SYNTHESIS OF NOVEL FERULIC ACID – BASED MANNICH BASES

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Abstract

The synthesis of novel Mannich bases based on Ferulic acid is described. Ferulic acid (**1**) was first reacted with propargyl bromide and propargyl amine to give intermediates **2a** and **2b**, respectively. Next, the Mannich reaction of **2a** and **2b** with secondary amines in ethanol at reflux condition furnished two series of novel Mannich bases in good yields, **3a-h** and **4a-h**. All synthesized compounds were structurally characterized using spectroscopic methods NMR and MS.

Keywords: Ferulic acid, Mannich bases, secondary amines, propargyl bromide, propargyl amine.

1. INTRODUCTION

Mannich bases are beta-amino ketones, which are generally formed by the reaction between formaldehyde and a secondary amine. Mannich bases have been associated with increased bio-activity. Some chalcone - based Mannich bases were reported to exhibit a variety of biological activities, including anti-tubercular [1], anti-malarial [2], anti-cancer [3], and anti-inflammatory [4, 5].

The bio-activity of Mannich bases has been attributed to the cyclohexadienones resulting from the deamination of the Mannich base group in chalcones. These cyclohexadienones may then generate a number of molecular sites for nucleophilic attack by cellular thiols. In addition, chemical structure of α,β-unsaturated ketone may alkylate nucleophiles, especially toward thiols rather than hydroxyl and amino groups present in the nucleic acids [6, 7].

Ferulic acid is a natural phenolic compound. It is known to form various derivatives exhibiting a variety of biological activities by combining with other compounds. Some natural products like chlorogenic acids containing ferulic acid skeleton are reported to be potential anti-carcinogenesis as chemopreventive agents [8, 9]. Regarding the metabolism of ferulic acid, its bio-synthetically related secondary metabolite is 3-(4'-geranyloxy-3'-methoxyphenyl)-2-*trans*-propenoic acid, in which a geranyl chain is attached to the phenolic group [10]. The ethyl ester derivative of this compound exhibited a lot of interesting biological effects such as colon and tongue cancer chemoprevention [11, 12]. In addition, some its myo-inositol esters showed a good inhibitory activity on phorbol ester-induced superoxide generation and Epstein–Barr virus activation [13]. These esters were considered to be hydrolyzed to the parent acid once inside the cell, and thus, the true active principle exerting these biological effects would be 3-(4'-geranyloxy-3'-methoxyphenyl)-2-*trans*-propenoic acid. Then ferulic acid derivative, 3-(4'-geranyloxy-3'-methoxyphenyl)-2-*trans*-propenoic acid becomes a novel candidate as chemopreventive drug for the treatment of different types of cancer and as anti-inflammatory compound. According to our best knowledge, there are no reports about ferulic acid-based Mannich bases. Therefore, in this communication, we report the synthesis of novel Mannich bases, in which ferulic acid is used as starting materials for Mannich reaction.

2. EXPERIMENTAL SECTION

All chemicals and reaction solvents were purchased from Merck and Aldrich. Melting points were determined in open capillaries on

Electrothermal IA 9200 Shimadzu apparatus and uncorrected. IR spectra were recorded on FT-IR IMPACT-410 using KBr discs. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Aspect 300 spectrometer in $CDCl_3$, CD_3OD. Chemical shifts (δ) are in ppm relative to TMS, and coupling constants (J) are expressed in hertz (Hz). Low- and high-resolution FAB mass spectra were obtained on a Jeol JMS-AX505WA (FAB). Progress of the reaction was monitored by thin-layer chromatography (TLC) using glass pre-coated TLC sheets with Ultraviolet (UV) fluorescent silica gel. Multiplicities are shown as the abbreviations: s (singlet), brs (broad singlet), d (doublet), brd (broad doublet) t (triplet), m (multiplet). Flash chromatography was performed on Merck silica gel 60 (230-400 mesh; ASTM). Solvents were commercially available materials of reagent grade.

Synthesis of 3-(4-hydroxy-3-methoxy-phenyl)-acrylic acid prop-2-ynyl ester (2a)

To a solution of ferulic acid (5 g, 25.7 mmol), K_2CO_3 (3.53 g, 25.7 mmol) in DMF (30mL) was added propargyl bromide (2.84 mL, 25.7 mmol). The reaction mixture was stirred at room temperature for 24 h. The mixture was then extracted with CH_2Cl_2 and H_2O. The organic phase was separated, dried on anhydrous Na_2SO_4 and evaporated under reduced pressure. **2a** was obtained after column chromatography on silica gel using *n*-hexane:ethyl acetate as an eluent solvent system. Yield: 95 % (oil); IR (film, ν (cm^{-1})): 3271, 2944, 1710, 1631, 1569, 1489, 1245, 1151. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, J = 15.9 Hz, 1H), 7.12 (dd, J = 2.1 Hz, 8.5Hz, 1H), 7.05 (d, J = 2.1 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 6.36 (d, J = 15.9 Hz, 1H), 4.83 (d, J = 2.4 Hz, 2H), 3.95 (s, 3H), 2.52 (t, J = 2.4 Hz, 1H). ^{13}C NMR (75MHz, $CDCl_3$): 166.5, 148.4, 147.0, 146.2, 126.9, 123.5, 114.9, 114.6, 109.6, 78.1, 75.0, 56.2, 52.2.

General procedure for the synthesis of Mannich bases (3a-d)

A mixture of paraformaldehyde (6.13 mmol, 1.5 eq), secondary amines (4.09 mmol) in ethanol (20mL) was refluxed for 1 h. Compound **2a** (4.09 mmol) was then added to the above reaction mixture and refluxed for 24 hours. Ethanol was removed under vacuum. The residue was diluted with water and extracted with dichloromethane. The organic phase was separated, dried on anhydrous Na_2SO_4, and evaporated under reduced pressure. **3a-h** was obtained by flash column chromatography on silica gel using dichloromethane: methanol as eluent solvent system.

3-[4-Hydroxy-3-methoxy-5-(4-methyl-piperidin-1-ylmethyl)-phenyl]-acrylic acid prop-2-ynylester (3a)

Mp: 100-102 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, J = 15.9 Hz, 1H), 6.98 (d, J = 1.8 Hz, 1H), 6.79 (d, J = 1.8 Hz, 1H), 6.31 (d, J = 15.9 Hz), 4.81 (d, J = 2.5 Hz, 2H), 3.90 (s, 3H), 3.72 (s, 2H), 3.0 (d, J = 12 Hz, 2H), 2.51 (t, J = 2.4 Hz, 1H), 2.18 (t, J = 11.5 Hz, 2H), 1.72 (d, J = 12.9 Hz, 2H), 1.48-1.41 (m, 1H), 1.26-1.23 (m, 2H), 0.95 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): 166.6, 151.1, 148.5, 146.5, 124.9, 122.4, 121.8, 113.6, 109.8, 78.2, 74.9, 61.5, 56.1, 53.5, 51.9, 34.2, 30.5, 21.8. FAB-MS: 344.3 [M^++1].

3-[4-Hydroxy-3-methoxy-5-(4-methyl-piperazin-1-ylmethyl)-phenyl]-acrylic acid prop-2-ynylester (3b)

Mp: 99-100 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65 (d, J = 15.9 Hz, 1H), 6.98 (d, J = 1.5 Hz, 1H), 6.81 (d, J = 1.5Hz, 1H), 6.30 (d, J = 15.9 Hz, 1H), 4.79 (d, J = 2.5 Hz, 2H), 3.89 (s, 3H), 3.74 (s, 2H), 2.61-2.56 (brs, 8H), 2.49 (t, J = 2.5 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$): 166.5, 150.4, 148.4, 146.2, 125.3, 122.4, 121.3, 113.8, 109.9, 78.1, 74.9, 61.0, 56.0, 54.9, 52.6, 51.9, 46.0. FAB-MS: 345.18 [M^++1].

3-[4-Hydroxy-3-methoxy-5-(3-methyl-piperidin-1-ylmethyl)-phenyl]-acrylic acid prop-2-ynylester (3c)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.61 (d, J = 15.9 Hz, 1H), 6.91 (d, J = 1.8 Hz, 1H), 6.72 (d, J = 1.8 Hz, 1H), 6.22 (d, J = 15.9 Hz, 1H), 4.71 (d, J = 2.4 Hz, 2H), 3.82 (s, 3H), 3.62 (s, 2H), 2.45 (t, J = 2.4 Hz, 1H), 2.01-1.95 (m, 1H), 2.87-2.79 (m, 4H), 1.66-1.58 (m, 4H), 0.81 (d, J = 6 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): 166.3, 150.7, 148.2, 146.2, 125.1, 122.1, 121.0, 113.3, 109.5, 77.9, 74.7, 61.4, 60.8, 55.8, 53.2, 51.7, 36.4, 32.3, 25.1, 19.7. FAB-MS: 344.3 [M^++1].

3-[4-Hydroxy-3-methoxy-5-(4-ethyl-piperidin-1-ylmethyl)-phenyl]-acrylic acid prop-2-ynyl eser (3d)

Mp: 116-117 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65 (d, J = 15.9 Hz, 1H), 6.98 (d, J =1.5 Hz, 1H), 6.82 (d, J = 1.5 Hz, 1H), 6.31 (d, J = 15.9 Hz, 1H), 4.79 (d, J = 2.7 Hz, 2H), 3.89 (s, 3H), 3.74 (s, 2H), 2.59 (brs, 8H), 2.49 (t, J = 2.4 Hz, 1H), 2.44 (q, J = 6.9 Hz, 2H), 1.08 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 166.5, 150.4, 148.4, 146.2, 125.3, 122.4, 121.4, 113.8, 109.9, 78.1, 74.9, 61.1, 56.1, 52.6, 52.3, 52.0, 12.1. FAB-MS: 359.3 [M^++1].

Synthesis of 3-(4-Hydroxy-3-methoxy-phenyl)-N-prop-2-ynyl-acrylamide (2b)

A mixture of ferulic acid (1.94 g, 10 mmol), Carbonyl diimidazole (CDI) (1.3 eq) in anhydrous

THF (25 mL) was stirred at room temperature for 1 h. Propargyl amine (1.3 eq) was then added, and the reaction was continuously stirred overnight. THF was removed under vacuum. The residue was diluted with water and extracted with dichloromethane. Organic phase was separated, dried on anhydrous Na_2SO_4, and evaporated under reduced pressure. **2b** was obtained by flash column chromatography on silica gel using dichloromethane:methanol as eluent solvent system. Yield: 75%; Mp: 128-129 ^oC. IR (KBr, ν (cm^{-1})): ^1H NMR (300 MHz, CD_3OD): δ = 7.50 (d, *J* = 15.6 Hz, 1H), 7.11 (s, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.45 (d, *J* = 15.6 Hz, 1H), 4.08 (d, *J* = 2 Hz, 2H), 3.87 (s, 3H), 2.61 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (75MHz, CD_3OD): 168.9, 150.1, 149.4, 142.9, 128.2, 123.5, 118.2, 116.6, 111.8, 80.7, 72.4, 29.7.

General procedure for the synthesis of Mannich bases (4a-d)

A mixture of paraformaldehyde (6.41 mmol, 1.5 eq), secondary amines (4.27 mmol) in ethanol (25mL) was refluxed for 1 h. Compound **2b** (4.27 mmol) was then added to the above reaction mixture and refluxed for 24 hours. Ethanol was removed under vacuum. The residue was diluted with water and extracted with dichloromethane. Organic phase was separated, dried on anhydrous Na_2SO_4, and evaporated under reduced pressure. **4a-h** was obtained by flash column chromatography on silica gel using dichloromethane:methanol as eluent solvent system.

3-[4-Hydroxy-3-methoxy-5-(4-methyl-piperidin-1-ylmethyl)-phenyl]-N-prop-2-ynyl-acrylamide (4a)

Mp: 73-74 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 15.6 Hz, 1H), 6.95 (d, *J* = 1.8 Hz, 1H), 6.75 (d, *J* = 1.8 Hz, 1H), 6.28 (d, *J* = 15.6 Hz, 1H), 4.19 (q, *J* = 2.4 Hz, 2H), 3.88 (s, 3H), 3.68 (s, 2H), 2.99 (d, *J* = 11.7 Hz, 2H), 2.26 (t, *J* = 2.4 Hz, 1H), 2.16-2.05 (m, 2H), 1.71 (d, *J* = 12.4 Hz, 2H), 1.47-1.44 (m, 1H), 1.35-1.23 (m, 2H), 0.94 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): 166.2, 150.2, 148.4, 142.3, 125.4, 121.8, 121.7, 116.7, 109.7, 79.9, 71.8, 61.5, 56.1, 53.4, 34.2, 30.6, 29.6, 21.8. FAB-MS: 343.3[M^++1].

3-[4-Hydroxy-3-methoxy-5-(4-methyl-piperazin-1-ylmethyl)-phenyl]-N-prop-2-ynyl-acrylamide (4b)

Mp 151-152 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.56 (d, *J* = 15.3 Hz, 1H), 6.95 (d, *J* = 1.8 Hz, 1H), 6.76 (d, *J* = 1.8 Hz, 1H), 6.29 (d, *J* = 15.3 Hz, 1H), 4.18 (q, *J* = 2.4 Hz, 2H), 3.87 (s, 3H), 3.70 (s, 2H), 2.59-2.51 (brs, 8H), 2.29 (s, 3H), 2.25 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (75MHz, $CDCl_3$): 166.1, 149.6, 148.3, 142.1, 125.8, 121.8, 121.4, 117.0, 109.9, 79.9, 71.8, 61.1, 56.1, 54.9, 52.6, 46.0, 29.5. FAB-MS: 345.18 [M^++2].

3-[4-Hydroxy-3-methoxy-5-(3-methyl-piperidin-1-ylmethyl)-phenyl]-N-prop-2-ynyl-acrylamide (4c)

Mp: 73-74 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 15.3Hz, 1H), 6.95 (d, *J* = 1.8 Hz, 1H), 6.75 (d, *J* = 1.8 Hz, 1H), 6.28 (d, *J* = 15.3 Hz, 1H), 4.19 (q, *J* = 2.4 Hz, 2H), 3.88 (s, 3H), 3.68 (s, 2H), 2.25 (t, *J* = 2.4 Hz, 1H), 2.17 (m, 4H), 2.04-2.0 (m, 1H), 1.75 -1.63 (m, 4H), 0.88 (d, *J* = 5.7 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): 166.2, 150.2, 148.3, 142.3, 125.5, 121.8, 121.7, 116.7, 109.6, 79.8, 71.8, 61.8, 61.0, 56.1, 53.5, 32.6, 31.3, 29.5, 25.4, 19.5. FAB-MS: 343.3 [M^++1].

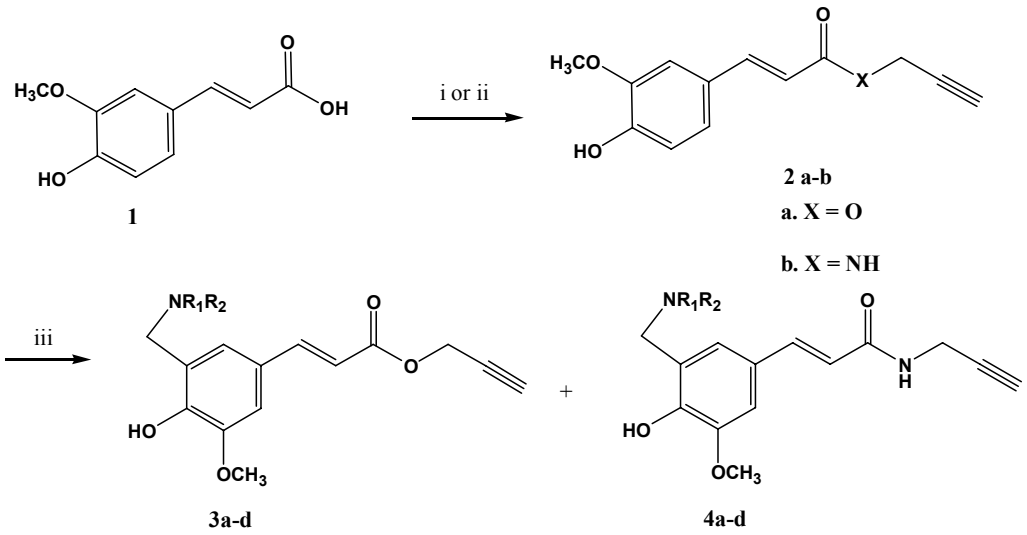
3-[4-Hydroxy-3-methoxy-5-(4-ethyl-piperazin-1-ylmethyl)-phenyl]-N-prop-2-ynyl-acrylamide (4d)

Mp: 78-79 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 15.6 Hz, 1H), 6.95 (s, 1H), 6.78 (s, 1H), 6.28 (d, *J* = 15.6 Hz, 1H), 4.19 (d, *J* = 2.4 Hz, 2H), 3.89 (s, 3H), 3.72 (s, 2H), 2.63 (brs, 8H), 2.44 (q, *J* = 7.2 Hz, 2H), 2.26 (t, *J* = 2.4 Hz, 1H), 1.08 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): 166.1, 149.7, 148.4, 142.2, 125.8, 121.8, 121.4, 116.9, 109.9, 79.8, 71.8, 61.2, 56.1, 52.6, 52.3, 29.6, 12.1. FAB-MS: 358.21 [M^++1].

3. RESULTS AND DISCUSSION

The synthesis of novel Mannich bases derivatives was outlined in scheme 1. Firstly, ester **2a** and amide **2b** were synthesized. The compound **2a** was obtained in 95% yield by the reaction of ferulic acid (**1**) with propargyl bromide in dimethylformamide (DMF) in carbonyldiimidazole (CDI) in 24 hours gave **2b** in 75% yield. The structure of these two compounds was elucidated based on spectroscopic methods. Next, the Mannich reaction of **2a** and **2b** with paraformaldehyde and secondary amines in ethanol at reflux condition gave two series of novel Mannich bases in moderate to good yields. All compounds were obtained by flash column chromatography using CH_2Cl_2:MeOH as eluent solvent systems. For structure elucidation, compound **3b** was an example. The presence of mono Mannich base was confirmed by the disappearance of ABC splitting pattern of ferulic acid. Instead, two protons of phenyl ring were observed at δ = 6.98 and 6.81 ppm as a doublet (*J* = 1.5 Hz). The methylene protons appeared as a singlet at δ = 3.74 ppm, and 8 protons of piperazine nucleus were observed as a broad singlet at δ = 2.61-2.56 ppm. In the ^{13}C NMR spectrum the methylene carbon of Mannich group was appeared at δ = 51.9 ppm, and

two couple of equivalent carbons of piperazine nucleus with strong intensity signals were at 54.9 and 52.6 ppm. In addition, protons of α,β-unsaturated ketone were observed as doublets with J = 15.9 Hz at δ = 7.65 ppm for H_β and 6.30 ppm for H_α. Besides, acetylene chain was observed through the appearance of two proton at δ = 4.79 ppm, and characteristic shift of acetylene ptoton as a triplet (J = 2.4 Hz) at δ = 2.49 ppm. In the ^{13}C NMR spectrum, characteristic signals of two acetylene carbons were also observed at δ = 78.1 and 74.9 ppm.



a. -NR_1R_2 = 4-methylpiperidine

b. -NR_1R_2 = 4 -methylpiperazine

c. -NR_1R_2 = 3-methylpiperidine

d. -NR_1R_2 = 4-ethylpiperazine

Scheme 1: Reagents and conditions: (i): Propargyl bromide, K_2CO_3, DMF, r.t, 24h; 95% (ii): Propargyl amine, CDI, THF, r.t, 24 h; 75% (iii): secondary amines, paraformaldehyde, EtOH, reflux, 24 h, 65-78% for **3a-d**; 64-78% for **4a-d**

4. CONCLUSIONS

We have presented the synthesis of novel Mannich bases **3a-d** and **4a-d** via a two-step procedure. The synthesized compounds were structurally confirmed using different spectroscopic methods: IR, NMR and MS.

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REFERENCES

1. S. Joshi, N. Khosla, P. Tiwari. *In vitro study of some medicinally important Mannich bases derived from antitubercular agent*, Bioorg. Med. Chem., **12(3)**, 571-576 (2004).
2. F. Lopes, R. Capela, J. O. Goncaves, P. N. Horton, M. P. Hursthouse, J. Iley, C. M. Casimiro, J. Bom, R. Moreira. *Amidomethylation of amodiaquine: antimalarial N-Mannich base derivatives*, Tetrahedron Lett., **45**, 7663-7666 (2004).
3. a) B. S. Holla, B. Veerandra, M. K. Shivanada, P. Boja. *Synthesis characterization and anticancer activity studies on some Mannich bases derived from 1,2,4-triazoles*. Eur. J. Med. Chem. **38(7-8)**, 759-767 (2003). b) Hieu, B. T.; Thuy, L. T.; Thuy, V. T.; Tien, H. X.; Chinh, L. V.; Hoang, V. D.; Vu, T. K. *Design, Synthesis and In Vitro Cytotoxic Activity Evaluation of New Mannich Bases*, Bull. Korean Chem. Soc. **33(5)**, 1586-1594 (2012).
4. H. Suleyman, H. I. Gul, M. Gul, M. Alkan, F. Gocer. *Anti-inflammatory Activity of Bis(3-aryl-3-oxo-propyl)methylamine Hydrochloride in Rat*. Biol. Pharm. Bull., **30(1)**, 63-67 (2007).
5. H. I. Gul, H. Suleyman, M. Gul. *Evaluation of the anti-inflammatory activity of N,N'-Bis(3-dimethylamino-1-phenyl-propylidene)hydrazine dihydrochloride*. Pharm. Biol., **47(10)**, 968-972 (2009).

6. J. R. Dimmock, P. Kumar. *Anticancer and Cytotoxic Properties of Mannich Bases*, Curr. Med. Chem., **4**, 1-22 (1997).
7. J. A. Benvenuto, T. H. Connor, D. K. Monteith, J. L. Laidlaw, S. C. Adams, T. S. Matney and J. Theiss. *Degradation and inactivation of antitumor drugs*, J. Pharm. Sci., **82(10)**, 988-991 (1993).
8. M. T. Huang, R. C. Smart, C. Q. Wong, A. H. Conney. *Inhibitory Effect of Curcumin, Chlorogenic Acid, Caffeic Acid, and Ferulic Acid on Tumor Promotion in Mouse Skin by 12*-O-*Tetradecanoylphorbol-13-acetate*, Cancer Res., **48(21)**, 5941-5946 (1988).
9. H. Mori, T. Tanaka, H. Shima, T. Kuniyasu, M. Takahashi. *Inhibitory effect of chlorogenic acid on methylazoxymethanol acetate-induced carcinogenesis in large intestine and liver of hamsters*. Cancer Lett, **30(1)**, 49-54 (1986).
10. R. H. Prager, H. M. Thregold. *Some neutral constituents of Acronychia baueri*, Aust. J. Chem., **19**, 451-462 (1966).
11. B. S. Han, C. B. Park, N. Takasuka, A. Naito, K. Sekine, E. Nomura, H. Taniguchi, T. Tsuno, H. Tsuda. *A ferulic acid derivative, ethyl 3-(4'-geranyloxy-3-methoxyphenyl)-2-propenoate, as a new candidate chemopreventive agent for colon carcinogenesis in the rat*, Jpn. J. Cancer Res., **92(4)**, 404-409 (2001).
12. T. Tanaka, H. Kohno, E. Nomura, H. Taniguchi, T. Tsuno, H. Tsuda. *A Novel Geranylated Derivative, Ethyl 3-(4'-Geranyloxy-3'-Methoxyphenyl)-2-Propenoate, Synthesized from Ferulic Acid Suppresses Carcinogenesis and Inducible Nitric Oxide Synthase in Rat Tongue*, Oncology, **64(2)**, 166-175 (2003).
13. A. Hosoda, E. Nomura, A. Murakami, K. Koshimizu, H. Ohigashi, K. Mizuno, H. Taniguchi. *Synthesis of feruloyl-myo-inositols and their inhibitory effects on superoxide generation*, Bioorg. Med. Chem. Lett., **10(13)**, 1439-1442 (2000).

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