Journal of the Korean Chemical Society
2020, *Vol. 64, No. 2*
Printed in the Republic of Korea
https://doi.org/10.5012/jkcs.2020.64.2.130

Note

Synthesis of 7-O-alkyl or 7-O-acyl Derivatives of Naringenin and Apigenin

Mingi Chu and Dong Wook Kang*
Department of Pharmaceutical Engineering & Natural Science Research Institute & TH Co., Ltd., Catholic University of Daegu, Hayang-ro 13-13, Kyeongsan-si, Gyeongsangbuk-do, 38430, Korea.
**E-mail: dwkang@cu.ac.kr*
(Received January 24, 2020; Accepted February 24, 2020)

Key words: Naringenin, Apigenin, Flavonoid, Alkylation, Acylation

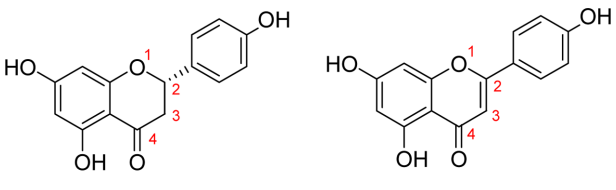
Naringenin and apigenin are natural flavonoids that differ structurally only by the presence or absence of a double bond between carbons 2 and 3 (*Fig*. 1).

Flavonoids are secondary metabolites of plants and fungi, and are found in many foods, such as vegetables and fruits.[1,2] Flavonoids have been reported to therapeutically benefit cardiovascular disease,[3] cancer,[4] and inflammation,[5] among others, and have been well known for the prevention of oxidative stress in the human body.[6] In addition, they are being studied as therapeutic agents for various diseases.[7]

Among the flavonoids, naringenin, which has a flavanone structure, is found mainly in grapes, citrus fruits, and herbs, and is considered to be beneficial for human health. In addition, it is known to exhibit various biological and pharmacological activities, including antioxidant, anticancer, antiviral, antibacterial, anti-lipogenic and cardioprotective effects[6–14] (*Figure* 2).

Naringenin is also known to enhance memory and reduce beta-amyloid and tau proteins in mouse models of Alzheimer's disease.[15] In addition, naringenin causes apoptosis in adipocytes, resulting in anti-lipogenic activity,[16] and studies have shown it to lower plasma and liver cholesterol levels.[17]

On the other hand, apigenin has been observed to suppress various cancers through a number of effects, including cell-cycle arrest and apoptosis.[18]



Naringenin Apigenin

***Figure* 1.** Chemical structures of naringenin and apigenin.

When introduced into the body, flavonoids become methylated, sulfated, glucuronidated, and phenolated through phase-two metabolism.[19] Since oral administration of flavonoids is difficult due to a lack of absorption in the gastrointestinal tract,[20] the synthesis of derivatives that improve their absorption rates and activities in the body is necessary in order to increase their potential as therapeutic agents.

Herein, we studied methods for the alkylation and acylation of the 7-hydroxy group of naringenin. In addition, we also studied the conversions of these compounds into the corresponding apigenin derivatives.

The 7-hydroxy group of naringenin (**1**) has previously been alkylated using alkyl iodides, but in yields lower than 35%.[21,22] In order to improve the yield, we used dialkyl sulfates instead of alkyl iodides to produce the 7-O-monoalkylated naringenin products **2**–**5** in yields of 80–92% (*Scheme* 1). Furthermore, when naringenin was reacted with an alkyl anhydride in pyridine as the base and solvent,

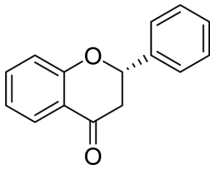
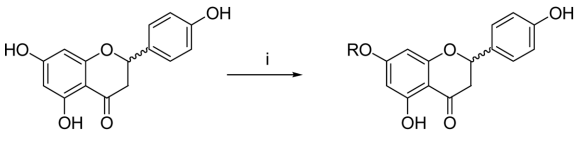
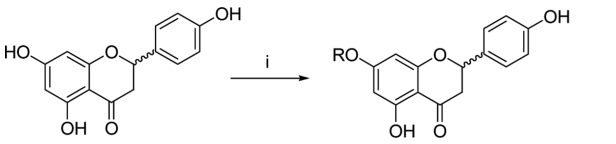


***Figure* 2.** The flavanone skeleton.



2;R = -CH_3, 92%
3;R = -CH_2CH_3, 90%
4;R = -$CH_2CH_2CH_3$, 84%
5;R = -$CH_2(CH_2)_2CH_3$, 80%

***Scheme* 1.** Reagents and conditions: i) R_2SO_4, K_2CO_3, DMF, r.t., 12h, 80~92%.



1

6;R = -$COCH_3$, 73%
7;R = -$COCH_2CH_3$, 66%
8;R = -$CO(CH_2)_2CH_3$, 60%
9;R = -$CO(CH_2)_6CH_3$, 53%

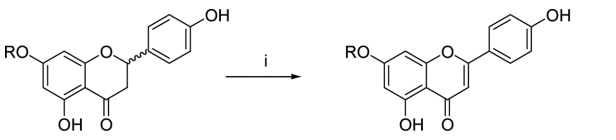
***Scheme* 2.** Reagents and conditions: i) Alkyl anhydride, pyridine, THF, r.t., 6-12h, 53-73%.

7,4-O-diacylated or 7,4',5-O-triacylated naringenin was synthesized.[23] In order to synthesize a 7-O-monoacylated naringenin derivative,[24] the reaction was carried out using pyridine as a base in THF as the solvent, with products **6**–**9** obtained in yields of 53–73% (*Scheme* 2).

The attempted selective alkylation or acylation of the 7-hydroxyl group of apigenin either failed to proceed or gave the corresponding product in yields of less than 20%. In order to obtain a compound in which an alkyl group or an acyl group was introduced at the 7-hydroxy group of apigenin, we converted the substituted naringenins **2**–**9** to the corresponding apigenins.[25,26] Hence, eight apigenin derivatives **10**–**17** were synthesized by oxidizing the previously prepared eight naringenin derivatives with DDQ in yields of 60–95%.

Since various pharmacological effects of flavonoid compounds have been actively studied. It is also important to study the synthesis of flavonoid derivatives to confirm these pharmacological effects. Although the 7-hydroxy group of naringenin had been alkylated in low yields (20–35%) in previous studies, in this study the products were obtained in yields of 80–92% using dialkyl sulfates instead of alkyl iodides as the alkylating agents, while this hydroxy group was monoacylated using pyridine and an alkyl anhydride in THF as the solvent in yields of 53–73%.

Direct alkylation and acylation methods were used in attempts to directly alkylate or acylate the 7-hydroxyl group of apigenin, but these reaction did not progress or provided products in yields of less than 20%. Consequently, 7-alkyl or acyl substituted naringenin derivatives 2–9 were oxidized using DDQ to give the corresponding alkyl- or acyl substituted derivatives of apigenin 10–17 in yields of 60–95%.



2 R = -CH_3
3 R = -CH_2CH_3
4 R = -$CH_2CH_2CH_3$
5 R = -$CH_2(CH_2)_2CH_3$
6 R = -$COCH_3$
7 R = -$COCH_2CH_3$
8 R = -$CO(CH_2)_2CH_3$
9 R = -$CO(CH_2)_6CH_3$

10 R = -CH_3, 70%
11 R = -CH_2CH_3, 60%
12 R = -$CH_2CH_2CH_3$, 62%
13 R = -$CH_2(CH_2)_2CH_3$, 67%
14 R = -$COCH_3$, 95%
15 R = -$COCH_2CH_3$, 94%
16 R = -$CO(CH_2)_2CH_3$, 95%
17 R = -$CO(CH_2)_6CH_3$, 89%

***Scheme* 3.** Reagents and conditions: i) DDQ, 1,4-dioxane, reflux, 9h, 60~95%.

In summary, eight 7-alkoxy or 7-acyloxy derivatives of naringenin were synthesized, while the corresponding apigenin derivatives were prepared by oxidizing these substituted naringenins.

EXPERIMENTAL

General

Reagents and solvents were purchased from Aldrich, TCI, Alfa-aesar, Samchun, etc. and used without purification.

Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Merck silica gel plates (60F254) using UV light as the 254 nm agent. For the separation of samples by flash chromatography using Merck silica gel 60 (40–63 μm). ^{1}H NMR spectra were obtained using a JEOL superconducting magnet JMTC-400/54/JJ/YH (400 MHz). Chemical shifts were recorded in ppm downfield from tetramethylsilane (TMS), and coupling constant (*J*) values are given in Hertz.

Experimental Procedure

General procedure for 7-O-alkylated naringenin derivatives 2~5 (*Scheme* 1): Dialkyl sulfate (1 mmol) and potassium carbonate (1 mmol) were added to a solution of naringenin **1** (1 mmol) in DMF (3 mL). The mixture was stirred at room temperature for 12 h. The resulting mixture was diluted with water (70 mL) and extracted with EtOAc (100 mL×2). The organic layer was washed with brine (30 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduce pressure. The crude material was purified by SiO_2 column chromatography using *n*-hexane:EtOAc or CH_2Cl_2:EtOAc as eluent to give the naringenin derivatives.

5-Hydroxy-2-(4-hydroxy-phenyl)-7-methoxy-chroman-4-one (2): Column chromatography using CH_2Cl_2:EtOAc=50:1 as eluent to give **2** (99 mg, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.80 (1H, dd, *J* = 17.2, 3.0 Hz), 3.12 (1H, m), 3.80 (3H, s), 5.14 (1H, s), 5.36 (1H, dd, *J* = 13.0, 2.8 Hz), 6.06 (2H, dd, *J* = 11.7, 2.1 Hz), 6.88 (2H, d, *J* = 8.5 Hz), 7.33 (2H, d, *J* = 8.5 Hz), 12.00 (1H, s); HRMS(ES+) calcd for $C_{16}H_{15}O_5$: 287.0914, Found: 287.0917.

7-Ethoxy-5-hydroxy-2-(4-hydroxy-phenyl)-chroman-4-one (3): Column chromatography using *n*-hexane:

EtOAc=4:1 as eluent to give **3** (298 mg, 90%).; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.41 (3H, t, J = 7.0 Hz), 2.79 (1H, dd, J = 17.2, 2.9 Hz), 3.12 (1H, m), 4.05 (2H, d, J = 14.0 Hz), 5.10 (1H, s), 5.36 (1H, dd, J = 13.0, 2.8 Hz), 6.04 (2H, dd, J = 12.1, 2.1 Hz), 6.88 (2H, d, J = 8.5 Hz), 7.33 (2H, d, J = 8.5 Hz), 12.00 (1H, s); HRMS(ES+) calcd for $C_{17}H_{17}O_5$: 301.1071, Found: 301.1071.

5-Hydroxy-2-(4-hydroxy-phenyl)-7-propoxy-chroman-4-one (4): Column chromatography using *n*-hexane: EtOAc=6:1 as eluent to give **4** (293 mg, 84%).; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.02 (3H, t, J = 7.4 Hz), 1.82 (2H, m), 2.79 (1H, dd, J = 17.2, 2.9 Hz), 3.11 (1H, m), 3.93 (2H, t, J = 6.6 Hz), 4.98 (1H, s), 5.35 (1H, dd, J = 13.0, 2.8 Hz), 6.05 (2H, dd, J = 11.0, 2.0 Hz), 6.88 (2H, d, J = 8.4 Hz), 7.33 (2H, d, J = 8.4 Hz), 12.00 (1H, s); HRMS(ES+) calcd for $C_{18}H_{19}O_5$: 315.1227, Found: 315.1222.

7-Butoxy-5-hydroxy-2-(4-hydroxy-phenyl)-chroman-4-one (5): Column chromatography using CH_2Cl_2:EtOAc =50:1 as eluent to give **5** (290 mg, 80%).; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.97 (3H, t, J = 7.4 Hz), 1.49 (2H, m), 1.77 (2H, m), 2.79 (1H, dd, J = 17.2, 2.9 Hz), 3.11 (1H, m), 3.97 (2H, t, J = 6.5 Hz), 5.07 (1H, s), 5.36 (1H, dd, J = 13.0, 2.8 Hz), 6.05 (2H, dd, J = 11.1, 2.0 Hz), 6.88 (2H, d, J = 8.5 Hz), 7.33 (2H, d, J = 8.4 Hz), 12.00 (1H, s); HRMS(ES+) calcd for $C_{19}H_{21}O_5$: 329.1384, Found: 315.1380.

General procedure for 7-O-acylated naringenin derivatives 6~9 (*Scheme* 2): Alkyl anhydride (1 mmol) and pyridine (1 mmol) were added to a solution of naringenin **1** (1 mmol) in THF (5 mL). The mixture was stirred at room temperature for 6 h. The resulting mixture was diluted with water (70 mL) and extracted with EtOAc (100 mL×2). The organic layer was washed with brine (30 mL). The organic layer dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduce pressure. The crude material was purified by column chromatography using CH_2Cl_2:EtOAc=50:1 as eluent to give the naringenin derivatives.

Acetic 5-hydroxy-2-(4-hydroxy-phenyl)-4-oxo-chroman-7-yl ester (6): yield **6** (254 mg, 73%).; ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 2.31 (3H, s), 2.82 (1H, dd, J = 17.2, 2.8 Hz), 3.07 (1H, m), 5.41 (1H, dd, J = 12.9, 2.8 Hz), 6.00 (2H, d, J = 6.0 Hz), 7.15 (2H, d, J = 8.4 Hz), 7.46 (2H, d, J = 8.4 Hz), 12.00 (1H, s); HRMS(ES+) calcd for $C_{17}H_{15}O_6$: 315.0863, Found: 315.0866.

Propionic 5-hydroxy-2-(4-hydroxy-phenyl)-4-oxo-chroman-7-yl ester (7): yield **7** (240 mg, 66%).; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, t, J = 7.5 Hz), 2.63 (2H, q, J = 7.5 Hz), 2.83 (1H, dd, J = 17.2, 2.9 Hz), 3.08 (1H, m), 5.42 (1H, dd, J = 13.0, 2,7 Hz), 5.98 (2H, d, J = 5.3 Hz), 7.15 (2H, d, J = 8.4 Hz), 7.46 (2H, d, J = 8.4 Hz), 12.00 (1H, s); HRMS(ES+) calcd for $C_{18}H_{17}O_6$: 329.1020, Found: 329.1021.

Butyric 5-hydroxy-2-(4-hydroxy-phenyl)-4-oxo-chroman-7-yl ester (8): yield **8** (227 mg, 60%).; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.05 (3H, t, J = 7.4 Hz), 1.83 (2H, m), 2.57 (2H, t, J = 7.4 Hz), 2.82 (1H, dd, J = 17.2, 3.0 Hz), 3.08 (1H, m), 5.42 (1H, dd, J = 13.0, 2.7 Hz), 5.98 (2H, d, J = 5.6 Hz), 7.15 (2H, d, J = 8.4 Hz), 7.46 (2H, d, J = 8.4 Hz), 12.00 (1H, s); HRMS(ES+) calcd for $C_{19}H_{19}O_6$: 343.1176, Found: 343.1178.

Octanoic 5-hydroxy-2-(4-hydroxy-phenyl)-4-oxo-chroman-7-yl ester (9): yield **9** (233mg, 53%).; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.90 (3H, t, J = 6.5 Hz), 1.37 (8H, m), 1.78 (2H, m), 2.58 (1H, t, J = 7.5 Hz), 2.81 (1H, dd, J = 16.6, 1.7 Hz), 3.07 (1H, m), 5.40 (1H, d, J = 11.2 Hz), 5.98 (2H, d, J = 6.3 Hz), 7.14 (2H, d, J = 8.2 Hz), 7.45 (2H, d, J = 8.2 Hz), 12.00 (1H, s); HRMS(ES+) calcd for $C_{23}H_{27}O_6$: 399.1802, Found: 399.1803.

General procedure for 7-O-alkylated or acylated apigenin derivatives 10~17 (scheme 3): DDQ (3 mmol) were added to a solution of compound **2**~**9** (1 mmol) in 1,4-dioxane (10 mL). The mixture was stirred at 120 ºC for 9 h. The resulting mixture was diluted with water (70 mL) and extracted with EtOAc (100 mL×2). The organic layer was washed with brine (30 mL). The organic layer dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduce pressure. The crude material was purified by column chromatography using *n*-hexane:EtOAc or *n*-hexane:acetone as eluent to give the apigenin derivatives.

5-Hydroxy-2-(4-hydroxy-phenyl)-7-methoxy-chromen-4-one (10): Column chromatography using *n*-hexane:acetone=4:1 as eluent to give **10** (73 mg, 70%).; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.83 (3H, s), 6.34 (1H, d, J = 2.0 Hz), 6.74 (1H, d, J = 1.96 Hz), 6.82 (1H, s) 6.90 (2H, d, J = 8.7 Hz), 7.94 (2H, d, J = 8.7 Hz), 10.36 (1H, s), 12.93 (1H, s); HRMS (ES+) calcd for $C_{16}H_{13}O_5$: 285.0757, Found: 285.0758.

7-Ethoxy-5-hydroxy-2-(4-hydroxy-phenyl)-chromen-4-one (11): Column chromatography using *n*-hexane: EtOAc=2:1 as eluent to give **11** (60 mg, 60%).; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.34 (3H, t, J = 6.8 Hz), 4.14 (2H, d, J = 6.92 Hz), 6.31 (1H, s), 6.72 (1H, s), 6.81 (1H, s), 6.90 (2H, d, J = 8.4 Hz), 7.93 (2H, d, J = 8.4 Hz), 10.35 (1H, s), 12.91 (1H, s); HRMS(ES+) calcd for $C_{17}H_{15}O_5$: 299.0914, Found: 299.0914.

5-Hydroxy-2-(4-hydroxy-phenyl)-7-propoxy-chromen-4-one (12): Column chromatography using *n*-hexane: EtOAc=2:1 as eluent to give **12** (62 mg, 62%).; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.97 (3H, t, J = 7.4 Hz), 1.76 (2H, m), 4.04 (2H, t, J = 6.6 Hz), 6.32 (1H, d, J = 2.0 Hz), 6.73

(1H, d, J = 2.0 Hz), 6.81 (1H, s), 6.90 (2H, d, J = 8.7 Hz), 7.93 (2H, d, J = 8.7 Hz), 10.33 (1H, s), 12.90 (1H, s); HRMS (ES+) calcd for $C_{18}H_{17}O_5$: 313.1071, Found: 313.1068.

7-Butoxy-5-hydroxy-2-(4-hydroxy-phenyl)-chromen-4-one (13): Column chromatography using *n*-hexane: EtOAc=2:1 as eluent to give **13** (50 mg, 67%).; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.92 (3H, t, J = 7.4 Hz), 1.45 (2H, m), 1.72 (2H, m), 4.07 (2H, t, J = 6.5 Hz), 6.32 (1H, d, J = 2.0 Hz), 6.74 (1H, d, J = 2.0 Hz), 6.81 (1H, s), 6.90 (2H, d, J = 8.8 Hz), 7.94 (2H, d, J = 8.7 Hz), 10.35 (1H, s), 12.91 (1H, s); HRMS (ES+) calcd for $C_{19}H_{19}O_5$: 327.1227, Found: 327.1221.

Acetic 5-hydroxy-2-(4-hydroxy-phenyl)-4-oxo-4H chromen-7-yl ester (14): Column chromatography using *n*-hexane:EtOAc=2:1 as eluent to give **14** (97 mg, 95%).; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.27 (3H, s), 6.18 (1H, s), 6.49 (1H, s), 6.94 (1H, s), 7.32 (2H, d, J = 8.6 Hz), 8.10 (2H, d, J = 8.6 Hz), 10.90 (1H, s), 12.78 (1H, s); HRMS (ES+) calcd for $C_{17}H_{13}O_6$: 313.0707, Found: 313.0700.

Propionic 5-hydroxy-2-(4-hydroxy-phenyl)-4-oxo-4H-chromen-7-yl ester (15): Column chromatography using *n*-hexane:EtOAc=2:1 as eluent to give **15** (95 mg, 94%).; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.13 (3H, t, J = 6.6 Hz), 2.62 (2H, t, J = 7.0 Hz), 6.19 (1H, s), 6.49 (1H, s), 6.95 (1H, s), 7.32 (2H, d, J = 8.0 Hz), 8.10 (2H, d, J = 8.1 Hz), 10.90 (1H, s), 12.78 (1H, s); HRMS (ES+) calcd for $C_{18}H_{17}O_6$: 329.1020, Found: 329.1026.

Butyric 5-hydroxy-2-(4-hydroxy-phenyl)-4-oxo-4H-chromen-7-yl ester (16): Column chromatography using *n*-hexane:EtOAc=2:1 as eluent to give **16** (95 mg, 95%).; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.96 (3H, t, J = 7.4 Hz), 1.68 (2H, m), 2.58 (2H, t, J = 7.2 Hz), 6.49 (1H, d, J = 1.7 Hz), 6.88 (1H, s), 6.93 (2H, d, J = 8.2Hz), 7.02 (1H, d, J = 1.7 Hz), 7.96 (2H, d, J = 8.7 Hz), 10.90 (1H, s), 12.78 (1H, s); HRMS (ES+) calcd for $C_{19}H_{17}O_6$: 341.1020, Found: 341.1010.

Octanoic 5-hydroxy-2-(4-hydroxy-phenyl)-4-oxo-4H-chromen-7-yl ester (17): Column chromatography using *n*-hexane:EtOAc=2:1 as eluent to give **17** (90 mg, 89%).; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.85 (3H, t, J = 7.5Hz), 1.25 (8H, d, J = 16.9Hz), 1.65 (2H, m), 2.59 (2H, t, J = 7.4 Hz), 6.59 (1H, d, J = 1.8 Hz), 6.89 (1H, s), 6.93 (2H, d, J = 8.6 Hz), 7.02 (1H, d, J = 1.8 Hz), 7.96 (2H, d, J = 8.7 Hz), 10.90 (1H, s), 12.78 (1H, s); HRMS (ES+) calcd for $C_{23}H_{25}O_6$: 397.1646, Found: 397.1643.

Acknowledgments. This work was supported by research grants from Daegu Catholic University in 2019.

Conflicts of Interest: The authors declare no conflict of interest.

REFERENCES

1. Bohm, B. A. *Introduction to Flavonoids*; Harwood Academic: Amsterdam, 1998.
2. *Flavonoids and other Polyphenols. Methods in Enzymology*; Packer, L., Ed.; Academic: San Diego, 2001; Vol. 335.
3. Yoshizumi, M.; Tsuchiya, K.; Kirima, K.; Kyaw, M.; Suzaki, Y.; Tamaki, T. *Mol. Pharmacol*. **2001**, *60*, 656.
4. Choi, J. A.; Kim, J. Y.; Lee, J. Y.; Kang, C. M.; Kwon, H. J.; Yoo, Y. D.; Kim, T. W.; Lee, Y. S.; Lee, S. J. *Int. J. Oncol*. **2001**, *19*, 837.
5. Izzi, V.; Masuelli, L.; Tresoldi, I. *Front. Biosci*. **2012**, *7*, 2396.
6. Pietta, P. G. *J. Nat. Prod*. **2000**, *63*, 1035.
7. Stipcevic, T.; Piljac, D.; Berghe, D. V. *Plant Foods for Human Nutrition*. **2006**, *61*, 29.
8. Ferreira, R. J.; Baptista, R.; Moreno, A.; Madeira, P. G. *Future Medicinal Chemistry.* **2018**, *10*, 725.
9. Nahmias, Y.; Goldwasser, J.; Casali, M.; van Poll, D. *Hepatology* **2008**, *47*, 1437.
10. Rauha, J.-P.; Remes, S. *Int. J. Food Microbiol*. **2000**, *56*, 3.
11. Hsu, C.-L.; Huang, S.-L.; Yen, G.-C. *J. Agric. Food Chem*. **2006**, *54*, 4191.
12. Mulvihill, E. E.; Allister, E. M.; Sutherland, B. G.; Telford, D. E.; Sawyez, C. G.; Edwards, J. Y.; Markle, J. M.; Hegele, R. A.; Huff, M. W. *Diabetes* **2009**, *58*, 2198.
13. Lee, S. H.; Park, Y. B.; Bae, K. H.; Bok, S. H.; Kwon, Y. K.; Lee, E. S.; Choi, M. S. *Ann. Nutr. Metab*. **1999**, *43*, 173.
14. Yoon, H.; Kim, T.-W.; Shin, S.-Y. *Bioorganic & Medicinal Chemistry Letters*, **2013**, *23*, 232.
15. Ma, J.; Yang, W. Q.; Zha, H.; Yu, H. R. *Journal of Chinese Medicinal Materials*, **2013**, *36*, 271.
16. Yang, Z. *Phytotherapy Res*. **2019**, *33*, 1114.
17. Yang, Z. *Front. Pharmacol*. **2017**, *8*, 340.
18. Yan, X.; Qi, M.; Li, P.; Zhan, Y.; Shao, H. *Cell & Bioscience*. **2017**, *7*, 50.
19. Ader, P.; Wessmann, A.; Wolffram, S. *Free Rad. Biol. Med*. **2000**, *28*, 1056.
20. Choudhury, R.; Srai, S. K.; Debnam, E.; Rice-Evans, C. A. *Free Rad. Biol. Med*. **1999**, *27*, 278.
21. Kozlowska, J.; Grela, E.; Baczyńska, D.; Grabowiecka, A. *Molecules* **2019**, *24*, 679.
22. Kozlowska, J.; Potaniec, B.; Zarowsha, B. *Molecules* **2017**, *22*, 1485.
23. Li, B.-W.; Zhang, F.-H.; Serrao, E.; Chen, H.; Sanchez, T. W.; Yang, L.-M.; Neamati, N.; Zheng, Y.-T.; Wang, H.; Long, Y.-Q. *Bioorg. Med. Chem*. **2014**, *22*, 3146.
24. Li, J.; Grosslight, S.; Milner, S.-J. *ACS Catal*. **2019**, *9*, 9794.
25. Kim, J.-Y.; Park, K.-S.; Lee, C.-W.; Chang, Y.-H. *Bull. Korean Chem. Soc*. **2007**, *28*, 2527.
26. Oyama, K.-I.; Kondo, T.; Yoshida, K. *Heterocycles*. **2008**, *76*, 1607.