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SYNTHESIS AND STRUCTURE CHARACTERIZATION OF NOVEL LUTEOLIN DERIVATIVES

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A series of novel luteolin derivatives was synthesized employing the Vilsmeier-Haak-Arnold reaction from the intermediate compound 3′,4′,7-trichloro-5-hydroxyflavone, which was obtained from luteolin. These derivatives may be used to improve the pharmacological activities of luteolin.

Keywords: luteolin, derivatives, 3′,4′,7-trichloro-5-hydroxyflavone, synthesis.

Luteolin, one of the flavones, exists mainly in herbs of *Lonicera japonica*, *Chrysanthemum morifolium, Nepeta cateria* L., and *Ajuga decumbens* Thunb. Luteolin has been studied extensively as it possesses important pharmacological activities, such as antiviral, antimicrobial, anticholesterol, etc. [1–3]. However, there are few reports about the derivatives of luteolin. Based on the fact that Schiff bases have been reported as anticancer [4], antibacterial and anti-inflammatory agents [5, 6], we used the Vilsmeier-Haak-Arnold reaction to obtain new luteolin derivatives, in which we expected to find some compounds with better pharmacological activities.

A series of luteolin (**1**) derivatives was obrained by the reaction of 3′,4′,7-trichloro-5-hydroxyflavone and R-NH_2 [7] based on the Vilsmeier-Haak-Arnold reaction. Synthesis of the title compounds is outlined in Scheme 1. 3′,4′,7-Trichloro-5-hydroxyflavone (**2**) was obtained in good yield by adding luteolin to $POCl_3$ in DMF with heating [8–10], then recrystallized in ethanol to give compound **3a**. We found from its ^{1}H NMR and ^{13}C NMR data that there was one molecular ethanol in **3a** structure. The synthesis routes are as shown in Scheme 1.

The ^{13}C NMR spectroscopy of compound **3a** indicated that there were 15 peaks of carbon between δ 102 and δ 182. Comparison of the ^{13}C NMR data of compound **3a** and luteolin suggested that the hydroxyl groups connected to C-3′, C-4′, and C-7 were replaced by chlorine.

In the IR spectra of compounds **3c**, **3d**, and **3e**, the absorption peaks at 1460 cm^{-1} and 1380 cm^{-1} indicated that there were methyl and methylene in the compounds. The IR absorption peaks (1385, 1460, and 1370 cm^{-1}) showed that compound **3d** included the $(CH_3)_2CH$-group. In the ^{1}H NMR of compound **3f**, the proton peaks at δ 7.24, 7.29, 7.31, 7.34, and 7.52 ppm were observed to agree with -CH_2-C_6H_5. MS and NMR data further confirmed their structures.

EXPERIMENTAL

Materials and Methods. Chemicals were purchased from Baoji Aimu Food Co. and used as such without further purification; TLC was performed on silica gel plates with visualization by UV light; melting points were taken in an X-4 digital melting point apparatus; all compounds were characterized by a combination of GC-MS, IR, NMR, and elemental analyses. IR spectra in KBr pellets were recorded on FT-IR. ^{1}H NMR (400 MHz) and ^{13}C NMR (400 MHz) spectra were recorded on a Bruker 5000 spectrometer in DMSO-d_6 (with TMS for ^{13}C NMR as an internal reference). GC-MS analyses were performed with QP5050A. Elemental analyses of all compounds were performed on a Perkin–Elmer 2400 analyzer.

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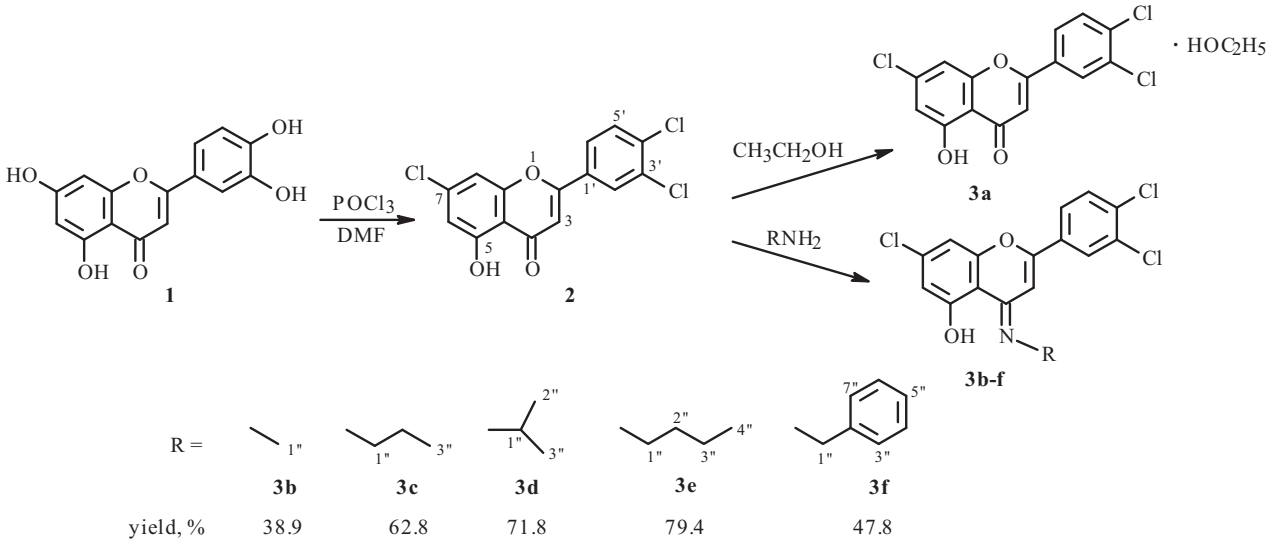

Scheme 1. Synthesis of luteolin derivatives.

3′,4′,7-Trichloro-5-hydroxyflavone (3 mmol) in anhydrous DMF (2 mL) and methylamine (1 mL) were added to ethyl acetate. The reaction solution was stirred for 5 min and gave a yellow precipitate, which was filtered and recrystallized to give product **3b** in a yield of 38.9%. 3′,4′,7-Trichloro-5-hydroxyflavone reacted with different amines under the same condition to give compounds **3c–3f** as shown in Scheme 1.

All the products were characterized by IR, GC-MS, ^{1}H NMR, and elemental analyses. The analytical data of compounds **3a–3f** are as follows:

Compound 3a: mp 244–245°C; IR (KBr, ν, cm^{-1}): 3445, 2923, 1562, 1480, 1432; ^{1}H NMR (DMSO-d$_6$, δ, ppm, J/Hz): 1.05 (3H, t, J = 6.6, H-3″), 3.43 (2H, m, J = 6.6, H-2″), 4.35 (1H, s, H-1″), 6.93 (1H, s, H-6), 6.99 (1H, s, H-8), 7.28 (1H, s, H-3), 7.32 (1H, d, J = 8.4, H-5′), 7.47(1H, s, H-2′), 7.51 (1H, d, J = 8.4, H-6′), 12.83 (1H, s, 5-OH); ESI-MS (*m/z*): 342.9 [M + 1]$^+$.

Compound 3b: mp 240–242°C; IR (KBr, ν, cm^{-1}): 3415, 2923, 1651, 1480, 1430; ^{1}H NMR (DMSO-d$_6$, δ, ppm, J/Hz): 2.35 (3H, s, H-1″), 6.86 (1H, s, H-6), 6.91 (1H, s, H-8), 7.15 (1H, s, H-3), 7.33 (1H, d, J = 8.4, H-5′), 7.43 (1H, s, H-2′), 7.47 (1H, d, J = 8.4, H-6′); ESI-MS (*m/z*): 353.8 [M + 1]$^+$.

Compound 3c: mp 246–247°C; IR (KBr, ν, cm^{-1}): 3415, 1653, 1460, 1380; ^{1}H NMR (DMSO-d$_6$, δ, ppm, J/Hz): 0.86 (3H, t, J = 7.4, H-3″), 1.45 (2H, m, J = 7.4, 7.3, H-2″), 2.62–2.65 (2H, t, J = 7.3, H-1″), 6.80 (1H, s, H-6), 6.84 (1H, s, H-8), 7.05 (1H, s, H-3), 7.22 (1H, d, J = 8.5, H-5′), 7.39 (1H, s, H-2′), 7.41 (1H, d, J = 8.5, H-6′); ESI-MS (*m/z*): 381.8 [M + 1]$^+$.

Compound 3d: mp 243–245°C; IR (KBr, ν, cm^{-1}): 3426, 1651, 1385, 1370, 1460; ^{1}H NMR (DMSO-d$_6$, δ, ppm, J/Hz): 1.13 (6H, d, J = 6.4, H-2″, H-3″), 3.18–3.24 (1H, m, J = 6.4, H-1″), 6.85 (1H, d, J = 1.7, H-6), 6.89 (1H, s, H-8), 7.12 (1H, d, J = 1.7, H-3), 7.32 (1H, dd, J = 8.4, 1.9, H-5′), 7.44 (1H, s, H-2′), 7.47 (1H, dd, J = 8.4, 1.9, H-6′); ESI-MS (*m/z*): 381.9 [M + 1]$^+$.

Compound 3e: mp 241–243°C; IR (KBr, ν, cm^{-1}): 3415, 3072, 1650, 1380, 1460; ^{1}H NMR (DMSO-d$_6$, δ, ppm, J/Hz): 0.83–0.87 (3H, t, J = 7.2, H-4″), 1.24–1.34 (2H, m, J = 7.2, 7.6, H-3″), 1.38–1.45 (2H, m, J = 7.6, 7.3, H-2″), 2.62–2.66 (2H, t, J = 7.3, H-1″), 6.80 (1H, s, H-6), 6.84 (1H, s, H-8), 7.05 (1H, s, H-3), 7.21 (1H, d, J = 8.0, H-5′), 7.38 (1H, s, H-2′), 7.40 (1H, d, J = 8.0, H-6′); ESI-MS (*m/z*): 395.9 [M + 1]$^+$.

Compound 3f: mp 238–240°C; IR (KBr, ν, cm^{-1}): 3438, 1646, 1609, 1552, 1474; ^{1}H NMR (DMSO-d$_6$, δ, ppm): 3.77 (2H, s, H-1″), 6.91 (1H, d, J = 1.5, H-6), 6.96 (1H, s, H-8), 7.22 (1H, s, H-3), 7.24 (1H, m, H-5″), 7.29 (1H, d, J = 6.5, H-7″), 7.31 (1H, d, J = 6.5, H-3″), 7.34 (1H, d, J = 8.5, H-5′), 7.39 (1H, s, H-2′), 7.42 (1H, d, J = 8.5, H-6′), 7.49 (1H, m, H-6″), 7.52 (1H, m, H-4″); ESI-MS (*m/z*): 429.9 [M + 1]$^+$.

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REFERENCES

1. X. X. Li and Ch. Guo, *Chin. Pharm*., **18**, 1421 (2007).
2. Y. Lee and L. R. Howard, *J. Food Sci*., **60**, 476 (1995).
3. X. K. Wang, *Natural Medicinal Chemistry*, Beijing, China, 272 (1994).
4. D. K. Yuan, Zh. M. Li, and W. G. Zhao, *Chin. J. Appl. Chem.*, **20**, 624 (2003).
5. B. Havesteen, *Biochem. Pharm*., **32**, 1141 (1983).
6. J. Q. Sha, J. F. Li, and H. Yan, *Heilongjiang Med. Pharm*., **27**, 12 (2004).
7. Q. Y. Xing, R. Q. Xu, Zh. Zhou, and W. W. Pei, *Basic Organic Chemistry*, Beijing, China, 732 (1994).
8. M. M. Charles, *Tetrahedron*, **48**, 3659 (1992).
9. H. Bohme and H. G. Viche, *Adv. Org. Chem*., USA, **9**, 225 (1976).
10. V. L. Zbarskii, *Zh. Org. Khim*., **27**, 2460 (1991).