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

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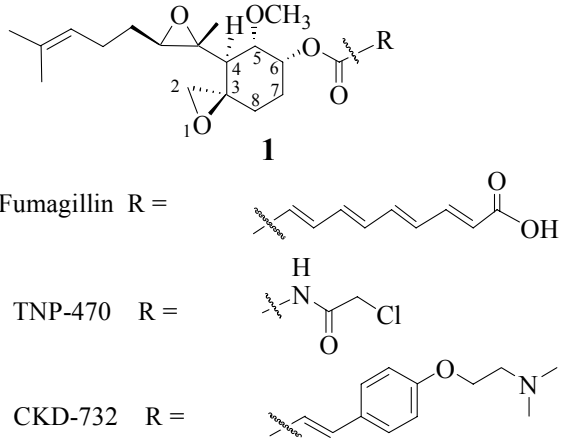
Abstract – Borohydride Exchange Resin (BER) – nickel acetate system readily reduces nitrocinnamoylfumagillols to the corresponding amines in excellent yields, high chemoselectivity, and simple procedure. Especially, this system tolerates two epoxides (spiro-epoxide and the one on C4 alkene side chain)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

Fumagillin (**1a**), a natural product isolated from *Aspergillius 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.



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1a Fumagillin R =

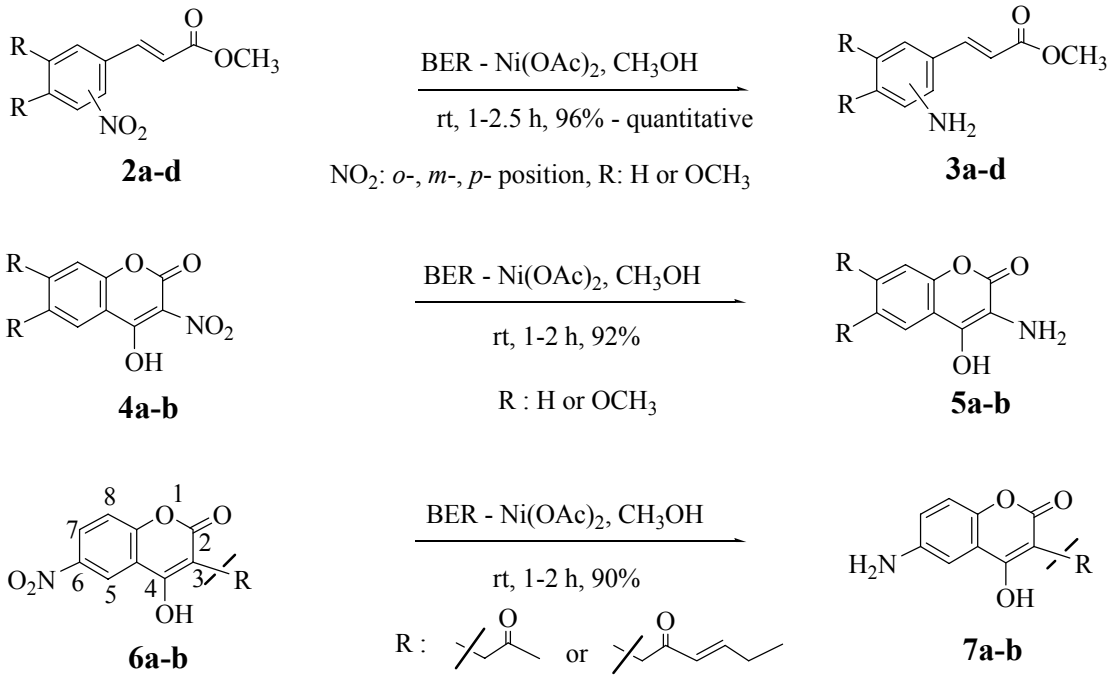
1b TNP-470 R =

1c CKD-732 R =

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 Baily[8] in 1977, and further modified by Yoon *et al*.[9] As a result, we found that borohydride exchange resin (BER) - $Ni(OAc)_2$ system was an excellent chemoselective reduction reagent for nitro compounds to the corresponding amines[10] compared with $NaBH_4$ - $NiCl_2$. In addition, another advantage of this procedure was very simple workup, because BER - $Ni(OAc)_2$ was easily removed by filtration. Therefore, in this paper, we wish to report that BER - $Ni(OAc)_2$ system chemoselectively reduced nitrocinnamoylfumagillols to the corresponding aminocinnamoylfumagillols in excellent yields by handling for 1-2.5 h at 0 ^oC 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 $Ni(OAc)_2 \cdot 4H_2O$ (1.5 mmol, 0.15 equiv.) in methanol at 0 ℃. 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.

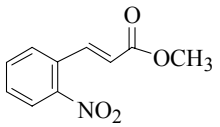
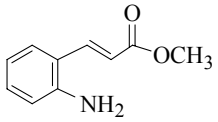
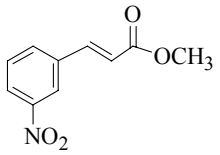
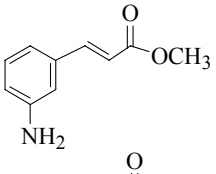
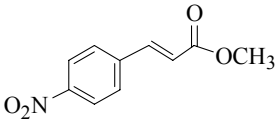
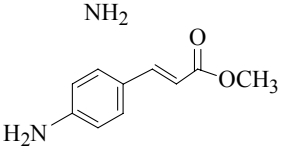
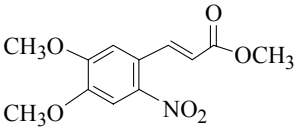
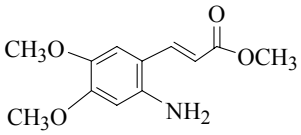
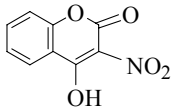
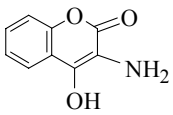
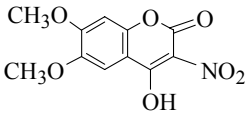
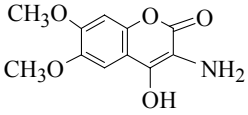
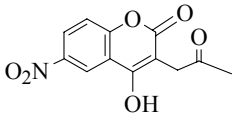
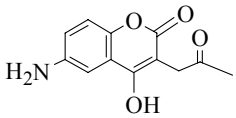
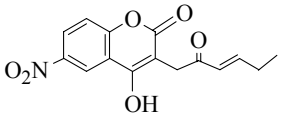
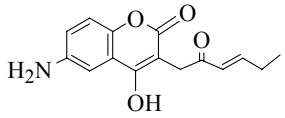


Scheme 2

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 - $Ni(OAc)_2$ at room temperature in methanol. We also found that BER - $Ni(OAc)_2$ 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.

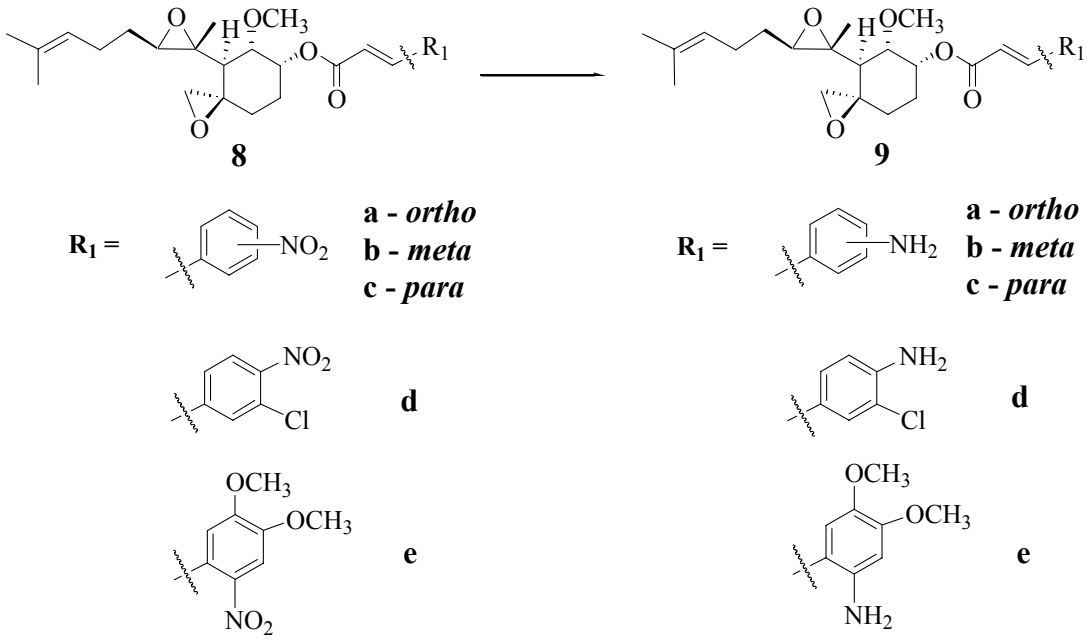
Table 1. Reduction of nitro compounds to the corresponding amino compounds with BER - $Ni(OAc)_2$ in methanol at room temperature.

	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 ℃. 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.

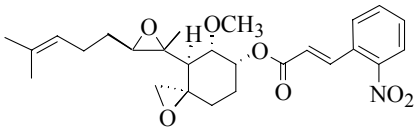
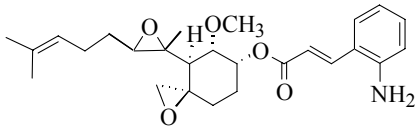
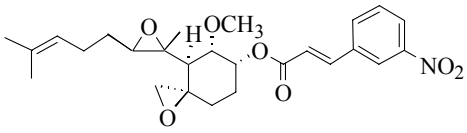
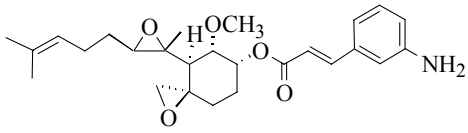
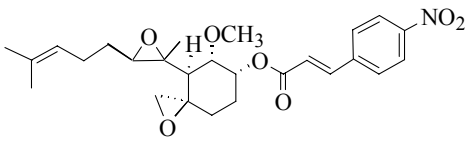
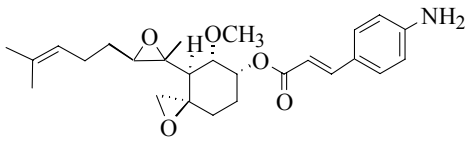
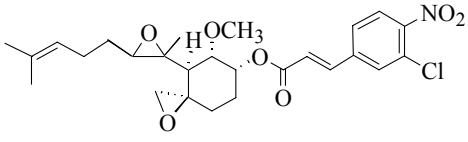
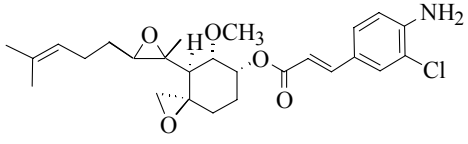
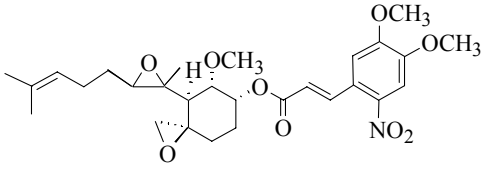
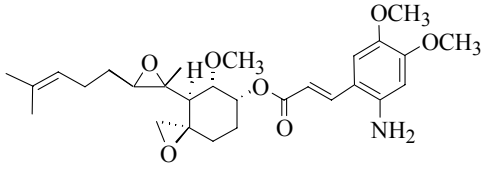


Scheme 3

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 lowing 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 $CDCl_3$ 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 F_{254}) 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 $NaBH_4$. 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 BH_4^- per gram. The dried resin was stored under nitrogen in refrigerator (around at 4 ^oC). 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 $Ni(OAc)_2 \cdot 4H_2O$ (0.18 g, 0.72 mmol) at 0 ^oC.

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 ^{o}C for 2.5 h, BER- $Ni(OAc)_2$ was removed by filtration, and the filtrated was concentrated under the reduced pressure. The obtained residue was purified by column chromatography on SiO_2 with EtOAc-*n*-Hexane (1:2, v/v) as elution solvent to give 0.86 g (quantitative yield) as yellowish solid. mp 112-115 ^{o}C (from EtOH). IR (KBr) ν_{max} cm^{-1}: 3414 (NH_2), 3358, 1701 (CO), 1623, 1200. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.78 (s, 3H, CH_3), 6.37 (d, 1H, *J* = 16.0 Hz, -CH=C**H**-Ph), 6.84 (m, 2H), 7.21 (m, 1H), 7.42 (m, 1H), 7.88 (d, 1H, *J* = 16.0 Hz, -C**H**=CH-Ph). ^{13}C NMR (100 MHz, $CDCl_3$) 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^+) $C_{10}H_{11}NO_2$ Requires, 177.0787; Found, 177.0786. *Anal*. Calcd for $C_{10}H_{11}NO_2$: 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 ^{o}C (from EtOH). IR (KBr) ν_{max} cm^{-1}: 3446 (NH_2), 3355, 1703 (CO), 1633, 1178. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.80 (s, 3H, CH_3), 6.38 (d, 1H, *J* = 16.0 Hz, -CH=C**H**-Ph), 6.74 (m, 1H), 6.85 (s, 1H), 6.95 (d, 1H, *J* = 7.8 Hz, -C**H**=CH-Ph), 7.18 (t, 1H, *J* = 7.8 Hz), 7.60 (d, 1H, *J* = 16.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) 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^+) $C_{10}H_{11}NO_2$ Requires, 177.0787; Found, 177.0795. *Anal*. Calcd for $C_{10}H_{11}NO_2$: 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 ^{o}C (from EtOH). IR (KBr) ν_{max} cm^{-1}: 3444 (NH_2), 3355, 1687 (CO), 1593, 1174. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.78 (s, 3H, CH_3), 6.26 (d, 1H, *J* = 16.0 Hz, -CH=C**H**-Ph), 6.75 (m, 2H), 7.37 (m, 2H), 7.61 (d, 1H, *J* = 16.0 Hz, -C**H**=CH-Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 51.48, 113.33, 114.89, 124.78, 129.92, 145.11, 148.65, 168.12. HR-MS *m/z* (M^+) $C_{10}H_{11}NO_2$ Requires, 177.0787; Found, 177.0793. *Anal*. Calcd for $C_{10}H_{11}NO_2$: 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 (NH_2), 3376, 1695 (CO), 1613, 1172. ^1H NMR (400 MHz, $CDCl_3$) δ: 3.77 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.25 (d, 1H, *J* = 16.0 Hz, -CH=C**H**-Ph), 6.49 (s, 1H), 6.93 (s, 1H), 7.87 (d, 1H, *J* = 16.0 Hz, -C**H**=CH-Ph). ^{13}C NMR (100 MHz, $CDCl_3$) 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^+) $C_{12}H_{15}NO_4$ Requires, 237.0997, Found, 237.0996. *Anal*. Calcd for $C_{12}H_{15}NO_4$: 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 $Ni(OAc)_2 \cdot 4H_2O$ (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- Ni_2B was removed by filtration; and the filtrated was concentrated under the reduced pressure. The obtained residue was purified by column chromatography on SiO_2 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 CH_2Cl_2/IPA, 5/1, v/v). IR (KBr) ν_{max} cm^{-1}: 3510 (OH), 3424 (NH_2), 1757 (CO, ester), 1607. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.25 (m, 3H), 7.71 (d, 1H, *J* = 9.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 102.67, 121.38, 125.20, 126.75, 127.61, 128.95, 145.62, 150.82, 162.07. HR-MS *m/z* (M^+) $C_9H_7NO_3$ Requires, 177.0424; Found, 177.0420. *Anal*. Calcd for $C_9H_7NO_3$: 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 CH_2Cl_2/IPA, 5/1, v/v). IR (KBr) ν_{max} cm^{-1}: 3578 (OH), 3413 (NH_2), 1760 (CO, ester), 1601. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.35 (s, 3H, OCH_3), 2.43 (s, 3H, OCH_3), 7.01 (s, 1H), 7.46 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) 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^+) $C_{11}H_{11}NO_3$ Requires, 205.0736, Found, 205.0737. *Anal*. Calcd for

$C_{11}H_{11}NO_3$: 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 CH_2Cl_2/EtOH, 5/1, v/v). IR (KBr) ν_{max} cm^{-1}: 3503 (OH), 3428 (NH_2), 1748 (CO, ester), 1709 (CO), 1601. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.21 (s, 3H, CH_3), 3.35 (s, 2H, CH_2), 6.68 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 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^+) $C_{12}H_{11}NO_4$ Requires, 233.0685; Found, 233.0689. *Anal*. Calcd for $C_{12}H_{11}NO_4$: 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 CH_2Cl_2/EtOH, 5/1, v/v). IR (KBr) ν_{max} cm^{-1}: 3506 (OH), 3420 (NH_2), 1751 (CO, ester), 1668 (CO), 1604. ^1H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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^+) $C_{15}H_{15}NO_4$ Requires, 273.0997; Found, 273.0992. *Anal*. Calcd for $C_{15}H_{15}NO_4$: 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 $Ni(OAc)_2 \cdot 4H_2O$ (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-Ni_2B was removed by filtration; and the methanol was concentrated under the reduced pressure. The obtained residue was purified by column chromatography on SiO_2 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 (NH_2), 2927, 1712 (CO), 1640, 1172. ^1H NMR (400 MHz, $CDCl_3$) 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=C**H**-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, -C**H**=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 $C_{25}H_{33}NO_5$, 427.2350; Found, 427.2352. *Anal*. Calcd for $C_{25}H_{33}NO_5$: 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-oxa-spiro[2.5]oct-6-yl ester (9b). Yield: 0.84 g, 88% as pale yellowish foam. mp 59-62 ^{o}C (from *n*-Hexane). IR (KBr) ν_{max} cm^{-1}: 3455 (NH_2), 3367, 2927, 1708 (CO), 1635, 1168. ^{1}H-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* = 4Hz), 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=C**H**-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, -C**H**=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, 112.8,1 114.33, 116.25, 117.64, 125.80, 129.21, 133.22, 135.73, 142.85, 146.64, 165.01. HR-MS *m/z* (M^+) Requires $C_{25}H_{33}NO_5$, 427.2350, Found, 427.2346. *Anal*. Calcd for $C_{25}H_{33}NO_5$: 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-oxa-spiro[2.5]oct-6-yl ester (9c). Yield: 0.91 g, 95% as pale yellowish foam. mp 65-68 ^{o}C (from *n*-Hexane). IR (KBr) ν_{max} cm^{-1}: 3461 (NH_2), 3365, 2927, 1702 (CO), 1599, 1160. ^{1}H-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=C**H**-Ph), 6.74 (m, 2H), 7.34 (m, 2H), 7.55 (d, 1H, *J* =

16.0 Hz, -C**H**=CH-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 $C_{25}H_{33}NO_5$: 427.2350; Found: 427.2360. *Anal*. Calcd for $C_{25}H_{33}NO_5$: 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 ^{o}C (from *n*-Hexane). IR (KBr) ν_{max} cm^{-1}: 3460 (NH_2), 3365, 2927, 1703 (CO), 1600, 1160. ^{1}H 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, -CH=C**H**-Ph), 6.76 (m, 1H), 7.41 (m, 2H), 7.57 (d, 1H, *J* = 16.0 Hz, -C**H**=CH-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 $C_{25}H_{32}NO_5Cl$: 461.1959. Found: 461.1963. *Anal*. Calcd for $C_{25}H_{32}NO_5Cl$: 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 ^{o}C (from *n*-Hexane). IR (KBr) ν_{max} cm^{-1}: 3367 (NH_2), 2929, 2831, 1702 (CO), 1609, 1160. ^{1}H 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, -CH=C**H**-Ph), 6.91 (s, 1H), 7.81 (d, 1H, *J* = 16.0 Hz, -C**H**=CH-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 $C_{27}H_{37}NO_7$: 487.2560; Found: 487.2583. *Anal*. Calcd for $C_{27}H_{37}NO_7$: C, 67.04; H, 7.84; N,

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

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11. Nitrocinnamoylfumagillol compounds were prepared as follows: To a stirred suspension of a nitrocinnamic acid (2.5 equiv.) in toluene was added $SOCl_2$ (5 equiv.) and the mixture was refluxed for 2 h. Toluene was removed under vacuum evaporation, and the residue was used without further purification for the next step. To the residue in DMF (10 mL) was added NaH (6 equiv.) at 0 ℃. Fumagillol (1 equiv.) was added to the mixture, maintaining at that temperature. After addition, the reaction mixture was allowed to warm to rt and stirred for 2 h. The mixture was quenched with sat. NH_4Cl and washed with ethyl acetate. The organic layer was washed with sat. NH_4Cl twelve times, and brine in sequence. The seperated organic layer was dried over $MgSO_4$ and concentrated in reduced pressure, giving a residue, which was subjected to column chromatography (SiO_2, EtOAc : n-Hexane = 1 : 1) to afford the desired product and the product was used without further purification in the next step.

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