3e-3h**, indicating that an additional hydroxyl group in the 5'-position of the B-ring can alter superoxide anion scavenging activities significantly. The lipid peroxidation inhibitory effects of synthesized compounds were evaluated using rat liver homogenates.[22] In our previous work, it has been found that glycosylation of luteolin reduced lipid peroxidation inhibitory activity slightly.[15] However, every aminoethyl-flavones **3a-3h** exhibited enhanced activities when compared to **1** and **2**. The different amino groups at the 7-position and the degree of hydroxylation on the B-ring have no significant effects on lipid peroxidation inhibitory activity as suggested by similar activity of all compounds.

In conclusion, we synthesized aminoethyl flavones **3a-3h** to increase the hydrophilic and lipophilic characteristics of luteolin while retaining antioxidant activity. The synthesized compounds showed DPPH radical scavenging activities, but their potencies were slightly lower than those of the parent compounds. However, compounds **3a-3d**, which possess two hydroxyl groups in the 3',4'-positions of the B-ring had significantly increased superoxide anion radical scavenging activities. Interestingly, the introduction of an additional hydroxyl group in the 5'-position in the B-ring of the flavones decreased these activities significantly. Irrespective of the types of amino groups examined and the degree of hydroxylation on the B-ring, almost all aminoethyl flavones exhibited potent lipid peroxidation inhibitory activities. Of the synthesized compounds, **3b** and **3d** exhibited the most potent and well-balanced antioxidant activities in the three antioxidant assay systems. Taken together, these findings suggest that the introduction of the aminoethyl moiety to luteolin may improve pharmacokinetic properties as well as antioxidant activities although their activities in cell-based assay systems remain to be investigated.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Gemini Varian-300 (300 and 75 MHz, respectively). Analytical thin layer chromatographies (TLC) were carried out by precoated silica gel (E. Merck Kiesegel $60F_{254}$ layer thickness 0.25 mm). Flash column chromatographies were performed with Merck Kiesegel 60 Art 9385 (230-400 mesh). All solvents used were purified according to standard procedures.

3-(3,4-Bis-benzyloxy-phenyl)-1-(2-hydroxy-4,6-bis-methoxymethoxy-phenyl)-propenone (6a): To a stirred solution of **4** (1.6 g, 6.24 mmol) in DMF (47 mL) was added NaH (60% dispersed in mineral oil, 0.98 g, 25.0 mmol). To this solution was added a solution of **5a** (2.36 g, 7.4 mmol) in DMF (20 mL) dropwise at 0 °C. After stirring for 3 h at rt, the reaction was carefully quenched with water. DMF was evaporated under vacuum and the residue was dissolved in EtOAc before washing with water and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated, and crystallized from EtOH to give **6a** (3.33 g, 96% yield). ^1H NMR ($CDCl_3$) δ 7.80 (1H, *J* = 15.3 Hz), 7.31 (1H, *J* = 15.3 Hz), 7.35-7.50 (10H, m), 7.19-7.24 (2H, m), 6.99 (1H, d, *J* = 8.4 Hz), 6.35 (1H, d, *J* = 2.1 Hz), 6.27 (1H, d, *J* = 2.1 Hz), 5.26 (2H, s), 5.25 (2H, s), 5.24 (2H, s), 5.22 (2H, s), 3.53 (3H, s), 3.52 (3H, s).

1-(2-Hydroxy-4,6-bis-methoxymethoxy-phenyl)-3-(3,4,5-tris-benzyloxy-phenyl)-propenone (6b): Compound **6b** was prepared from **4** and **5b** using the procedure described for **6a**. Yield 90%; ^1H NMR ($CDCl_3$) δ 7.83 (1H, d, *J* = 15.9 Hz), 7.80 (1H, d, *J* = 15.9 Hz), 7.29-7.47 (15H, m), 6.95 (1H, s), 6.94 (1H, s), 6.35 (1H, m), 6.24 (1H, m), 5.16-5.23 (8H, m), 3.51-3.52 (6H, m).

3',4'-Dibenzyloxy-5,7-dimethoxymethyl-flavone (7a): To a stirred solution of the **6a** (774 mg, 1.39 mmol) in MeOH (30 mL) was added a solution of KOH (583 mg, 10.39 mmol) in MeOH (10 mL) slowly at 0 °C. After stirring for 10 min, phenyliodine diacetate (PIDA, 1.16 g, 3.6 mmol) was added in three portions and the resulting mixture was stirred at rt for 24 h. The solution was concentrated and water was added to the residue. The mixture was extracted with CH_2Cl_2 and the combined organic layer was dried over anhydrous $MgSO_4$, filtered, evaporated, and purified by flash column chromatography (EtOAc/*n*-hexane = 1:2) to afford 7**a** (263 mg, 37% yield). ^1H NMR ($CDCl_3$) δ 7.29-7.54 (12H, m), 7.03 (1H, d, *J* = 9.0 Hz), 6.85 (1H, d, *J* = 2.4 Hz), 6.77 (1H, d, *J* = 2.4 Hz), 6.54 (1H, s), 5.37 (2H, s), 5.30 (2H, s), 5.27 (4H, s), 3.59 (3H, s), 3.56 (3H, s).

3',4',5'-Tribenzyloxy-5,7-dimethoxymethyl-flavone (7b): Compound **7b** was prepared from **6b** using the procedure described for **7a**. Yield 61%; ^1H NMR ($CDCl_3$) δ 7.29-7.51 (15H, m), 7.18 (2H, s), 6.85 (1H, d, *J* = 2.4 Hz), 6.79 (1H, d, *J* = 2.4 Hz), 5.38 (2H, s), 5.31 (2H, s), 5.20 (4H, s), 5.17 (2H, s), 3.60 (3H, s), 3.58 (3H, s).

2-(3,4-Bis(benzyloxy)phenyl)-5,7-dihydroxy-4*H*-chromen-4-one (8a): The a stirred solution of **7a** (1.2 g, 2.16 mmol) in MeOH (150 mL) was treated with 10% hydrochloric acid (38 mL) and heated at reflux for 5 h. The reaction mixture was diluted with water and the resulting precipitate was separated and washed with MeOH to afford **8a** (0.96 g, 94%). ^1H NMR (DMSO-d_6) δ 7.71 (1H, d, *J* = 2.0 Hz), 7.65 (1H, dd, *J* = 2.0, 8.6 Hz), 7.32-7.52 (10H, m), 7.21 (1H, d, *J*

= 8.6 Hz), 6.93 (1H, s), 6.51 (1H, d, J = 2.0 Hz), 6.20 (1H, d, J = 2.0 Hz), 5.27 (2H, s), 5.25 (2H, s).

2-(3,4,5-Tris(benzyloxy)phenyl)-5,7-dihydroxy-4*H*-chromen-4-one (8b): Compound **8b** was prepared from **7b** using the procedure described for **8a**. Yield 95%; ^{1}H NMR (DMSO-d_6) δ 7.33-7.35 (15H, m), 7.11 (2H, s), 7.10 (1H, s), 6.60 (1H, s), 6.26 (1H, s), 5.30 (4H, s), 5.08 (2H, s).

General Procedure for the Preparation of 3a-3h. To a stirred solution of compound **8a** or **8b** (1.0 mmol) in acetone (60 mL) was added K_2CO_3 (4.0 mmol) and corresponding alkyl halide (1.3 mmol). The reaction mixture was heated at reflux for 1-6 h. The mixture was concentrated and the residue was treated with EtOAc and water. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH = 10:1) to afford **9a-9h**. To a solution of **9a-9h** in EtOH and cyclohexene (1:1) was added $Pd(OH)_2$/C (*ca.* 0.2 weight %). The reaction mixture was refluxed for the period of time (TLC monitoring), filtered through Celite and concentrated. The residue was dissolved in absolute EtOH and then saturated with HCl gas at 0 ºC until the mixture become acidic. The resulting precipitate was filtered to afford **3a-3h**.

7-(2-(Piperidin-1-yl)ethoxy)-5-hydroxy-2-(3,4-dihydroxyphenyl)-4*H*-chromen-4-one Hydrochloride (3a): Yield 46%; ^{1}H NMR (CD_3OD) δ 7.43 (1H, s), 6.99 (1H, d, J = 8.1 Hz), 6.95 (1H, d, J = 8.1 Hz), 6.77 (1H, d, J = 2.1 Hz), 6.63 (1H, s), 6.47 (1H, d, J = 2.1 Hz), 4.53-4.55 (2H, m), 3.65-3.70 (4H, m), 3.10-3.18 (2H, m), 1.88-2.04 (4H, m), 1.58-1.66 (2H, m).

7-(2-(Pyrrolidin-1-yl)ethoxy)-5-hydroxy-2-(3,4-dihydroxyphenyl)-4*H*-chromen-4-one Hydrochloride (3b): Yield 35%; ^{1}H NMR (CD_3OD) δ 7.46 (1H, d, J = 2.1 Hz), 7.43 (1H, dd, J = 8.4, 2.1 Hz), 6.94 (1H, d, J = 8.4 Hz), 6.78 (1H, d, J = 2.1 Hz), 6.64 (1H, s), 6.49 (1H, d, J = 2.1 Hz), 4.48 (2H, t, J = 5.1 Hz), 3.72 (2H, t, J = 5.1 Hz), 3.50 (4H, bs), 2.17-2.19 (4H, m).

7-(2-Morpholinoethoxy)-5-hydroxy-2-(3,4-dihydroxyphenyl)-4*H*-chromen-4-one Hydrochloride (3c): Yield 41%; ^{1}H NMR (CD_3OD) δ 7.45 (1H, m), 7.42 (1H, m), 6.94 (1H, d, J = 8.4 Hz), 6.77 (1H, d, J = 2.4 Hz), 6.64 (1H, s), 6.49 (1H, d, J = 2.1 Hz), 4.54 (2H, bs), 3.99 (4H, bs), 3.68 (2H, bs), 3.44 (4H, bs).

7-(2-(Diethylamino)ethoxy)-5-hydroxy-2-(3,4-dihydroxyphenyl)-4*H*-chromen-4-one Hydrochloride (3d): Yield 30%; ^{1}H NMR (CD_3OD) δ 7.43 (1H, m), 7.42 (1H, m), 6.94 (1H, d, J = 8.1 Hz), 6.76 (1H, d, J = 1.5 Hz), 6.63 (1H, s), 6.47 (1H, d, J = 1.5 Hz), 4.51 (2H, t, J = 4.8 Hz), 3.69 (2H, t, J = 4.8 Hz), 3.39-3.42 (4H, m), 1.41 (6H, t, J = 7.3 Hz).

7-(2-(Piperidin-1-yl)ethoxy)-5-hydroxy-2-(3,4,5-trihydroxyphenyl)-4*H*-chromen-4-one Hydrochloride (3e): Yield 38%; ^{1}H NMR (CD_3OD) δ 7.02 (2H, s), 6.71 (1H, d, J = 2.1 Hz), 6.56 (1H, s), 6.46 (1H, d, J = 2.1 Hz), 4.49 (2H, bs), 3.60 (2H, bs), 1.94 (4H, bs), 1.74 (2H, bs).

7-(2-(Pyrrolidin-1-yl)ethoxy)-5-hydroxy-2-(3,4,5-trihydroxyphenyl)-4*H*-chromen-4-one hydrochloride (3f): Yield 43%; ^{1}H NMR (D_2O + DMSO-d_6) δ 6.39 (2H, s), 6.04 (1H, s), 5.93 (2H, bs), 4.01 (2H, bs), 3.49 (2H, bs), 3.39 (4H, bs), 2.04 (4H, bs).

7-(2-Morpholinoethoxy)-5-hydroxy-2-(3,4,5-trihydroxyphenyl)-4*H*-chromen-4-one hydrochloride (3g): Yield 48%; ^{1}H NMR (CD_3OD) δ 7.04 (2H, s), 6.75 (1H, d, J = 1.5 Hz), 6.60 (1H, s), 6.50 (1H, d, J = 1.8 Hz), 4.56 (2H, bs), 4.02 (4H, bs), 3.71 (2H, bs), 3.71 (4H, bs).

7-(2-(Diethylamino)ethoxy)-5-hydroxy-2-(3,4,5-trihydroxyphenyl)-4*H*-chromen-4-one hydrochloride (3h): Yield 45%; ^{1}H NMR (D_2O + DMSO-d_6) δ 7.10 (2H, s), 6.83 (1H, d, J = 2.4 Hz), 6.69 (1H, s), 6.54 (1H, d, J = 2.4 Hz), 4.55 (2H, t, J = 4.8 Hz), 3.69 (2H, t, J = 4.8 Hz), 3.68-3.44 (4H, m), 1.44 (6H, t, J = 7.2 Hz).

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References

1. Battino, M.; Bullon, P.; Wilson, M.; Newman, H. *Crit. Rev. Oral Biol. Med.* **1999**, *10*, 458.
2. West, M.; Srivastava, S.; Bhatnagar, A. *Prog. Exp. Cardiol.* **2003**, *6*, 465.
3. Shi, H.; Liu, K. J. *Frontiers in Bioscience* **2007**, *12*, 1318.
4. Pratico, D.; Delanty, N. *Am. J. Med.* **2000**, *109*, 577.
5. Yanaka, A.; Zhang, S.; Tauchi, M.; Suzuki, H.; Shibahara, T.; Matsui, H.; Nakahara, A.; Tanaka, N.; Yamamoto, M. *Inflammopharmacol.* **2005**, *13*, 83.
6. Braca, A.; Fico, G.; Morelli, I.; De, S. F.; Tome, F.; De, T. N. *J. Ethnopharmacol.* **2003**, *86*, 63.
7. Dugas, Jr., A. J.; Castañeda-Acosta, J.; Bonin, G. C.; Price, K. L.; Fischer, N. H.; Winston, G. W. *J. Nat. Prod.* **2000**, *63*, 327.
8. Cai, Y.-Z.; Sun, M.; Xing, J.; Luo, Q.; Corke, H. *Life Sci.* **2006**, *78*, 2872.
9. Park, J.; Kang, K. A.; Zhang, R.; Piao, M. J.; Park, S.; Kim, J. S.; Kang, S. S.; Hyun, J. W. *J. Toxicol. Public Health* **2006**, *22*, 391.
10. Xu, K.; Liu, B.; Ma, Y.; Du, J.; Li, G.; Gao, H.; Zhang, Y.; Ning, Z. *Molecules* **2009**, *14*, 3486.
11. Matsumoto, M.; Chiji, H.; Hara, H. *Free Radical Res.* **2005**, *39*, 1139.
12. Milane, H. A.; Vandamme, T. F.; Zhao, M.-J.; Kessler, M.; Ubeaud, G.; Ochandio, B. A.; Jung, L. *Croat. Chem. Acta* **2005**, *78*, 35.
13. Kim, H.; Kim, H.-W.; Jung, S. *Bull. Korean Chem. Soc.* **2008**, *29*, 590.
14. Wu, C.; Cheng, L.; Li, Y.; Guo, D.; Yu, S.; Wu, X.; Wei, Y. *Lett. Org. Chem.* **2007**, *4*, 366.
15. Kim, S. H.; Kumar, Ch. N.; Kim, H. J.; Kim, D. H.; Cho, J., Jin, C.; Lee, Y. S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6009.
16. Yoo, H.; Kim, S. H.; Lee, J.; Kim, H. J.; Seo, S. H.; Chung, B. Y.; Jin, C.; Lee, Y. S. *Bull. Korean Chem. Soc.* **2005**, *26*, 2057.
17. Toshihiro, K.; Tomomi, M.; Shigeru, M.; Shingo, S.; Junichi, O. *Carbohydr. Res.* **2000**, *329*, 507.
18. Nay, B.; Arnaudinaud, V.; Vercauteren, J. *Eur. J. Org. Chem.* **2001**, *2001*, 2379.
19. Gulicsi, K.; Litkei , G.; Antus, S.; Gunda, T. E. *Tetrahedron* **1998**, *54*, 13867.
20. Bertrand , A.; Olivier, D. *Helv. Chim. Acta* **2001**, *84*, 1133.
21. Toda, S.; Kumura, M.; Ohnishi, M. *Planta Med.* **1991**, *57*, 8.
22. Sanz, M. J.; Ferrandiz, M. L.; Cejudo, M.; Terencio, M. C.; Gil, B.; Bustos, G.; Ubeda, A.; Gunasegaran, R.; Alcaraz, M. J. *Xenobiotica* **1994**, *24*, 689.