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**SELECTIVE REDUCTION OF NITROCINNAMOYL FUMAGILLOLS
WITH α,β -UNSATURATED ESTER USING BOROHYDRIDE
EXCHANGE RESIN (BER) - NICKEL ACETATE**

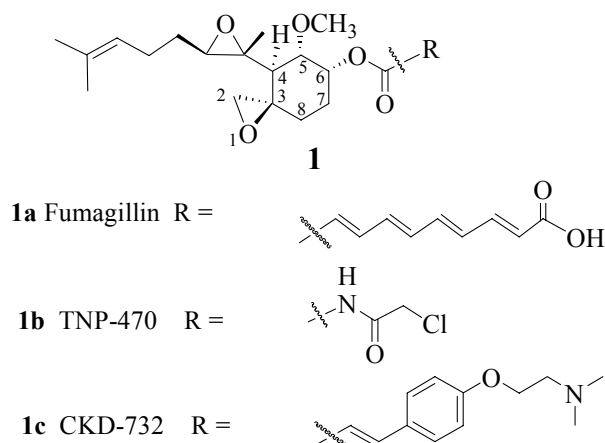
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Abstract – Borohydride Exchange Resin (BER) – nickel acetate system readily reduces nitrocinnamoylfumagillols to the corresponding amines in excellent yields, high chemoselectivity, and simple procedure. Especially, this system tolerates two epoxides (spiro-epoxide and the one on C4 alkene side chain) and the α,β -unsaturated ester moiety at C6 on the fumagillol.

Fumagillin (**1a**), a natural product isolated from *Aspergillus fumigatus*, has been shown to inhibit the growth of endothelial cell proliferation,^{1,2} and several analogues, especially including TNP-470 (**1b**)³ and CKD-732 (**1c**),⁴ had been semi-synthesis and presently in clinical trials (**Scheme 1**). From the results of the our biological tests, we found that the new aminocinnamoylfumagillol derivatives (**8a-e**) showed excellent *in vitro* and *in vivo* activity than previous reported references.^{3,4} For further pharmacological studies, we needed to hundreds grams scale of the new fumagillols. The selective reduction of nitro compounds to corresponding amines is an important reaction in organic synthesis. Especially, our new

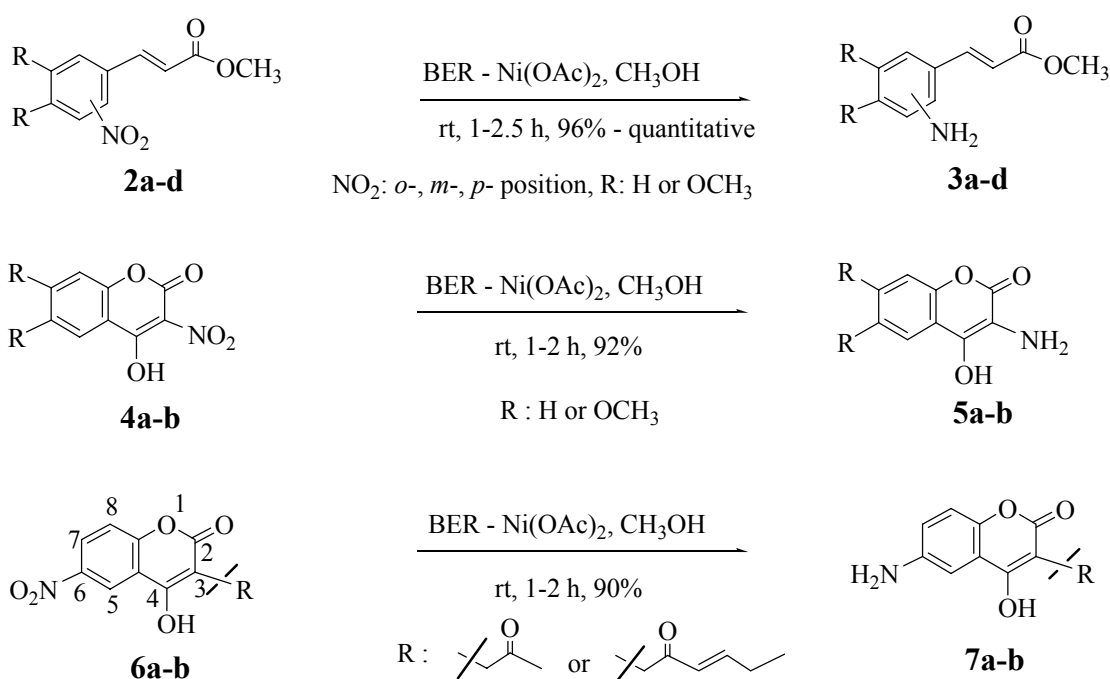
aminofumagillol derivatives (**8a-e**), having two epoxides (spiro-epoxide and the one on C4 alkene side chain) and the α,β -unsaturated ester at C6 position, were needed strict choice of reducing reagents.



Scheme 1

First, we tried on selective reduction with NaBH_4 using NiCl_2^5 or SnCl_2^6 as catalysts, because, they were reported that they exhibits enhanced reducing abilities when compared with NaBH_4 itself. However, none of these methods gave satisfied results in two requiring points, yields and selective reduction, although these low yields of nitrofumagillols with α,β -unsaturated ester were improved substantially in the presence of phase transfer catalysts.⁷ With the aim to obtain excellent selective reductions and high yields, recently, our extensive efforts were focused on the borohydride exchange resin (BER) introduced by Gibson and Baily⁸ in 1977, and further modified by Yoon *et al.*⁹ As a result, we found that borohydride exchange resin (BER) - $\text{Ni}(\text{OAc})_2$ system was an excellent chemoselective reduction reagent for nitro compounds to the corresponding amines¹⁰ compared with NaBH_4 - NiCl_2 . In addition, another advantage of this procedure was very simple workup, because BER - $\text{Ni}(\text{OAc})_2$ was easily removed by filtration. Therefore, in this paper, we wish to report that BER - $\text{Ni}(\text{OAc})_2$ system chemoselectively reduced nitrocinnamoylfumagillols to the corresponding aminocinnamoylfumagillols in excellent yields by handling for 1-2.5 h at 0 °C without any generating byproducts. First of all, in order to find optimal conditions, we tried model studies with suitable nitrocinnamic acids methyl ester or coumarins having a α,β -unsaturated ester system (Scheme 2). The procedure is very simple. For the nitro compounds with

α,β -unsaturated ester system, BER (30 mmol, 3.0 equiv.) was added to $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (1.5 mmol, 0.15 equiv.) in methanol at 0 °C. After five min, the nitro compounds (10 mmol, 1.0 equiv.) was added, and whole was stirred at room temperature for 30 min. BER (30 mmol, 3.0 equiv.) was added once more and stirring was continued for additional 30 min to 2 h in the same temperature. These reactions were completed in 1-2.5 h at room temperature giving 90% to quantitative isolated yield.

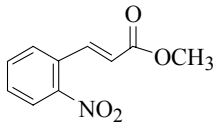
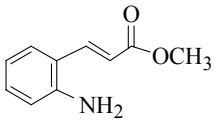
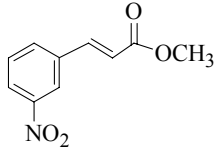
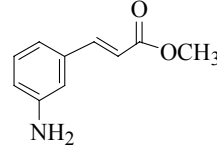
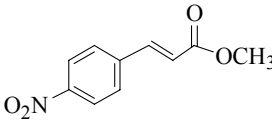
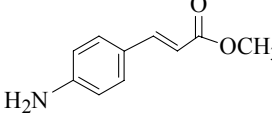
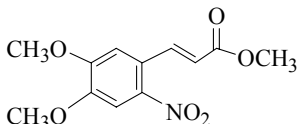
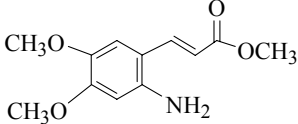
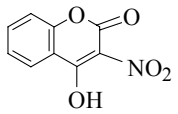
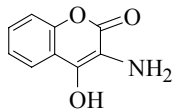
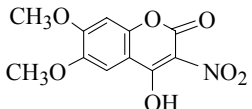
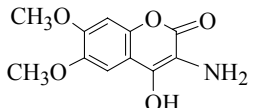
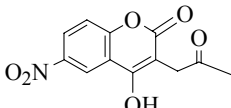
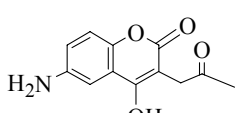
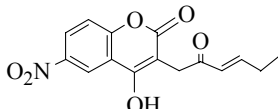
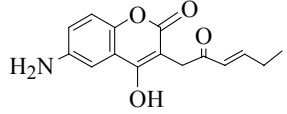


Scheme 2

As shown in Scheme 2, *o*-, *m*-, and *p*-nitrocinnamic acid methyl esters (**2a-c**) and 2-nitro-4,5-dimethoxycinnamic acid methyl ester (**2d**) were converted to the corresponding aminocinnamic acid methyl esters (**3a-d**) in 96% to quantitative yields by chemoselective reduction with BER - $\text{Ni}(\text{OAc})_2$ at room temperature in methanol. We also found that BER - $\text{Ni}(\text{OAc})_2$ system was readily and effectively reduced both 3-nitrocoumarins (**4a-b**) and 6-nitrocoumarins (**6a-b**) to the corresponding aminocoumarins (**5a-b**, **7a** and **b**) in excellent yields (90-95%) at room temperature without any generating byproducts respectively. The results are summarized in Table 1. On the basis of our model studies, we next have applied for a series of our novel fumagillol compounds, which have two epoxides (spiro-epoxide and the

one on C4 alkene side chain) and the α,β -unsaturated ester moiety at C6 as depicted in Scheme 3.

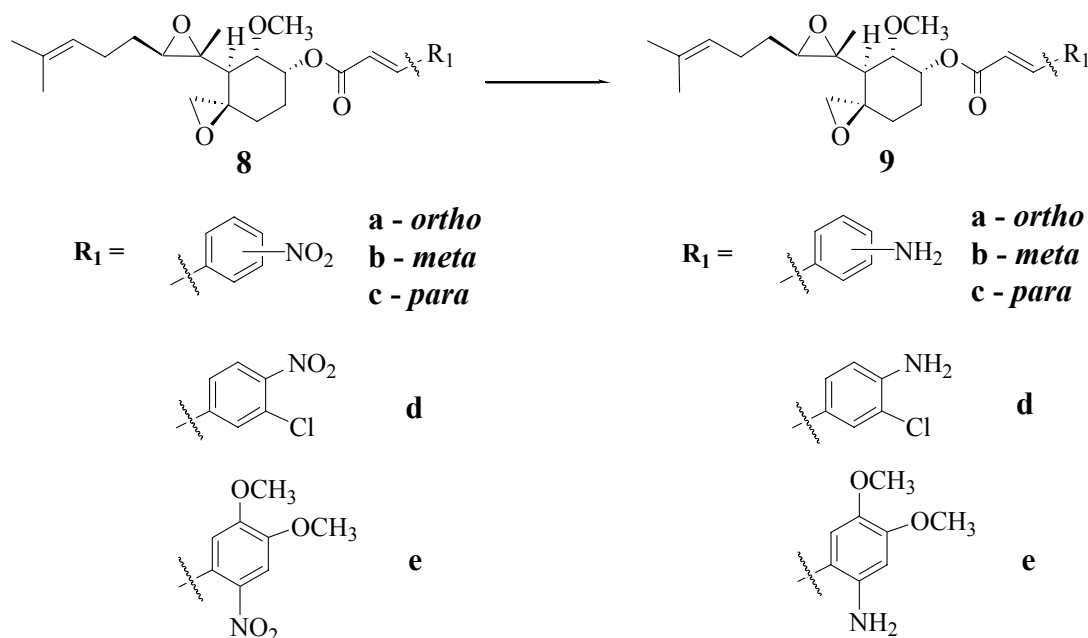
Table 1. Reduction of nitro compounds to the corresponding amino compounds with BER - Ni(OAc)₂ in methanol at room temperature.

Nitro Substrate	Amino Product ^{a)}	Reaction ^{b)} Time (h)	Yield (%)
2a 	3a 	1.0	quantitative
2b 	3b 	1.5	96
2c 	3c 	0.5	quantitative
2d 	3d 	2.5	98
4a 	5a 	2.0	92
4b 	5b 	1.0	95
6a 	7a 	1.0	90
6b 	7b 	2.0	90

a) Reductions were monitored by HPLC or TLC. b) Nitro compounds (10 mmol, 1 equiv.) were added to the reaction mixture of BER (60 mmol, 6 equiv.) and Ni(OAc)₂ (1.5 mmol, 0.15 equiv.) in methanol at rt. The reaction mixture was then stirred at room temperature for 0.5-2.5 h.

First, the same procedure was applied to the new fumagillol derivatives reduction. Against our expectation, five nitrocinnamoylfumagillol derivatives (**8a-e**) gave a several byproducts showing low yields relatively. Considering these results and the chemical property of fumagillols structure, first, we

tried to control the reaction temperature range within room temperature to 0 °C. As shown in Scheme 3, BER (60 mmol, 6.0 equiv.) was added to Ni(OAc)₂ (1.5 mmol, 0.15 equiv.) in methanol. After stirring for 30 min, the nitrocinnamoylfumagillol compound (10 mmol, 1.0 equiv.) was added and the mixture was stirred at 0 °C for 1-2.5 h. After completion of the conversion to the corresponding amines monitoring by HPLC and TLC, the resin was filtered off, and the methanol was removed under the reduced pressure to give the nearly pure products.

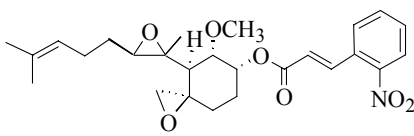
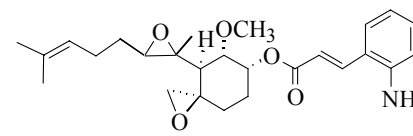
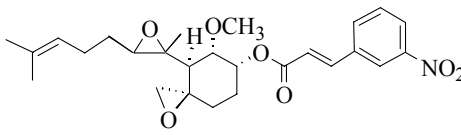
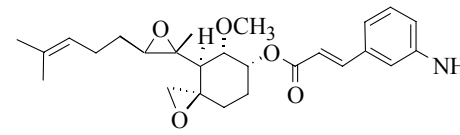
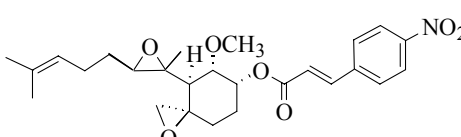
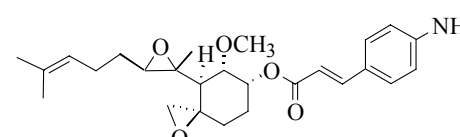
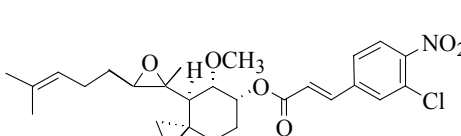
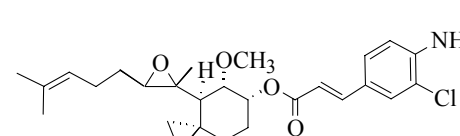
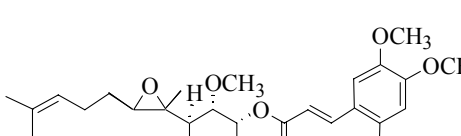
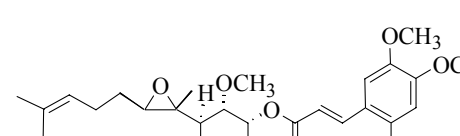


Scheme 3

In the cases of *o*-, *p*-nitrocinnamoylfumagillol compounds, (**8a**) and (**8c**), and *o*-nitro-4,5-dimethoxycinnamoylfumagillol compound (**8e**) were chemoselectively reduced to the corresponding aminocinnamoylfumagillols in excellent yields (92-95%) (see Table 2). However, *m*-nitrocinnamoylfumagillol (**8b**) and *m*-nitro-3-chlorocinnamoylfumagillol (**8d**) gave a slightly decreased yield (85-88%), but exhibited good chemoselectivity (see Table 2). In the cases, by lowering the reaction temperature to 0 °C, it was possible to reduce nitrocinnamoylfumagillol compounds chemoselectively without attacking two epoxides (spiro-epoxide and the one on C4 alkene side chain) and the α,β -unsaturated ester moiety at C6 on the fumagillol compound. The results are summarized in Table 2. In

conclusion, the nickel boride catalyst prepared on BER (BER - Ni(OAc)₂) system in methanol is an excellent reducing agent for the reduction of nitrocinnamoylfumagillols, possessing two epoxides (spiro-epoxide and the one on C4 alkene side chain) and additionally having the α,β -unsaturated ester moiety at C6, to the corresponding aminocinnamoylfumagillols because of its excellent yield (~ quantitative), high chemoselectivity and simple work up procedure due to removal of BER - Ni(OAc)₂ by filtration.

Table 2. Reduction of nitrocinnamoylfumagillols to the corresponding aminocinnamoylfumagillols with BER - Ni(OAc)₂ in methanol at 0 °C.

Substrate	Product ^{a)}	Reaction ^{b)} Time (h)	Yield (%)
 8a	 9a	1.5	92
 8b	 9b	2.5	88
 8c	 9c	1.0	95
 8d	 9d	2.5	85
 8e	 9e	1.0	92

a) All reactions were monitored by HPLC or TLC. b) Nitrofumagillol compounds (10 mmol, 1.0 equiv.) were added to the reaction mixture of BER (60 mmol, 6.0 equiv.) and Ni(OAc)₂ (1.5 mmol, 0.15 equiv.) in methanol at rt. The reaction mixture was then stirred at 0 °C for 0.5-2.5 h.

EXPERIMENTAL

Commercial available reagents were used without purification. Anion exchange resin (Amberlite IRA-400) was used supporting the polymer of borohydride exchange resin (BER). All reactions were conducted under anhydrous condition in solvents dried over molecular sieves type 4Å under nitrogen atmosphere and performed using oven dried glassware. Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. IR spectra were recorded on a Bruker Vector 22 FT-IR spectrophotometer. NMR spectra were recorded on a Bruker DPX 400 MHz instrument operating at 400 MHz for proton and 100 MHz for carbon and were performed in CDCl₃ solution using tetramethylsilane as the internal reference and chemical shift (δ) is reported in ppm downfield from internal tetramethylsilane. The coupling constants (J) are reported in Hz. MS spectra were recorded on a HP 5989B instrument. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh) according to the published procedure.¹⁰ TLC was performed on glass backed plates pre-coated with silica (0.2 mm, 60 F₂₅₄) and developed using standard visualizing agents UV fluorescence (254 and 365 nm), potassium permanganate and iodine. Nitrophenylacrylic acid methyl ester and nitrocinnamoylfumagillol compounds were synthesized and purified according to in house procedures.¹¹

General procedure: preparation of Borohydride Exchange Resin (BER).^{12,13} An aqueous solution of sodium borohydride (37.8 g, 1.0 mol, 1.0 L) was stirred with wet chloride-form anion exchange resin (Amberlite IRA-400 [20-50 mesh], 200 g) for 1 h. The resulting resin was washed thoroughly with distilled water until free from excess NaBH₄. The borohydride form anoin exchange resin was analyzed for borohydride content by hydride evolution on acidification with 2.0 N HCl, and the average hydride content of BER was found to be 3.3 mmol of BH₄⁻ per gram. The dried resin was stored under nitrogen in refrigerator (around at 4 °C). The hydride content was constant over 6 weeks.

General Procedure: 3-(2-aminophenyl)acrylic acid methyl ester (3a). To a stirred suspension of BER (9.68 g, 28.96 mmol) in dried methanol (50 mL) was added Ni(OAc)₂ ·4H₂O (0.18 g, 0.72 mmol) at 0 °C.

The reaction mixture was stirred for 30 min. When black coating of nickel boride was observed, 3-(2-nitrophenyl)acrylic acid methyl ester (1.0 g, 4.82 mmol) in dried methanol (20 mL) was added at the same temperature. After stirring at 0 °C for 2.5 h, BER- Ni(OAc)₂ was removed by filtration, and the filtrate was concentrated under the reduced pressure. The obtained residue was purified by column chromatography on SiO₂ with EtOAc-*n*-Hexane (1:2, v/v) as elution solvent to give 0.86 g (quantitative yield) as yellowish solid. mp 112-115 °C (from EtOH). IR (KBr) ν_{\max} cm⁻¹: 3414 (NH₂), 3358, 1701 (CO), 1623, 1200. ¹H NMR (400 MHz, CDCl₃) δ : 3.78 (s, 3H, CH₃), 6.37 (d, 1H, *J* = 16.0 Hz, -CH=CH-Ph), 6.84 (m, 2H), 7.21 (m, 1H), 7.42 (m, 1H), 7.88 (d, 1H, *J* = 16.0 Hz, -CH=CH-Ph). ¹³C NMR (100 MHz, CDCl₃) δ : 51.69, 117.11, 117.93, 119.43, 120.29, 128.13, 131.35, 140.25, 144.91, 167.69. HR-MS *m/z* (M⁺) C₁₀H₁₁NO₂ Requires, 177.0787; Found, 177.0786. *Anal.* Calcd for C₁₀H₁₁NO₂: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.72; H, 6.31; N, 7.95.

3-(3-Aminophenyl)acrylic acid methyl ester (3b). Yield: 0.82 g, 96% as yellowish solid. mp 113-116 °C (from EtOH). IR (KBr) ν_{\max} cm⁻¹: 3446 (NH₂), 3355, 1703 (CO), 1633, 1178. ¹H NMR (400 MHz, CDCl₃) δ : 3.80 (s, 3H, CH₃), 6.38 (d, 1H, *J* = 16.0 Hz, -CH=CH-Ph), 6.74 (m, 1H), 6.85 (s, 1H), 6.95 (d, 1H, *J* = 7.8 Hz, -CH=CH-Ph), 7.18 (t, 1H, *J* = 7.8 Hz), 7.60 (d, 1H, *J* = 16.0 Hz). ¹³C NMR (100 MHz, CDCl₃) δ : 51.69, 114.14, 117.17, 117.61, 118.75, 129.81, 135.44, 145.19, 146.74, 167.55. HR-MS *m/z* (M⁺) C₁₀H₁₁NO₂ Requires, 177.0787; Found, 177.0795. *Anal.* Calcd for C₁₀H₁₁NO₂: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.81; H, 6.22; N, 7.86.

3-(4-Aminophenyl)acrylic acid methyl ester (3c). Yield: 0.86 g, quantitative as yellowish solid. mp 122-125 °C (from EtOH). IR (KBr) ν_{\max} cm⁻¹: 3444 (NH₂), 3355, 1687 (CO), 1593, 1174. ¹H NMR (400 MHz, CDCl₃) δ : 3.78 (s, 3H, CH₃), 6.26 (d, 1H, *J* = 16.0 Hz, -CH=CH-Ph), 6.75 (m, 2H), 7.37 (m, 2H), 7.61 (d, 1H, *J* = 16.0 Hz, -CH=CH-Ph). ¹³C NMR (100 MHz, CDCl₃) δ : 51.48, 113.33, 114.89, 124.78, 129.92, 145.11, 148.65, 168.12. HR-MS *m/z* (M⁺) C₁₀H₁₁NO₂ Requires, 177.0787; Found, 177.0793. *Anal.* Calcd for C₁₀H₁₁NO₂: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.83; H, 6.30; N, 7.85.

3-(2-Amino-4,5-dimethoxyphenyl)acrylic acid methyl ester (3d). Yield: 0.87 g, 98% as yellow solid. mp 119-121 °C (from EtOH). IR (KBr) ν_{\max} cm^{-1} : 3449 (NH₂), 3376, 1695 (CO), 1613, 1172. ¹H NMR (400 MHz, CDCl₃) δ : 3.77 (s, 3H, CH₃), 3.85 (s, 3H, OCH₃), 3.88 (s, 3H, OCH₃), 6.25 (d, 1H, J = 16.0 Hz, -CH=CH-Ph), 6.49 (s, 1H), 6.93 (s, 1H), 7.87 (d, 1H, J = 16.0 Hz, -CH=CH-Ph). ¹³C NMR (100 MHz, CDCl₃) δ : 51.55, 55.85, 56.39, 100.85, 110.08, 111.37, 114.27, 139.66, 141.03, 142.78, 152.60, 168.08. HR-MS m/z (M⁺) C₁₂H₁₅NO₄ Requires, 237.0997, Found, 237.0996. *Anal.* Calcd for C₁₂H₁₅NO₄: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.82; H, 4.73; N, 6.59.

General Procedure: 3-amino-4-hydroxychromen-2-one (5a). To a stirred suspension of BER (9.59 g, 28.68 mmol) in dried methanol (50 mL) was added Ni(OAc)₂·4H₂O (0.18 g, 0.71 mmol) at 0 °C. The suspension was stirred for 30 min. When black coating of nickel boride was observed, 3-nitro-4-hydroxychromen-2-one (1.0 g, 4.78 mmol) in dried methanol (20 mL) was added at the same temperature. After stirring at 0 °C for 2 h, BER- Ni₂B was removed by filtration; and the filtrate was concentrated under the reduced pressure. The obtained residue was purified by column chromatography on SiO₂ with EtOAc-*n*-Hexane (1:1, v/v) as elution solvents to give 0.79 g (92% yield) as pale yellowish solid. mp 192-196 °C (from CH₂Cl₂/IPA, 5/1, v/v). IR (KBr) ν_{\max} cm^{-1} : 3510 (OH), 3424 (NH₂), 1757 (CO, ester), 1607. ¹H NMR (400 MHz, CDCl₃) δ : 7.25 (m, 3H), 7.71 (d, 1H, J = 9.2 Hz). ¹³C NMR (100 MHz, CDCl₃) δ : 102.67, 121.38, 125.20, 126.75, 127.61, 128.95, 145.62, 150.82, 162.07. HR-MS m/z (M⁺) C₉H₇NO₃ Requires, 177.0424; Found, 177.0420. *Anal.* Calcd for C₉H₇NO₃: C, 61.02; H, 3.98; N, 7.91. Found: C, 61.11; H, 4.02; N, 7.88.

3-Amino-4-hydroxy-6,7-dimethylchromen-2-one (5b). Yield: 0.84 g, 95% as pale yellowish solid. mp 240-243 °C (from CH₂Cl₂/IPA, 5/1, v/v). IR (KBr) ν_{\max} cm^{-1} : 3578 (OH), 3413 (NH₂), 1760 (CO, ester), 1601. ¹H NMR (400 MHz, CDCl₃) δ : 2.35 (s, 3H, OCH₃), 2.43 (s, 3H, OCH₃), 7.01 (s, 1H), 7.46 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ : 14.85, 14.99, 102.61, 121.93, 124.74, 127.26, 135.16, 138.09, 145.33, 147.79, 162.06. HR-MS m/z (M⁺) C₁₁H₁₁NO₃ Requires, 205.0736, Found, 205.0737. *Anal.* Calcd for

C₁₁H₁₁NO₃: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.45; H, 5.44; N, 6.81.

6-Amino-4-hydroxy-3-(2-oxopropyl)chromen-2-one (7a). Yield: 0.79 g, 90% as pale yellowish solid. mp 294-297 °C (from CH₂Cl₂/EtOH, 5/1, v/v). IR (KBr) ν_{\max} cm⁻¹: 3503 (OH), 3428 (NH₂), 1748 (CO, ester), 1709 (CO), 1601. ¹H NMR (400 MHz, CDCl₃) δ : 2.21 (s, 3H, CH₃), 3.35 (s, 2H, CH₂), 6.68 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δ : 25.12, 35.29, 91.67, 112.64, 114.75, 122.10, 129.32, 140.03, 143.56, 162.75, 165.98, 206.33. HR-MS m/z (M⁺) C₁₂H₁₁NO₄ Requires, 233.0685; Found, 233.0689. *Anal.* Calcd for C₁₂H₁₁NO₄: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.73; H, 4.73; N, 5.98.

6-Amino-4-hydroxy-3-(2-oxohex-3-enyl)chromen-2-one (7b). Yield: 0.81 g, 90% as pale yellowish solid. mp 317-319 °C (from CH₂Cl₂/EtOH, 5/1, v/v). IR (KBr) ν_{\max} cm⁻¹: 3506 (OH), 3420 (NH₂), 1751 (CO, ester), 1668 (CO), 1604. ¹H NMR (400 MHz, CDCl₃) δ : 1.12 (t, 3H, $J = 7.56$ Hz), 2.06 (m, 2H), 3.77 (s, 2H), 6.15 (d, 1H, $J = 16.0$ Hz), 6.58 (m, 1H), 6.89 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δ : 13.78, 19.26, 33.08, 91.56, 113.26, 114.73, 122.15, 128.61, 129.54, 140.88, 142.03, 142.63, 143.47, 162.05, 165.95, 196.57. HR-MS m/z (M⁺) C₁₅H₁₅NO₄ Requires, 273.0997; Found, 273.0992. *Anal.* Calcd for C₁₅H₁₅NO₄: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.87; H, 5.50; N, 5.16.

General Procedure: 3-(2-aminophenyl)acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)-oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester (9a). To a stirred suspension of BER (4.38 g, 13.11 mmol) in methanol (20 mL) was added Ni(OAc)₂·4H₂O (0.08 g, 0.32 mmol) at 0 °C. The suspension was stirred for 30 min. When black coating of nickel boride was observed, *O*-[4-(2-nitro)cinnamoyl]fumagillol (1.0 g, 2.19 mmol) in methanol (10 mL) was added at the same temperature. After stirring at 0 °C for 1.5 h, BER-Ni₂B was removed by filtration; and the methanol was concentrated under the reduced pressure. The obtained residue was purified by column chromatography on SiO₂ as elution solvents EtOAc-*n*-Hexane (1:1, v/v) to give 0.86 g (92% yield) as pale yellowish foam. mp 62-64 °C (from *n*-Hexane). IR (KBr) ν_{\max} cm⁻¹: 3453 (NH₂), 2927, 1712 (CO), 1640, 1172. ¹H NMR (400 MHz, CDCl₃) δ : 1.07 (d, 1H, $J = 13.1$

Hz), 1.23 (s, 3H), 1.62 (s, 3H), 1.71 (s, 3H), 1.89 (m, 2H), 2.00 (m, 2H), 2.15 (m, 3H), 2.37 (m, 1H), 2.58 (d, 2H, $J = 4.2$ Hz), 2.74 (t, 1H, $J = 6.4$ Hz), 2.99 (d, 1H, $J = 4.3$ Hz), 3.49 (s, 3H), 3.72 (dd, 1H, $J = 2.7, 11.3$ Hz), 5.17 (t, 1H, $J = 7.6$ Hz), 5.75 (s, 1H), 6.44 (d, 1H, $J = 16.0$ Hz, -CH=CH-Ph), 6.97 (m, 1H), 7.04 (d, 1H, $J = 7.6$ Hz), 7.17 (m, 1H), 7.22 (t, 2H, $J = 7.9$ Hz), 7.50 (d, 1H, $J = 16.0$ Hz, -CH=CH-Ph). ^{13}C NMR (100 MHz, CDCl_3) δ : 19.21, 19.43, 22.77, 25.22, 26.03, 29.45, 42.37, 49.91, 51.52, 52.09, 53.71, 61.54, 65.78, 73.13, 115.11, 117.75, 118.42, 121.59, 125.88, 127.01, 128.52, 133.18, 142.86, 165.02. HR-MS m/z (M^+) Requires $\text{C}_{25}\text{H}_{33}\text{NO}_5$, 427.2350; Found, 427.2352. *Anal.* Calcd for $\text{C}_{25}\text{H}_{33}\text{NO}_5$: C, 70.72; H, 7.99; N, 3.17. Found: C, 70.65; H, 7.93; N, 3.15.

3-(3-Aminophenyl)acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester (9b). Yield: 0.84 g, 88% as pale yellowish foam. mp 59-62 °C (from *n*-Hexane). IR (KBr) ν_{max} cm^{-1} : 3455 (NH_2), 3367, 2927, 1708 (CO), 1635, 1168. ^1H -NMR (400 MHz, CDCl_3) δ : 1.12 (m, 1H), 1.25 (s, 3H), 1.66 (s, 3H), 1.74 (s, 3H), 2.19-1.88 (m, 5H), 2.38 (m, 1H), 2.56 (d, 1H, $J = 4.1$ Hz), 2.63 (t, 1H, $J = 6.3$ Hz), 3.00 (d, 1H, $J = 4\text{Hz}$), 3.47 (s, 3H), 3.72 (m, 1H), 5.21 (m, 1H), 5.75 (m, 1H), 6.45 (d, 1H, $J = 16.0$ Hz, -CH=CH-Ph), 6.75 (m, 1H), 6.88 (s, 1H), 6.93 (m, 1H), 7.20 (m, 1H), 7.66 (d, 1H, $J = 16.0$ Hz, -CH=CH-Ph). ^{13}C NMR (100 MHz, CDCl_3) δ : 19.32, 19.45, 22.73, 25.30, 26.16, 29.49, 42.37, 49.92, 51.88, 52.03, 53.76, 61.59, 65.72, 73.18, 112.8, 114.33, 116.25, 117.64, 125.80, 129.21, 133.22, 135.73, 142.85, 146.64, 165.01. HR-MS m/z (M^+) Requires $\text{C}_{25}\text{H}_{33}\text{NO}_5$, 427.2350, Found, 427.2346. *Anal.* Calcd for $\text{C}_{25}\text{H}_{33}\text{NO}_5$: C, 70.72; H, 7.99; N, 3.17. Found: C, 70.75; H, 7.95; N, 3.19.

3-(4-Aminophenyl)acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester (9c). Yield: 0.91 g, 95% as pale yellowish foam. mp 65-68 °C (from *n*-Hexane). IR (KBr) ν_{max} cm^{-1} : 3461 (NH_2), 3365, 2927, 1702 (CO), 1599, 1160. ^1H -NMR (400 MHz, CDCl_3) δ : 1.11 (m, 1H), 1.24 (s, 3H), 1.65 (s, 3H), 1.74 (s, 3H), 1.88 (m, 1H), 2.17-2.01 (m, 4H), 2.36 (m, 1H), 2.56 (d, 1H, $J = 4.2$ Hz), 2.64 (t, 1H, $J = 6.3$ Hz), 3.00 (d, 1H, $J = 4.2$ Hz), 3.45 (s, 3H), 3.69 (m, 1H), 5.19 (m, 1H), 5.73 (m, 1H), 6.29 (d, 1H, $J = 16.0$ Hz, -CH=CH-Ph), 6.74 (m, 2H), 7.34 (m, 2H), 7.55 (d, 1H, $J =$

16.0 Hz, $-\text{CH}=\text{CH}-\text{Ph}$). ^{13}C NMR (100 MHz, CDCl_3) δ : 19.32, 19.40, 22.71, 25.03, 26.38, 29.45, 42.38, 49.99, 51.67, 52.08, 53.71, 61.65, 65.78, 73.11, 115.09, 117.63, 124.90, 125.84, 127.03, 133.24, 142.86, 145.93, 165.08. HR-MS m/z (M^+) Requires $\text{C}_{25}\text{H}_{33}\text{NO}_5$: 427.2350; Found: 427.2360. *Anal.* Calcd for $\text{C}_{25}\text{H}_{33}\text{NO}_5$: C, 70.72; H, 7.99; N, 3.17. Found: C, 70.77; H, 8.06; N, 3.22.

3-(4-Amino-3-chlorophenyl)acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester (9d). Yield: 0.79 g, 85% as pale yellowish foam. mp 67-70 °C (from *n*-Hexane). IR (KBr) ν_{max} cm^{-1} : 3460 (NH_2), 3365, 2927, 1703 (CO), 1600, 1160. ^1H NMR (400 MHz, CDCl_3) δ : 1.09 (m, 1H), 1.24 (s, 3H), 1.67 (s, 3H), 1.75 (s, 3H), 1.91 (m, 1H), 2.19-2.04 (m, 4H), 2.35 (m, 1H), 2.54 (d, 1H, $J = 4.1$ Hz), 2.66 (t, 1H, $J = 6.4$ Hz), 3.08 (d, 1H, $J = 4.2$ Hz), 3.47 (s, 3H), 3.71 (m, 1H), 5.19 (m, 1H), 5.73 (m, 1H), 6.31 (d, 1H, $J = 16.0$ Hz, $-\text{CH}=\text{CH}-\text{Ph}$), 6.76 (m, 1H), 7.41 (m, 2H), 7.57 (d, 1H, $J = 16.0$ Hz, $-\text{CH}=\text{CH}-\text{Ph}$). ^{13}C NMR (100 MHz, CDCl_3) δ : 19.16, 19.33, 21.56, 23.85, 26.84, 30.14, 43.21, 50.01, 51.63, 52.38, 53.77, 60.99, 65.91, 73.42, 116.85, 117.34, 120.43, 125.41, 125.80, 126.39, 127.43, 133.25, 142.86, 146.32, 165.41. HR-MS m/z (M^+) Requires $\text{C}_{25}\text{H}_{32}\text{NO}_5\text{Cl}$: 461.1959. Found: 461.1963. *Anal.* Calcd for $\text{C}_{25}\text{H}_{32}\text{NO}_5\text{Cl}$: C, 65.60; H, 7.20; N, 2.94; Found: C, 65.31; H, 7.16; N, 3.00.

3-(2-Amino-4,5-dimethoxyphenyl)acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)-oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester (9e). Yield: 0.84 g, 92% as pale yellowish foam. mp 65-68 °C (from *n*-Hexane). IR (KBr) ν_{max} cm^{-1} : 3367 (NH_2), 2929, 2831, 1702 (CO), 1609, 1160. ^1H NMR (400 MHz, CDCl_3) δ : 1.07 (d, 1H, $J = 13.6$ Hz), 1.23 (s, 3H), 1.65 (s, 3H), 1.74 (s, 3H), 1.91 (m, 2H), 2.01-2.18 (m, 4H), 2.35 (m, 1H), 2.56 (d, 2H, $J = 4.2$ Hz), 2.64 (m, 1H), 2.99 (d, 1H, $J = 4.3$ Hz), 3.46 (s, 3H), 3.72 (dd, 1H, $J = 2.8, 11.2$ Hz), 3.86 (s, 6H), 5.19 (t, 1H, $J = 7.6$ Hz), 5.72 (s, 1H), 6.30 (d, 2H, $J = 16.0$ Hz, $-\text{CH}=\text{CH}-\text{Ph}$), 6.91 (s, 1H), 7.81 (d, 1H, $J = 16.0$ Hz, $-\text{CH}=\text{CH}-\text{Ph}$). ^{13}C NMR (100 MHz, CDCl_3) δ : 20.56, 20.67, 22.78, 26.58, 26.68, 29.43, 43.30, 50.16, 51.69, 52.23, 53.70, 56.99, 62.12, 65.74, 73.14, 101.62, 113.66, 114.82, 118.23, 125.12, 133.64, 138.94, 133.15, 142.83, 147.64, 167.09. HR-MS m/z (M^+) Requires $\text{C}_{27}\text{H}_{37}\text{NO}_7$: 487.2560; Found: 487.2583. *Anal.* Calcd for $\text{C}_{27}\text{H}_{37}\text{NO}_7$: C, 67.04; H, 7.84; N, 3.12.

2.79. Found: C, 66.91; H, 7.80; N, 2.75.

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