CHAPTER 3

RESULTS AND DISCUSSION

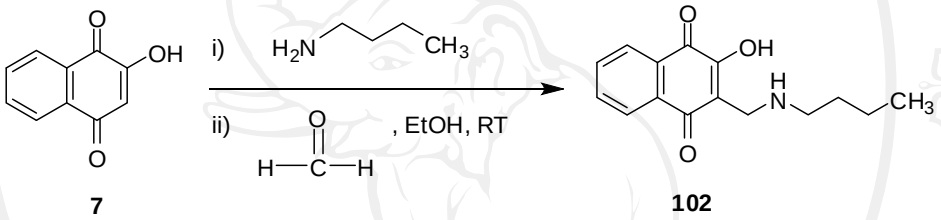
3.1 Synthesis of naphthoquinone derivatives 102-122

3.1.1 Synthesis of 2-((butylamino)methyl)-3-hydroxynaphthalene-1,4-dione (102)

2-Hydroxy-1,4-naphthoquinone (136.8 mg, 0.786 mmol) and n-butylamine (0.09 ml, 0.864 mmol) were dissolved in absolute ethanol (10 ml) and heated at 45 ^{o}C for 5 min. The formaldehyde (0.06 ml, 0.864 mmol) was then added with stirring vigorously. The product occurred as an orange precipitate in one hour and stirred the reaction mixture further for 3 hours. The product was filtered, washed with a little absolute ethanol and then with diethyl ether, in which owing to their switterionic nature, the products were almost insoluble. The pure product was obtained as an orange precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **102** (43.8 mg, 21.52 % yield) as orange solids from CH_2Cl_2/hexane, m.p. 168.5-170.0 ^{o}C.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 260.1285 $(M+H)^+$, corresponding to a molecular formula $C_{15}H_{18}NO_3$. The FT-IR spectrum showed absorption band at ν_{max} 3142 cm^{-1} (O-H and N-H), 3100 and 3050 cm^{-1}(C-H of aromatic), 2955 and 2869 cm^{-1}(C-H of CH_2/CH_3) and 1676 cm^{-1}

(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **102** in DMSO-d_6 showed four signals of aromatic protons of naphthoquinone at δ 7.56 (*t*, *J* = 7.4 Hz), 7.70 (*t*, *J* = 7.5 Hz), 7.81 (*d*, *J* = 7.1 Hz) and 7.93 (*d*, *J* = 7.1 Hz) ppm. The signals at δ 1.25-1.35 (*m*), 1.54-1.63 (*m*), 2.83 (*t*, *J* = 7.6 Hz) and 3.93 (*s*) ppm were assigned to the methylene groups. The signal of methyl group was observed at δ 0.87 (*t*, *J* = 7.4 Hz) ppm. The reaction was shown in Scheme 3.1, the reaction mechanism was shown in Scheme 3.2 and ^{1}H-NMR was shown in Figure 3.1.



Scheme 3.1 Synthesis of compound **102**

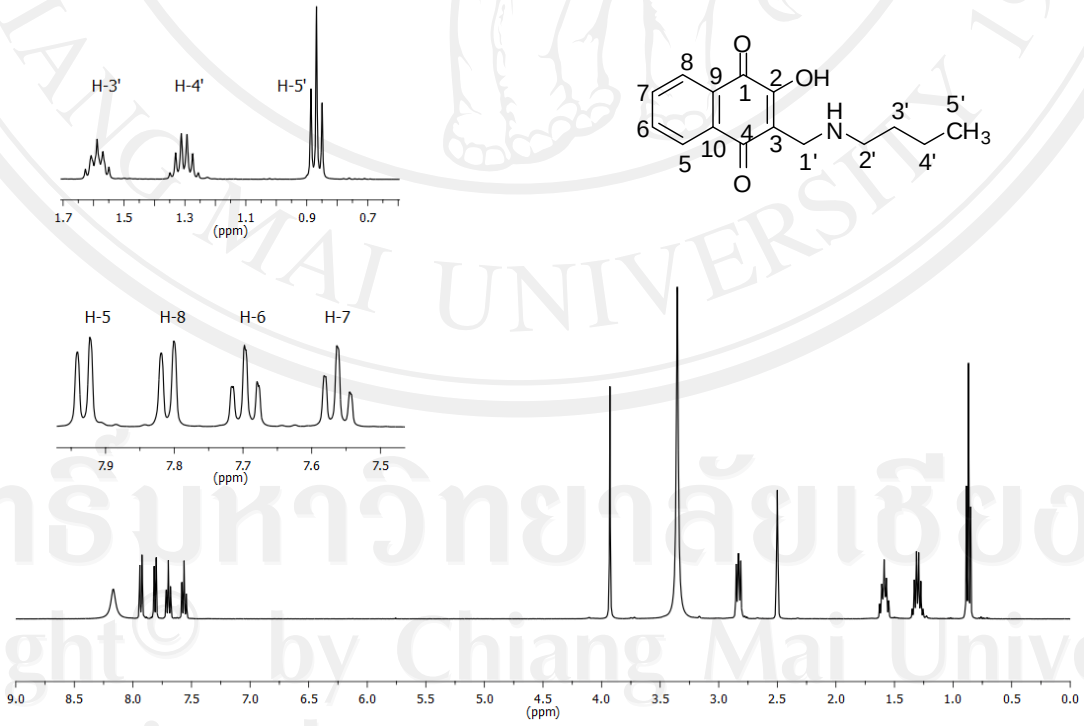
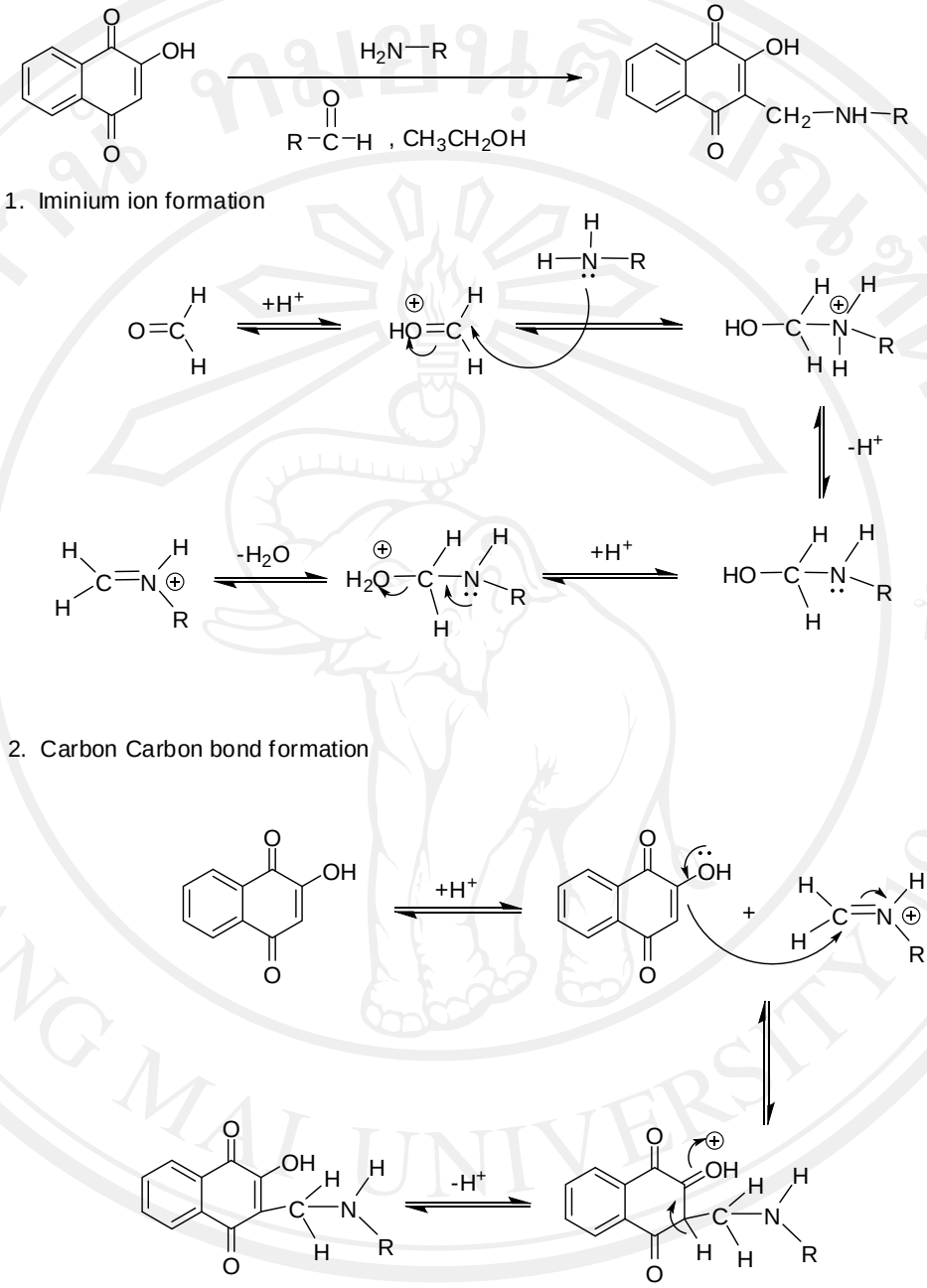


Figure 3.1 ^{1}H NMR spectra of compound **102**

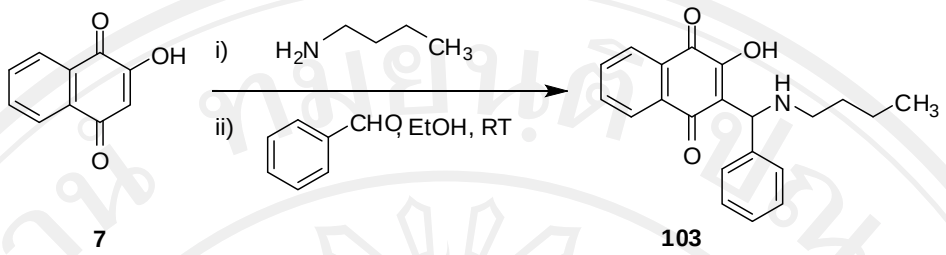


Scheme 3.2 Mechanism of naphthoquinone derivatives[52]

3.1.2. Synthesis of 2-((butylamino)(phenyl)methyl)-3-hydroxy naphthalene-1,4-dione (103)

The procedure was carried out as described in preparation **3.1.1** using 2-Hydroxy-1,4-naphthoquinone (202.6 mg, 1.164 mmol) and n-butylamine (0.13 ml, 1.281 mmol) as starting material and benzaldehyde (0.13 ml, 1.281 mmol) was then added with stirring vigorously. The pure product was obtained as an orange precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **103** (283.2 mg, 72.63 % yield) as orange solids from CH_2Cl_2/hexane, m.p. 185.0-186.0 ºC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 336.1602 $(M+H)^+$, corresponding to a molecular formula $C_{21}H_{22}NO_3$. The FT-IR spectrum showed absorption band at ν_{max} 3310 cm^{-1} (O-H and N-H), 3065 and 3050 cm^{-1}(C-H of aromatic), 2960 and 2933cm^{-1}(C-H of CH_2/CH_3) and 1680 cm^{-1} (C=O). ^{1}H-NMR (400 MHz) spectrum of compound **103** in DMSO-d_6 showed five signals of aromatic protons of naphthoquinone at δ 7.29-7.37 (*m*), 7.56-7.61 (*m*), 7.70 (*t*, *J* = 7.2 Hz), 7.82 (*d*, *J* = 7.3 Hz) and 7.91 (*d*, *J* = 6.8 Hz) ppm. The signal at δ 5.50 (*s*) ppm was assigned to the methine proton. The signal at δ 1.24-1.32 (*m*), 1.55-1.65 (*m*) and 2.87 (*t*, *J* = 7.7 Hz) ppm were assigned to the methylene protons and protons of methyl group were observed at δ 0.83 (*t*, *J* = 7.4 Hz) ppm. The reaction was shown in Scheme 3.3 and ^{1}H-NMR was shown in Figure 3.2. For the reaction mechanism was similar to Scheme 3.2.



Scheme 3.3 Synthesis of compound **103**

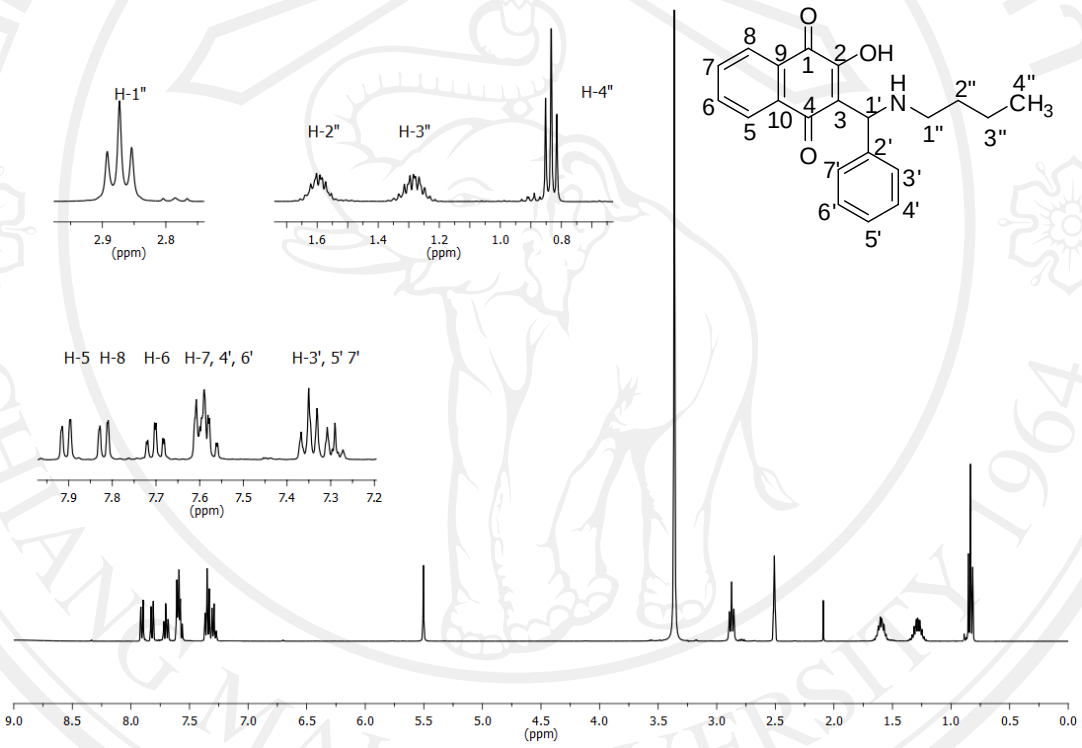


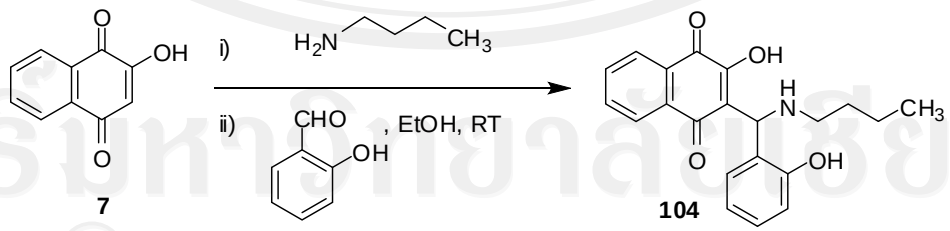
Figure 3.2 ^{1}H NMR spectra of compound **103**

3.1.3. Synthesis of 2-((butylamino)(2-hydroxyphenyl)methyl)-3-hydroxynaphthalene-1,4-dione (104)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (107.8 mg, 0.619 mmol) and n-butylamine (0.07 ml, 0.682 mmol) as starting material and salicylaldehyde (0.06 ml, 0.682 mmol) was

then added with stirring vigorously. The pure product was obtained as an orange precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **104** (64.3 mg, 29.59 % yield) as orange solids from CH_2Cl_2/hexane, m.p. 176.5-177.0 ºC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 352.1545 $(M+H)^+$, corresponding to a molecular formula $C_{21}H_{22}NO_4$. FT-IR spectrum showed absorption band at ν_{max} 3243 cm^{-1} (O-H and N-H), 3050 and 3025 cm^{-1}(C-H of aromatic), 2957 and 2905cm^{-1}(C-H of CH_2/CH_3) and 1681 cm^{-1} (C=O). ^{1}H-NMR (400 MHz) spectrum of compound **104** in DMSO-d_6 showed four signals of aromatic protons of naphthoquinone at δ 7.62 (*t*, *J* = 7.5 Hz), 7.72 (*t*, *J* = 7.4 Hz), 7.86 (*d*, *J* = 6.7 Hz) and 7.91 (*d* , *J* = 6.4 Hz) ppm. The signal at δ 6.74 (*t*, *J* = 7.1 Hz), 6.87 (*d*, *J* = 8.1 Hz), 7.15 (*td*, *J* = 8.1, 1.6 Hz) and 7.31 (*dd*, *J* = 7.7, 1.4 Hz) ppm were assigned to aromatic protons at the side chain. The protons of methyl group were observed at δ 0.84 (*t*, *J* = 7.4 Hz) ppm. The reaction was shown in Scheme 3.4 and ^{1}H-NMR was shown in Figure 3.3. For the reaction mechanism was similar to Scheme 3.2.



Scheme 3.4 Synthesis of compound **104**

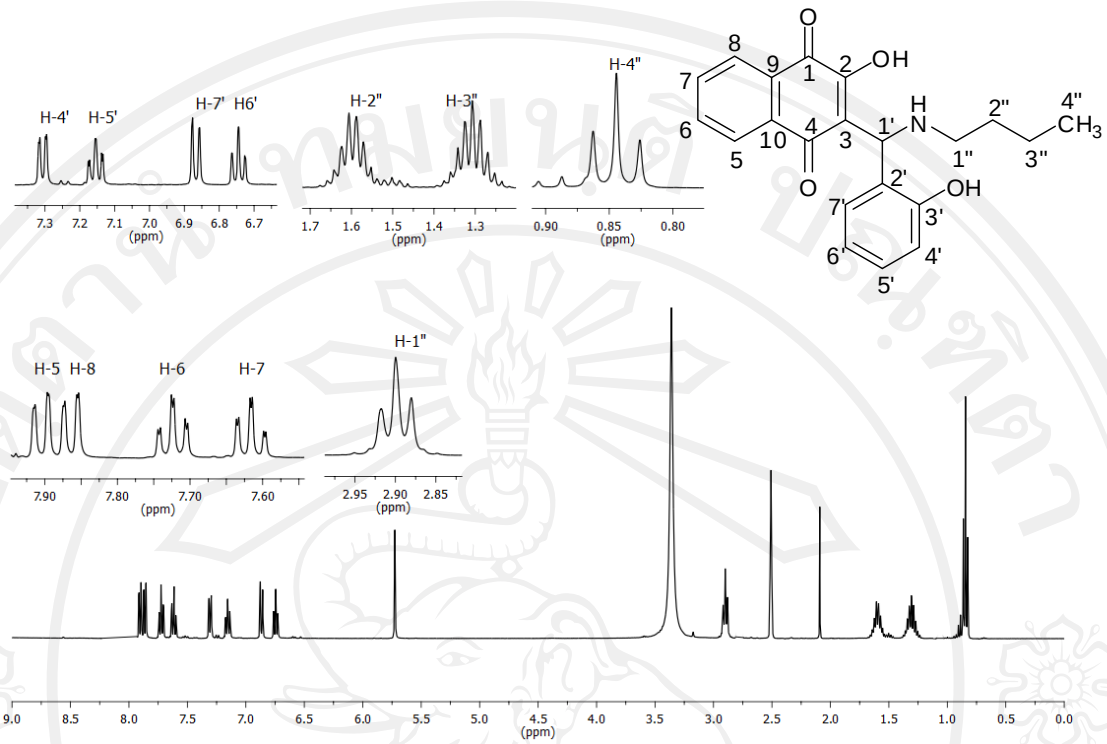


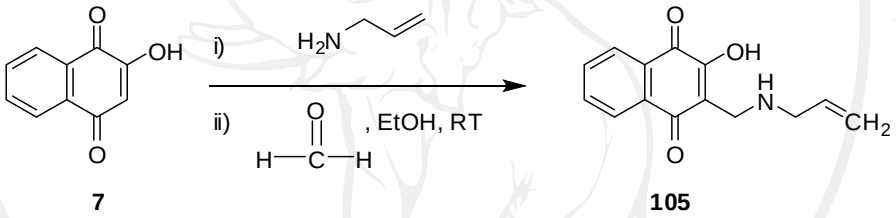
Figure 3.3 ^{1}H NMR spectra of compound **104**

3.1.4. Synthesis of 2-((allylamino)methyl)-3-hydroxynaphthalene-1,4-dione (105)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (232.6 mg, 1.337 mmol) and allylamine (0.11 ml, 1.471 mmol) as starting material and formaldehyde (0.11 ml, 1.471 mmol) was then added with stirring vigorously. The pure product was obtained as an orange precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **105** (137.4 mg, 42.15 % yield) as orange solids from CH_2Cl_2/hexane, m.p. 159.0-160.8 ºC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 244.0971 $(M+H)^+$, corresponding to a molecular formula $C_{14}H_{14}NO_3$. FT-IR spectrum showed absorption band at ν_{max} 3425 cm^{-1} (O-H and N-H), 3155 and

3025 cm^{-1}(C-H of aromatic and double bond), 2968 and 2937 cm^{-1}(C-H of CH_2/CH_3) and 1674 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **105** in DMSO-d_6 showed four signals of aromatic protons of naphthoquinone at δ 7.56 (*t*, *J* = 7.5 Hz), 7.69 (*t* , *J* = 7.4 Hz), 7.80 (*d*, *J* = 7.6 Hz) and 7.93 (*d*, *J* = 6.9 Hz) ppm. The signal at δ 3.53 (*d* , *J* = 6.7 Hz), 3.92 (*s*) and 5.37-5.51 (*m*) ppm were assigned to methylene protons. The methine proton was observed at δ 5.88-5.98 (*m*) ppm. The reaction was shown in Scheme 3.5 and ^{1}H-NMR was shown in Figure 3.4. For the reaction mechanism was similar to Scheme 3.2.



Scheme 3.5 Synthesis of compound **105**

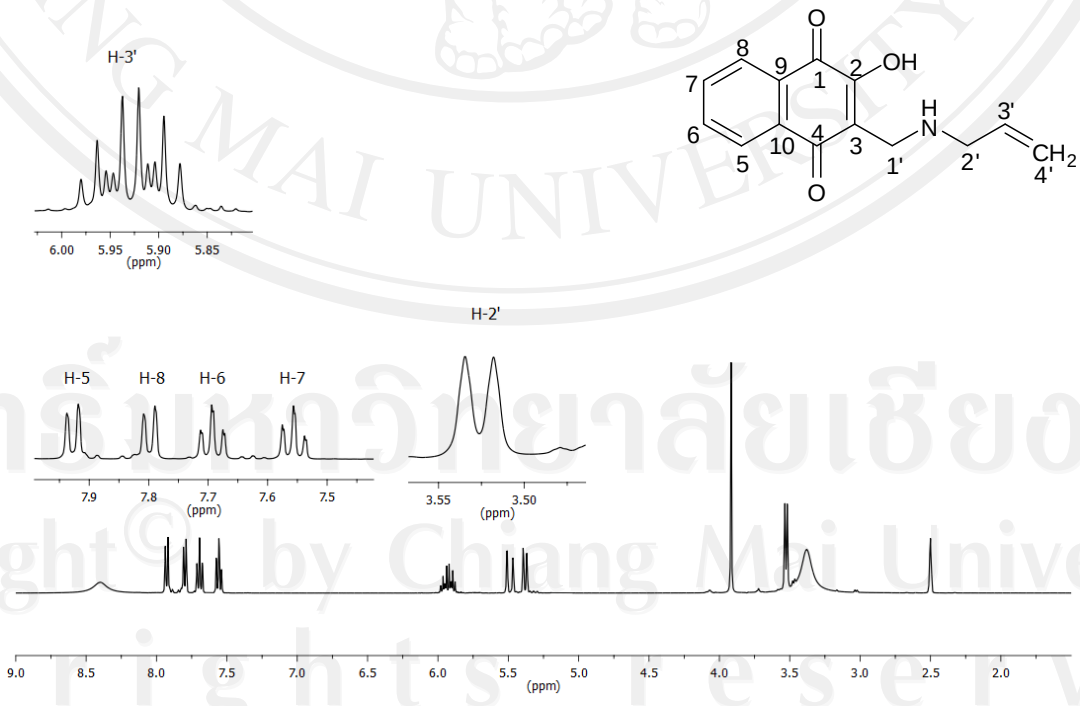
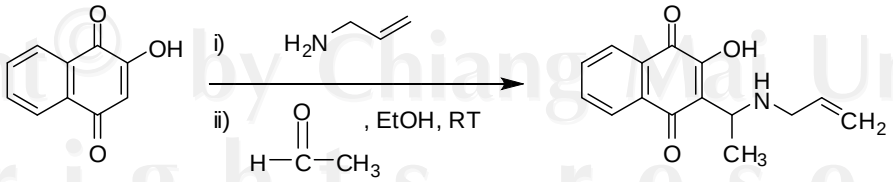


Figure 3.4 ^{1}H NMR spectra of compound **105**

3.1.5. Synthesis of 2-(1-(allylamino)ethyl)-3-hydroxynaphthalene-1,4-dione (106)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (218.6 mg, 1.256 mmol) and allylamine (0.10 ml, 1.382 mmol) as starting material and acetaldehyde (0.08 ml, 1.382 mmol) was then added with stirring vigorously. The pure product was obtained as an orange precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **106** (137.4 mg, 42.15 % yield) as orange solids from CH_2Cl_2/hexane, m.p. 162.0-163.0 ºC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 258.1130 $(M+H)^+$, corresponding to a molecular formula $C_{15}H_{16}NO_3$. FT-IR spectrum showed absorption band at ν_{max} 3405 cm^{-1} (O-H and N-H), 3068 and 3025 cm^{-1}(C-H of aromatic and double bond), 2984 cm^{-1}(C-H of CH_2/CH_3) and 1673 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **106** in DMSO-d_6 showed four signals of aromatic protons of naphthoquinone at δ 7.58 (*t*, *J* = 7.4 Hz), 7.71 (*t* , *J* = 7.2 Hz), 7.82 (*d*, *J* = 7.6 Hz) and 7.91 (*d*, *J* = 7.6 Hz) ppm. The signal at δ 4.50 (*q*, *J* = 6.8 Hz) ppm was assigned to methine proton at position 1′ and the protons of methyl group were observed at δ 1.42 (*d*, *J* = 6.7 Hz) ppm. The reaction was shown in Scheme 3.6 and ^{1}H-NMR was shown in Figure 3.5. For the reaction mechanism was similar to Scheme 3.2.



Scheme 3.6 Synthesis of compound **106**

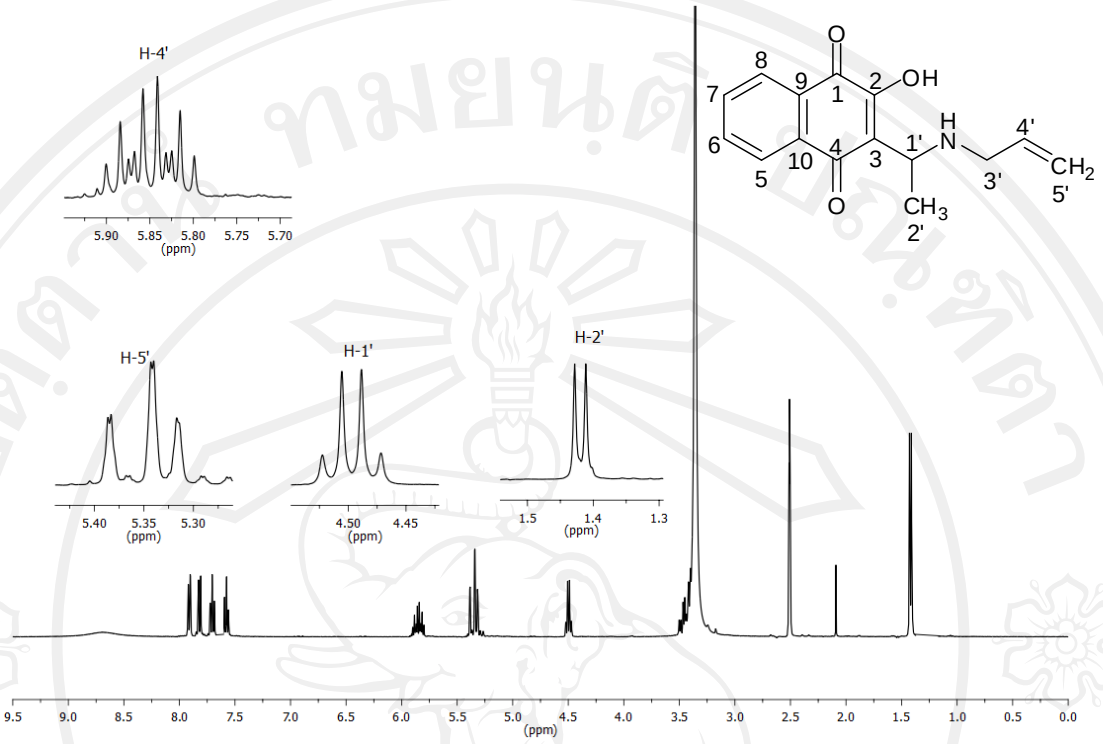


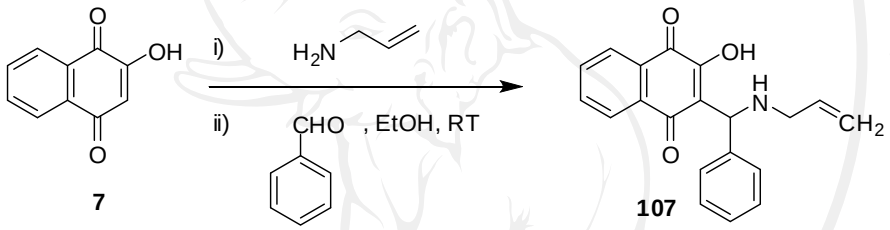
Figure 3.5 ^{1}H NMR spectra of compound **106**

3.1.6. Synthesis of 2-((allylamino)(phenyl)methyl)-3-hydroxy naphthalene-1,4-dione (107)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (230.8 mg, 1.326 mmol) and allylamine (0.11 ml, 1.459 mmol) as starting material and benzaldehyde (0.15 ml, 1.459 mmol) was then added with stirring vigorously. The pure product was obtained as an orange precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **107** (338.9 mg, 80.09 % yield) as orange solids from CH_2Cl_2/hexane, m.p. 191.0-192.4 ºC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 320.1295 $(M+H)^+$, corresponding to a molecular formula $C_{20}H_{18}NO_3$. FT-IR spectrum showed absorption band at ν_{max} 3425 cm^{-1} (O-H and N-H), 3063 and

3005 cm^{-1}(C-H of aromatic and double bond), 2985 cm^{-1}(C-H of CH_2/CH_3) and 1672 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **107** in DMSO-d_6 showed five signals of aromatic protons at δ 7.26-7.37 (*m*), 7.56-7.58 (*m*), 7.68 (*t*, *J* = 7.6 Hz), 7.81 (*d*, *J* = 7.6 Hz) and 7.90 (*d*, *J* = 7.7 Hz) ppm. The signal at δ 5.50 (*s*) ppm was assigned to methine proton. The reaction was shown in Scheme 3.7 and ^{1}H-NMR was shown in Figure 3.6. For the reaction mechanism was similar to Scheme 3.2.



Scheme 3.7 Synthesis of compound **107**

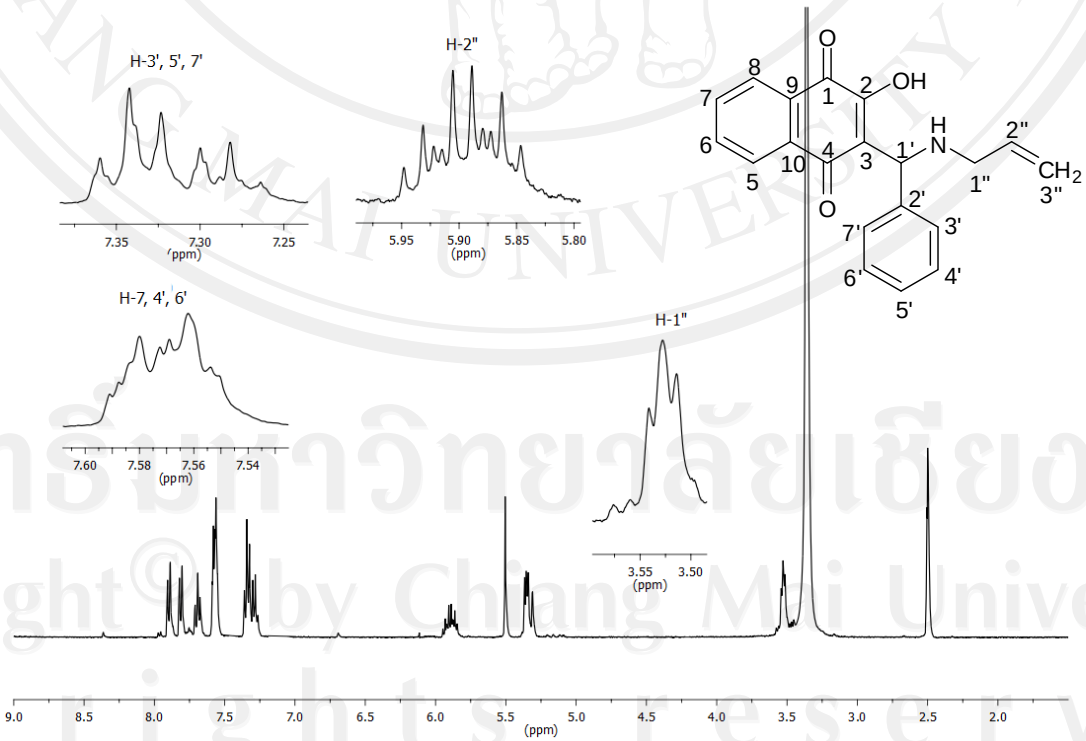
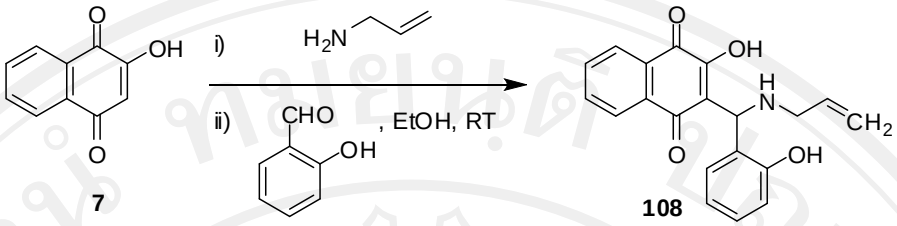


Figure 3.6 ^{1}H NMR spectra of compound **107**

3.1.7. Synthesis of 2-((allylamino)(2-hydroxyphenyl)methyl)-3-hydroxynaphthalene-1,4-dione (108)

The procedure was carried out as described in preparation **2.2.1.1** using 2-hydroxy-1,4-naphthoquinone (222.5 mg, 1.279 mmol) and allylamine (0.10 ml, 1.407 mmol) as starting material and salicylaldehyde (0.15 ml, 1.407 mmol) was then added with stirring vigorously. The pure product was obtained as an orange precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **108** (60.7 mg, 14.15 % yield) as orange solids from CH_2Cl_2/hexane, m.p. 183.0-184.5 ºC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 336.1236 $(M+H)^+$, corresponding to a molecular formula $C_{20}H_{18}NO_4$. FT-IR spectrum showed absorption band at ν_{max} 3465 cm^{-1} (O-H and N-H), 3060 and 3035 cm^{-1}(C-H of aromatic and double bond), 2995 and 2915 cm^{-1}(C-H of CH_2/CH_3) and 1680 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **108** in DMSO-d_6 showed four signals of aromatic protons of naphthoquinone at δ 7.61 (*t, J* = 7.4 Hz), 7.72 (*t, J* = 7.5 Hz), 7.86 (*d, J* = 7.6 Hz) and 7.90 (*d, J* = 7.7 Hz) ppm. The signals at δ 6.75 (*t, J* = 7.5 Hz), 6.86 (*d, J* = 8.1 Hz), 7.15 (*t, J* = 7.7 Hz) and 7.33 (*d, J* = 7.7 Hz) ppm were assigned to aromatic protons of side chain. The proton of methine at position 1' was observed at δ 5.75 (*s*) ppm. The reaction was shown in Scheme 3.8 and ^{1}H-NMR was shown in Figure 3.7. For the reaction mechanism was similar to Scheme 3.2.



Scheme 3.8 Synthesis of compound **108**

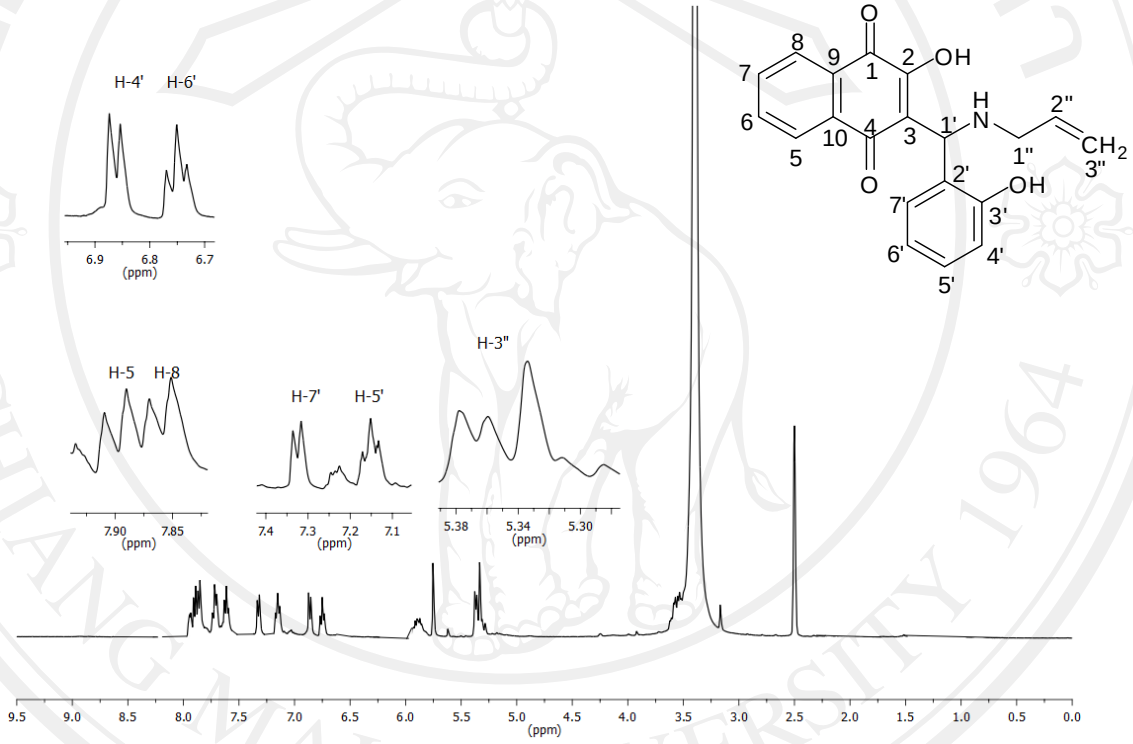


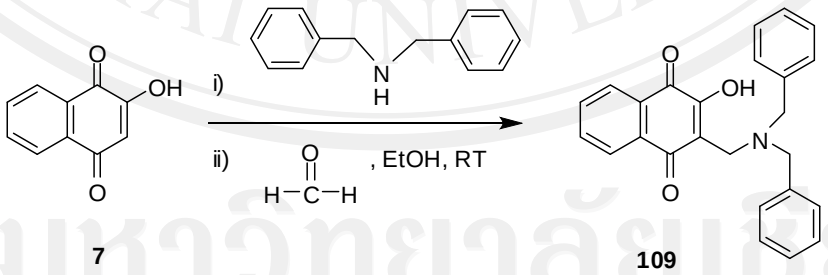
Figure 3.7 ^{1}H NMR spectra of compound **108**

3.1.8. Synthesis of 2-((dibenzylamino)methyl)-3-hydroxy naphthalene-1,4-dione (109)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (117.2 mg, 0.674 mmol) and dibenzylamine (0.14 ml, 0.741 mmol) as starting material and formaldehyde (0.06 ml, 0.741 mmol) was

then added with stirring vigorously. The pure product was obtained as an orange precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **109** (181.4 mg, 70.27 % yield) as orange solids from CH_2Cl_2/hexane, m.p. 167.0-168.8 ºC (60.7 mg, 14.15 % yield).

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 384.1596 $(M+H)^+$, corresponding to a molecular formula $C_{25}H_{22}NO_3$. FT-IR spectrum showed absorption band at ν_{max} 3315 cm^{-1} (O-H and N-H), 3033 and 3015 cm^{-1}(C-H of aromatic) and 1675 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **109** in DMSO-d_6 showed four signals of aromatic protons of naphthoquinone at δ 7.63 (*t*, *J* = 7.5 Hz), 7.72 (*t*, *J* = 7.5 Hz), 7.84 (*d*, *J* = 7.5 Hz) and 7.90 (*d*, *J* = 7.6 Hz) ppm and three signals of aromatic protons in side chain at δ 7.21-7.33 (*m*), 7.39-7.44 (*m*) and 7.48 (*dd*, *J* = 9.7, 3.9 Hz) ppm. The signals at δ 3.54 (*s*), 3.73 (*s*) and 4.16 (*s*) ppm were assigned to methylene protons. The reaction was shown in Scheme 3.9 and ^{1}H-NMR was shown in Figure 3.8. For the reaction mechanism was similar to Scheme 3.2.



7 **109**

Scheme 3.9 Synthesis of compound **109**

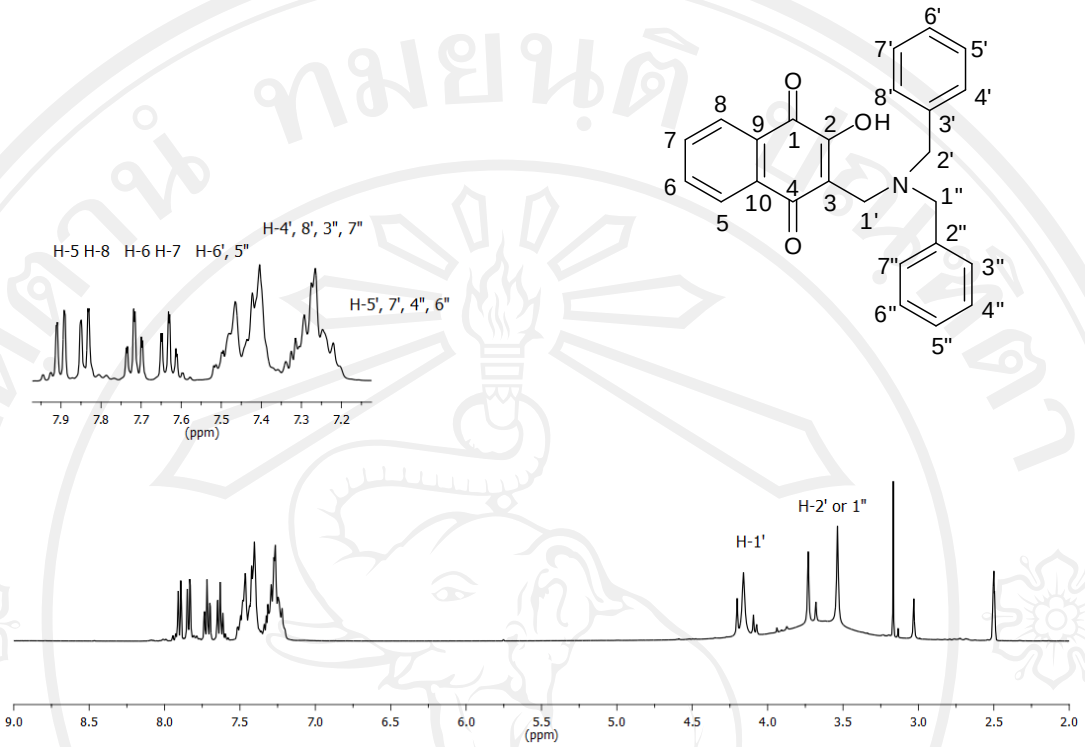


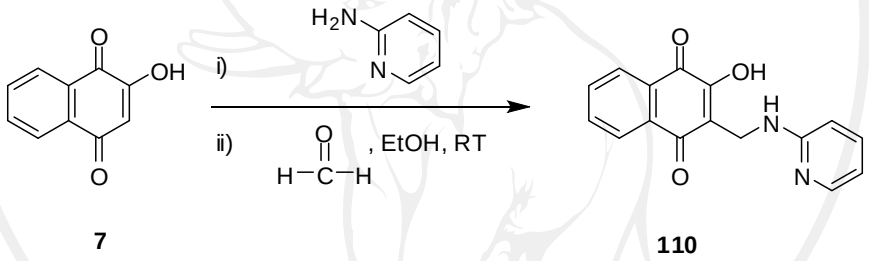
Figure 3.8 ^{1}H NMR spectra of compound **109**

3.1.9. Synthesis of 2-hydroxy-3-((pyridin-2-ylamino)methyl) naphthalene-1,4-dione (110)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (201.7 mg, 1.159 mmol) and 2-aminopyridine (120.0 mg, 1.275 mmol) as starting material and formaldehyde (0.09 ml, 1.275 mmol) was then added with stirring vigorously. The pure product was obtained as a yellow precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **110** (201.6 mg, 62.12 % yield) as yellow solids from CH_2Cl_2/hexane, m.p. 202.0-204.0 ºC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 281.0926 $(M+H)^+$, corresponding to a molecular formula $C_{16}H_{13}N_2O_3$. FT-IR

spectrum showed absorption band at ν_{max} 3192 cm^{-1} (O-H and N-H), 3064 and 3036 cm^{-1}(C-H of aromatic) and 1681 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **110** in $CDCl_3$ showed six signals of aromatic protons of naphthoquinone and pyridine at δ 6.49-6.58 (*m*), 6.92 (*d*, *J* = 9.5 Hz), 7.46 (*t*, *J* = 7.1 Hz), 7.56 (*t*, *J* = 7.4 Hz), 7.93 (*d*, *J* = 7.6 Hz) and 7.99 (*d*, *J* = 7.3 Hz) ppm. The signals at δ 4.33 (*s*) ppm was assigned to methylene protons. The reaction was shown in Scheme 3.10 and ^{1}H-NMR was shown in Figure 3.9. For the reaction mechanism was similar to Scheme 3.2.



7 **110**

Scheme 3.10 Synthesis of compound **110**

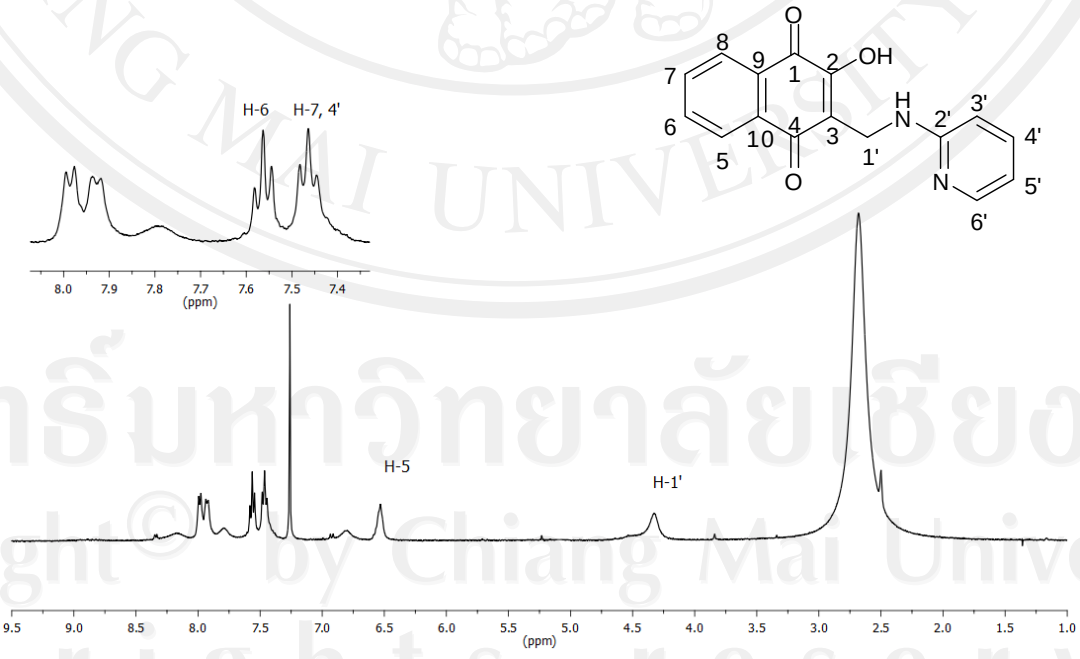
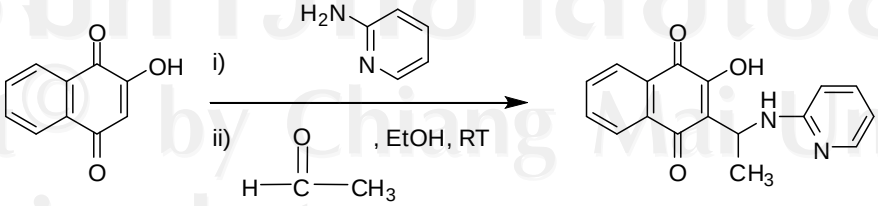


Figure 3.9 ^{1}H NMR spectra of compound **110**

3.1.10. Synthesis of 2-hydroxy-3-((pyridin-2-ylamino)ethyl) naphthalene-1,4-dione (111)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (200.7 mg, 1.153 mmol) and 2-aminopyridine (119.4 mg, 1.269 mmol) as starting material and acetaldehyde (0.07 ml, 1.269 mmol) was then added with stirring vigorously. The pure product was obtained as a red precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **111** (263.0 mg, 77.58 % yield) as red solids from CH_2Cl_2/hexane, m.p. 173.5-175.0 ºC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 295.1085 $(M+H)^+$, corresponding to a molecular formula $C_{17}H_{15}N_2O_3$. FT-IR spectrum showed absorption band at ν_{max} 3305 cm^{-1} (O-H and N-H), 3117 and 3074 cm^{-1}(C-H of aromatic), 2971 and 2928 cm^{-1}(C-H of CH_3) and 1681 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **111** in $CDCl_3$ showed three signals of aromatic protons of naphthoquinone at δ 7.65-7.75 (*m*), 7.96 (*d*, *J* = 7.5 Hz) and 8.16 (*d*, *J* = 7.6 Hz) ppm. The proton of methane was observed at δ 5.47 (*dq*, *J* = 13.8, 6.8 Hz) ppm. The signals at δ 1.82 (*d*, *J* = 6.8 Hz) ppm was assigned to methyl group. The reaction was shown in Scheme 3.11 and ^{1}H-NMR was shown in Figure 3.10. For the reaction mechanism was similar to Scheme 3.2.



7 **111**

Scheme 3.11 Synthesis of compound **111**

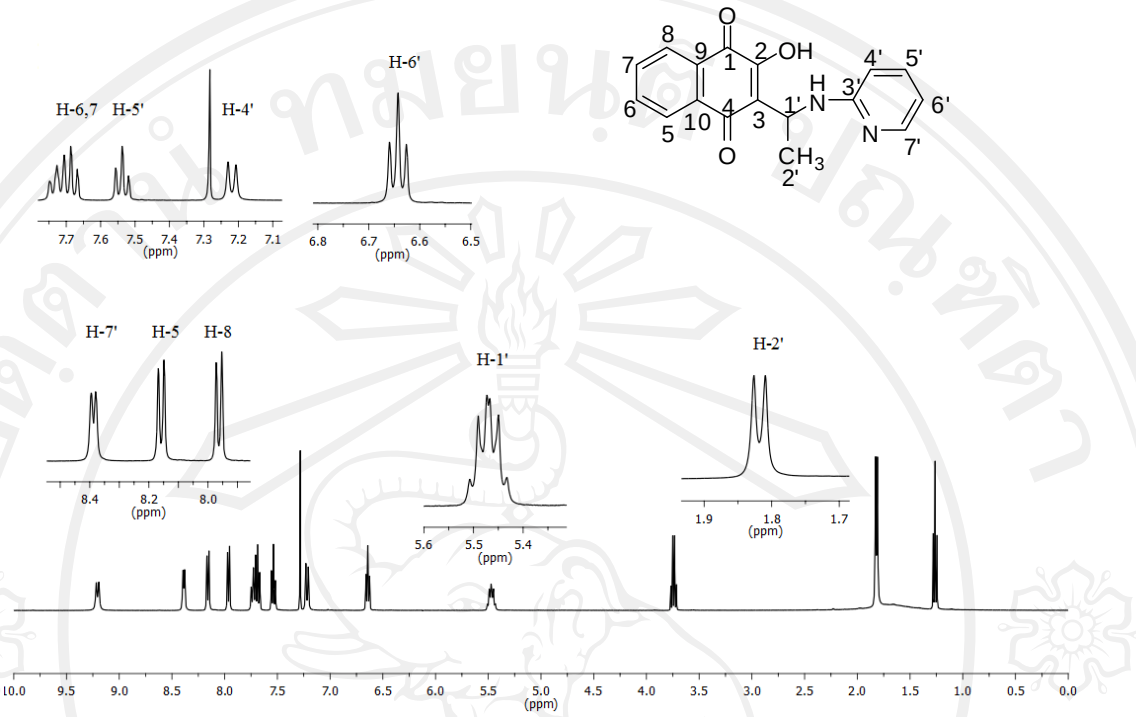


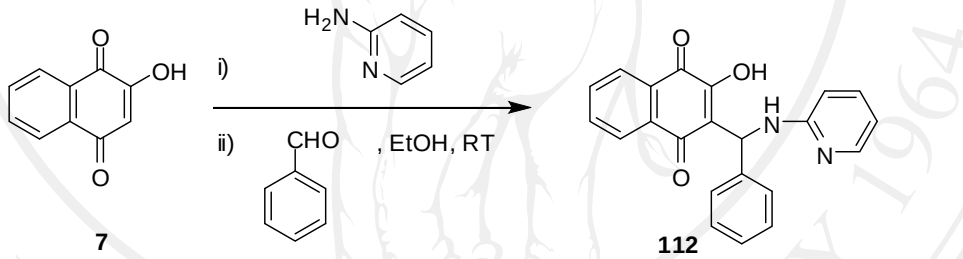
Figure 3.10 ^{1}H NMR spectra of compound **111**

3.1.11. Synthesis of 2-hydroxy-3-(phenyl(pyridin-2-ylamino) methyl)naphthalene-1,4-dione (112)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (224.3 mg, 1.290 mmol) and 2-aminopyridine (133.5 mg, 1.418 mmol) as starting material and benzaldehyde (0.14 ml, 1.418 mmol) was then added with stirring vigorously. The pure product was obtained as a red precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **112** (413.4 mg, 90.02 % yield) as red solids from CH_2Cl_2/hexane, m.p. 225.0-226.8 ºC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 357.1238 $(M+H)^+$, corresponding to a molecular formula $C_{22}H_{17}N_2O_3$. FT-IR

spectrum showed absorption band at ν_{max} 3314 cm^{-1} (O-H and N-H), 3033 and 3015 cm^{-1}(C-H of aromatic) and 1675 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **112** in $CDCl_3$ showed four signals of aromatic protons of naphthoquinone at δ 7.69 (*t*, *J* = 7.5 Hz), 7.77 (*t*, *J* = 7.9 Hz), 7.98 (*d*, *J* = 7.4 Hz) and 8.18 (*d*, *J* = 7.6 Hz) ppm. The signals at δ 7.19 (*d*, *J* = 7.0 Hz) and 7.50-7.58 (*m*) ppm were assigned to aromatic protons of side chain. The methane proton was observed at δ 6.64 (*d*, *J* = 9.8 Hz) ppm. The reaction was shown in Scheme 3.12 and ^{1}H-NMR was shown in Figure 3.11. For the reaction mechanism was similar to Scheme 3.2.



Scheme 3.12 Synthesis of compound **112**

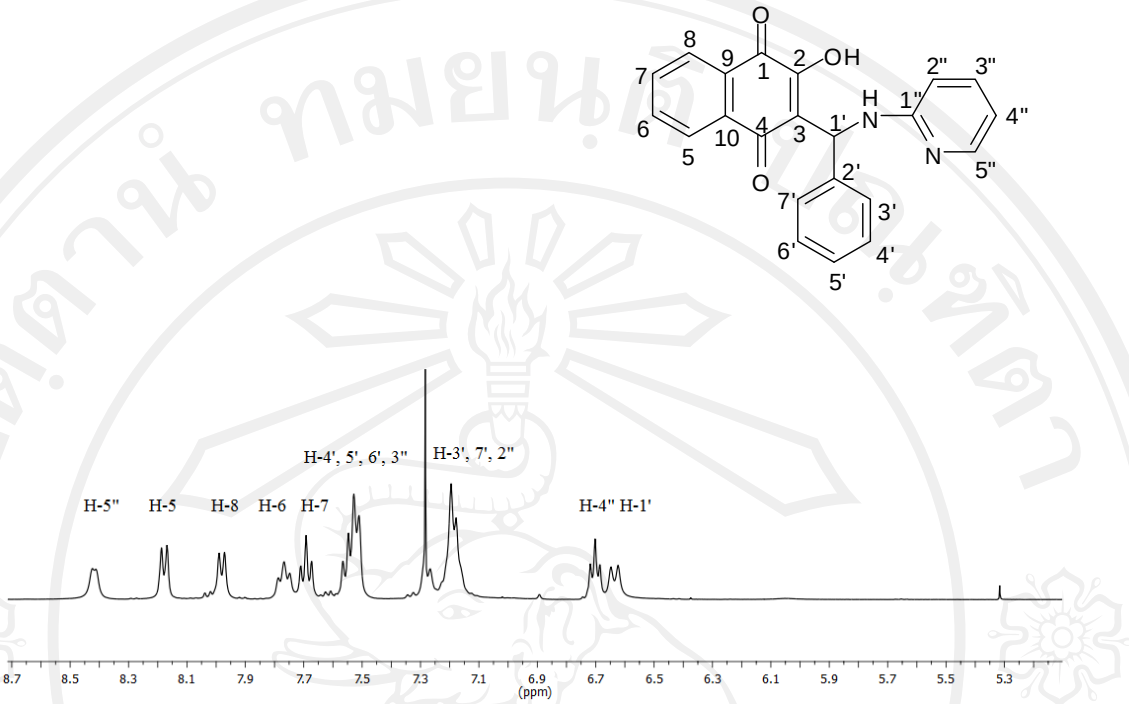


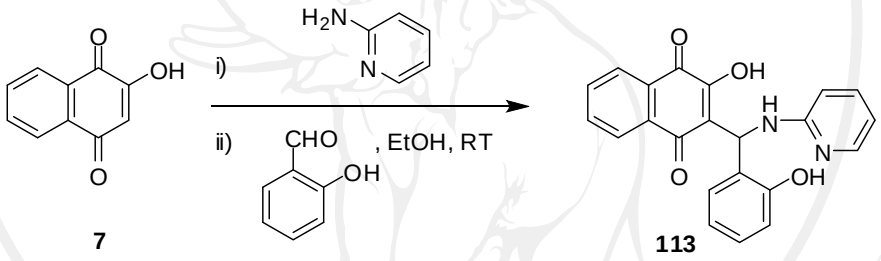
Figure 3.11 ^{1}H NMR spectra of compound **112**

3.1.12. Synthesis of 2-hydroxy-3-((2-hydroxyphenyl)(pyridin-2-ylamino)methyl)naphthalene-1,4-dione (113)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (218.4 mg, 1.255 mmol) and 2-aminopyridine (129.9 mg, 1.380 mmol) as starting material and salicylaldehyde (0.15 ml, 1.380 mmol) was then added with stirring vigorously. The pure product was obtained as a red precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **113** (294.5 mg, 63.08 % yield) as red solids from CH_2Cl_2/hexane, m.p. 173.3-175.0 ºC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 373.1189 $(M+H)^+$, corresponding to a molecular formula $C_{22}H_{17}N_2O_4$. FT-IR spectrum showed absorption band at ν_{max} 3324 cm^{-1} (O-H and N-H), 3105 and

3050 cm^{-1}(C-H of aromatic) and 1687 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **113** in $CDCl_3$ showed three signals of aromatic protons of naphthoquinone at δ 7.91 (*dd*, *J* = 5.1, 1.3 Hz), 7.98 (*d*, *J* = 7.6 Hz) and 8.19 (*d*, *J* = 7.6 Hz) ppm. The signals at δ7.14 (*d*, *J* = 8.1 Hz), 7.30 (*t*, *J* = 6.8 Hz), 7.37 (*d*, *J* = 7.3 Hz) and 7.54 (*t*, *J* = 8.7 Hz) ppm were assigned to aromatic protons of side chain. The methine proton was observed at δ5.63 (*s*) ppm. The reaction was shown in Scheme 3.13 and ^{1}H-NMR was shown in Figure 3.12. For the reaction mechanism was similar to Scheme 3.2.



Scheme 3.13 Synthesis of compound **113**

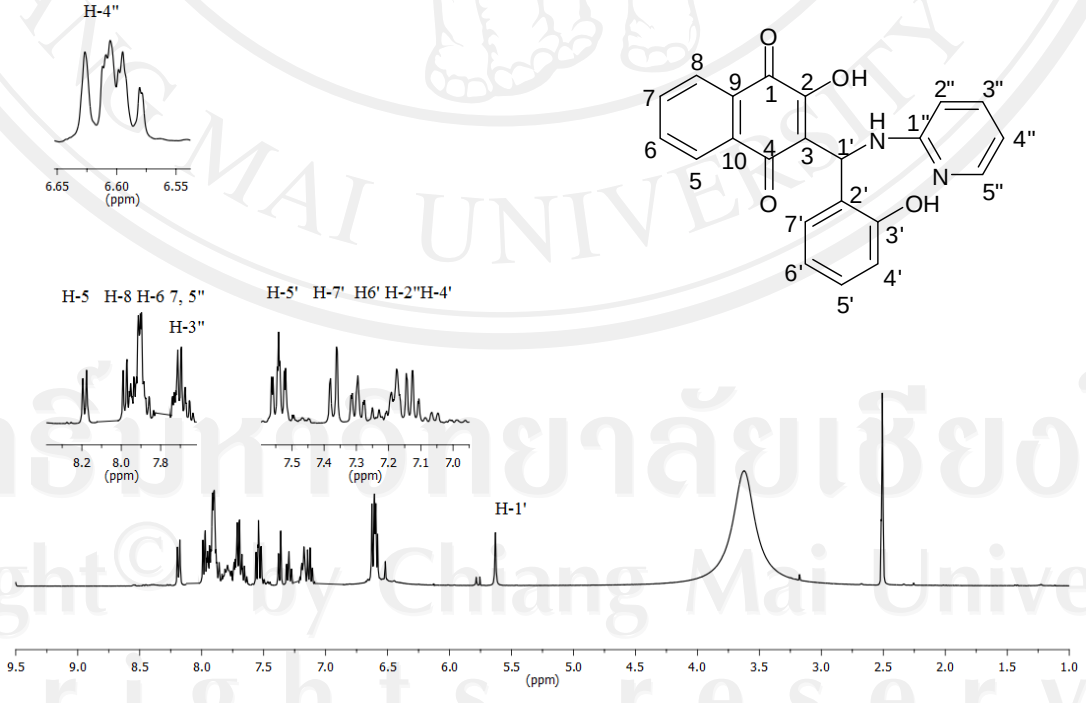
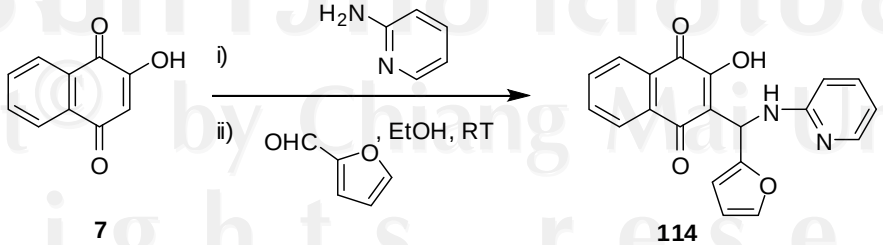


Figure 3.12 ^{1}H NMR spectra of compound **113**

3.1.13. Synthesis of 2-(furan-2-yl(pyridin-2-ylamino)methyl)-3-hydroxynaphthalene-1,4-dione (114)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (204.8 mg, 1.177 mmol) and 2-aminopyridine (121.9 mg, 1.295 mmol) as starting material and furfuraldehyde (0.11 ml, 1.295 mmol) was then added with stirring vigorously. The pure product was obtained as a brown precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **114** (110.1 mg, 27.03 % yield) as brown solids from CH_2Cl_2/hexane, m.p. 182.0-183.0 ºC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 347.1029 $(M+H)^+$, corresponding to a molecular formula $C_{20}H_{15}N_2O_4$. FT-IR spectrum showed absorption band at ν_{max} 3324 cm^{-1} (O-H and N-H), 3105 and 3050 cm^{-1}(C-H of aromatic) and 1687 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **114** in $CDCl_3$ showed three signals of aromatic protons of naphthoquinone at δ 7.59-7.68 (*m*), 7.97 (*d*, *J* = 7.9 Hz) and 8.14 (*d*, *J* = 7.7 Hz) ppm. The signals at δ 6.10 (*d*, *J* = 7.1 Hz), 6.24 (*m*) and 7.25 (*m*) ppm were assigned to protons of furan. The methine proton was observed at δ 6.82 (*s*) ppm. The reaction was shown in Scheme 3.14 and ^{1}H-NMR was shown in Figure 3.13. For the reaction mechanism was similar to Scheme 3.2.



Scheme 3.14 Synthesis of compound **114**

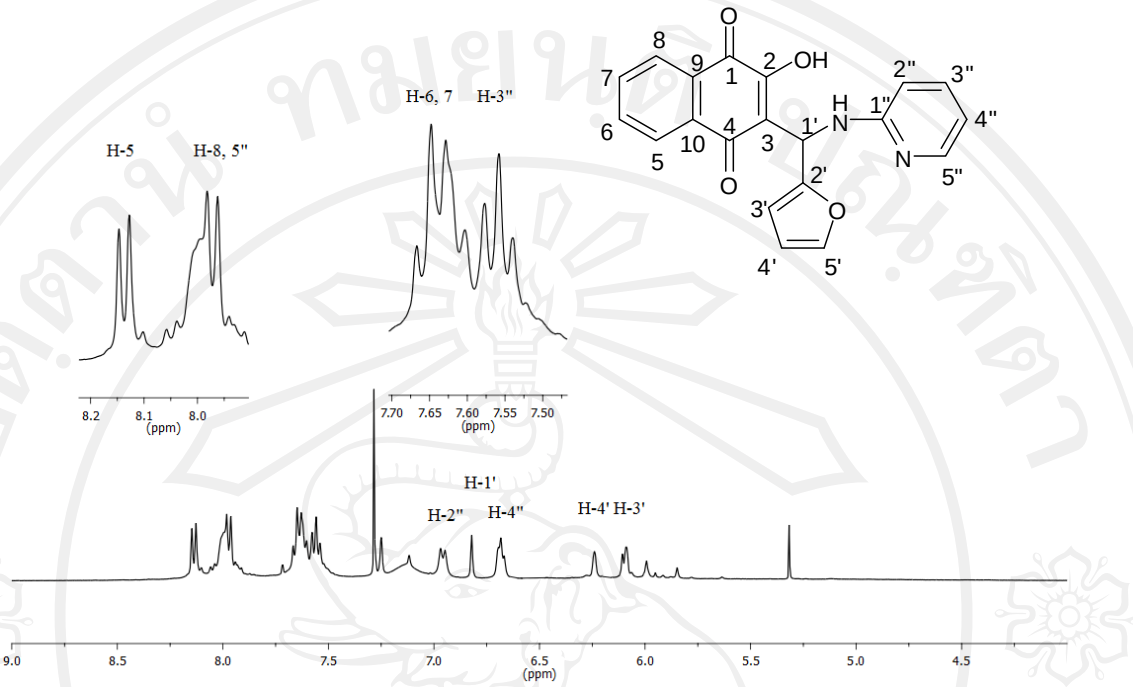
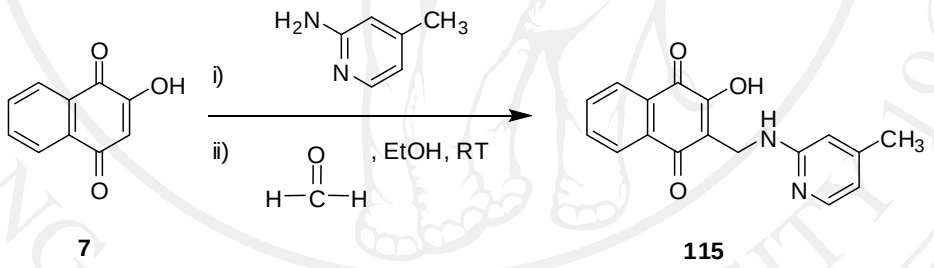


Figure 3.13 ^{1}H NMR spectra of compound **114**

3.1.14. Synthesis of 2-hydroxy-3-((4-methylpyridin-2-ylamino) methyl)naphthalene-1,4-dione (115)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (130.6 mg, 0.751 mmol) and 4-methyl-2-aminopyridine (89.3 mg, 0.826 mmol) as starting material and formaldehyde (0.06 ml, 0.826 mmol) was then added with stirring vigorously. The pure product was obtained as an orange precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **115** (148.8 mg, 67.39 % yield) as orange solids from CH_2Cl_2/hexane, m.p. 201.0-202.5 ^{o}C.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 295.1076 $(M+H)^+$, corresponding to a molecular formula $C_{17}H_{15}N_2O_3$. FT-IR spectrum showed absorption band at ν_{max} 3336 cm^{-1} (O-H and N-H), 3093 cm^{-1} (C-H of aromatic), 2952 cm^{-1}(C-H of CH_3) and 1665 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **115** in DMSO-d_6 showed four signals of aromatic protons of naphthoquinone at δ 7.59-7.67 (*m*), 7.68-7.79 (*m*), 7.85 (*t*, *J* = 7.2 Hz) and 7.91 (*d*, *J* = 6.1 Hz) ppm. The methylene protons were observed at δ 4.18 (*s*) ppm.The signals at δ 2.26 (*s*) ppm was assigned to protons of methyl group. The reaction was shown in Scheme 3.15 and ^{1}H-NMR was shown in Figure 3.14. For the reaction mechanism was similar to Scheme 3.2.



Scheme 3.15 Synthesis of compound **115**

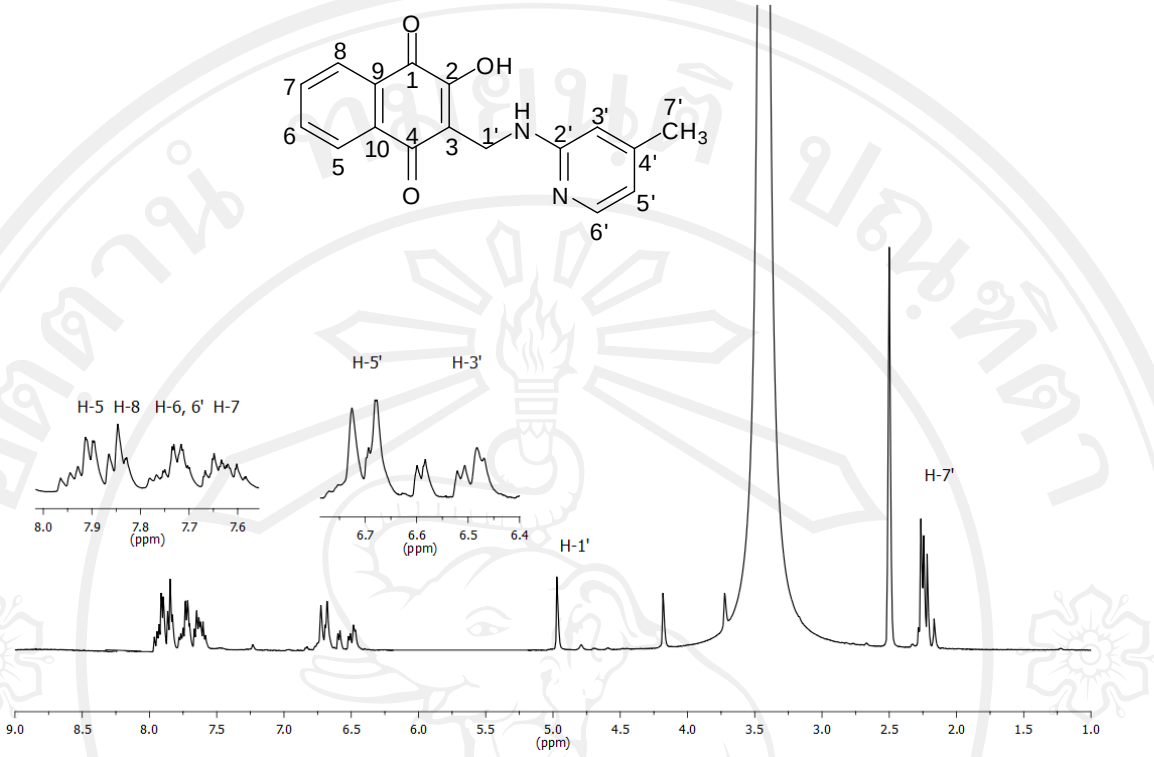
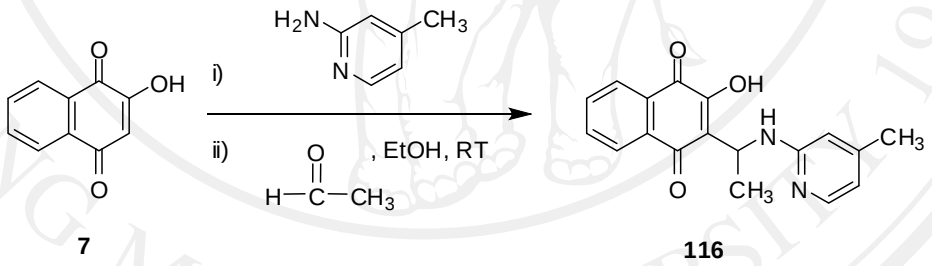


Figure 3.14 ^{1}H NMR spectra of compound **115**

3.1.15. Synthesis of 2-hydroxy-3-(1-(4-methylpyridin-2-ylamino) ethyl)naphthalene-1,4-dione (116)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (166.0 mg, 0.954 mmol) and 4-methyl-2-aminopyridine (113.5 mg, 1.049 mmol) as starting material and acetaldehyde (0.06 ml, 1.049 mmol) was then added with stirring vigorously. The pure product was obtained as an orange precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **116** (252.5 mg, 85.93 % yield) as orange solids from CH_2Cl_2/hexane, m.p. 172.0-172.5 ^{o}C.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 309.1239 $(M+H)^+$, corresponding to a molecular formula $C_{18}H_{17}N_2O_3$. FT-IR spectrum showed absorption band at ν_{max} 3343 cm^{-1} (O-H and N-H), 3120 and 3046 cm^{-1} (C-H of aromatic), 2940 and 2921 cm^{-1}(C-H of CH_3) and 1670 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **116** in $CDCl_3$ showed four signals of aromatic protons of naphthoquinone at δ 7.45 (*t*, *J* = 7.5 Hz), 7.60 (*t*, *J* = 7.6 Hz), 7.87 (*d*, *J* = 7.6 Hz) and 8.07 (*d*, *J* = 7.6 Hz) ppm. The methine proton was observed at δ 5.36 (*dq*, *J* = 13.7, 6.8 Hz) ppm.The signals at δ 1.69 (*d*, *J* = 6.8 Hz) and 2.29 (*s*) ppm were assigned to protons of methyl group. The reaction was shown in Scheme 3.16 and ^{1}H-NMR was shown in Figure 3.15. For the reaction mechanism was similar to Scheme 3.2.



Scheme 3.16 Synthesis of compound **116**

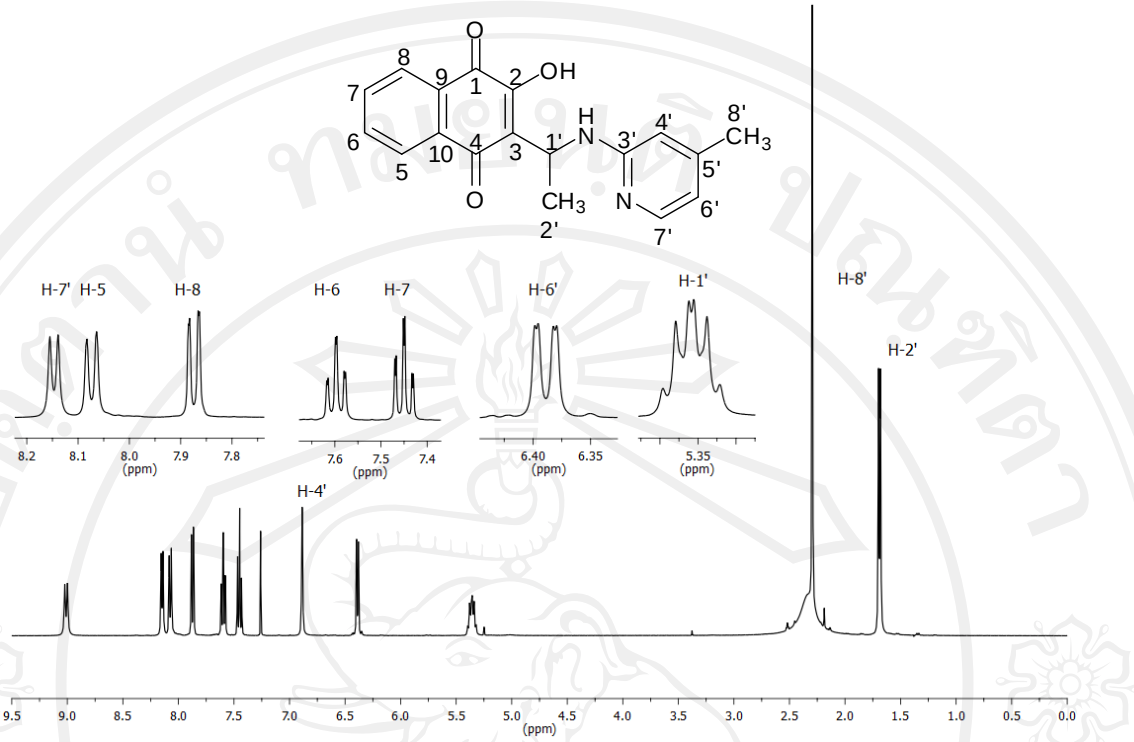


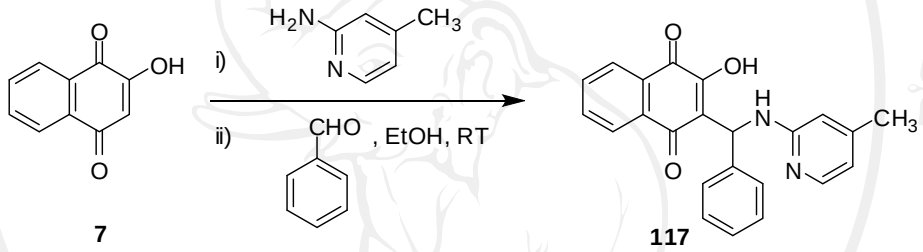
Figure 3.15 ^{1}H NMR spectra of compound **116**

3.1.16. Synthesis of 2-hydroxy-3-((4-methylpyridin-2-ylamino) (phenyl)methyl)naphthalene-1,4-dione (117)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (118.2 mg, 0.679 mmol) and 4-methyl-2-aminopyridine (80.78 mg, 0.747 mmol) as starting material and benzaldehyde (0.08 ml, 0.747 mmol) was then added with stirring vigorously. The pure product was obtained as an orange precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **117** (167.6 mg, 66.71 % yield) as orange solids from CH_2Cl_2/hexane, m.p. 217.5-218.0 ^{o}C.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 371.1394 $(M+H)^+$, corresponding to a molecular formula $C_{23}H_{19}N_2O_3$. FT-IR

spectrum showed absorption band at ν_{max} 3312 cm^{-1} (O-H and N-H), 3080 and 3047 cm^{-1} (C-H of aromatic), 2905 cm^{-1}(C-H of CH_3) and 1661 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **117** in DMSO-d_6 showed four signals of aromatic protons of naphthoquinone at δ 7.67 (*t*, *J* = 7.5 Hz), 7.77 (*dd*, *J* = 6.3, 3.3 Hz), 7.86-7.92 (*m*) and 7.96 (*d*, *J* = 7.6 Hz) ppm. The methine proton was observed at δ 6.69 (*s*) ppm. The reaction was shown in Scheme 3.17 and ^{1}H-NMR was shown in Figure 3.16. For the reaction mechanism was similar to Scheme 3.2.



Scheme 3.17 Synthesis of compound **117**

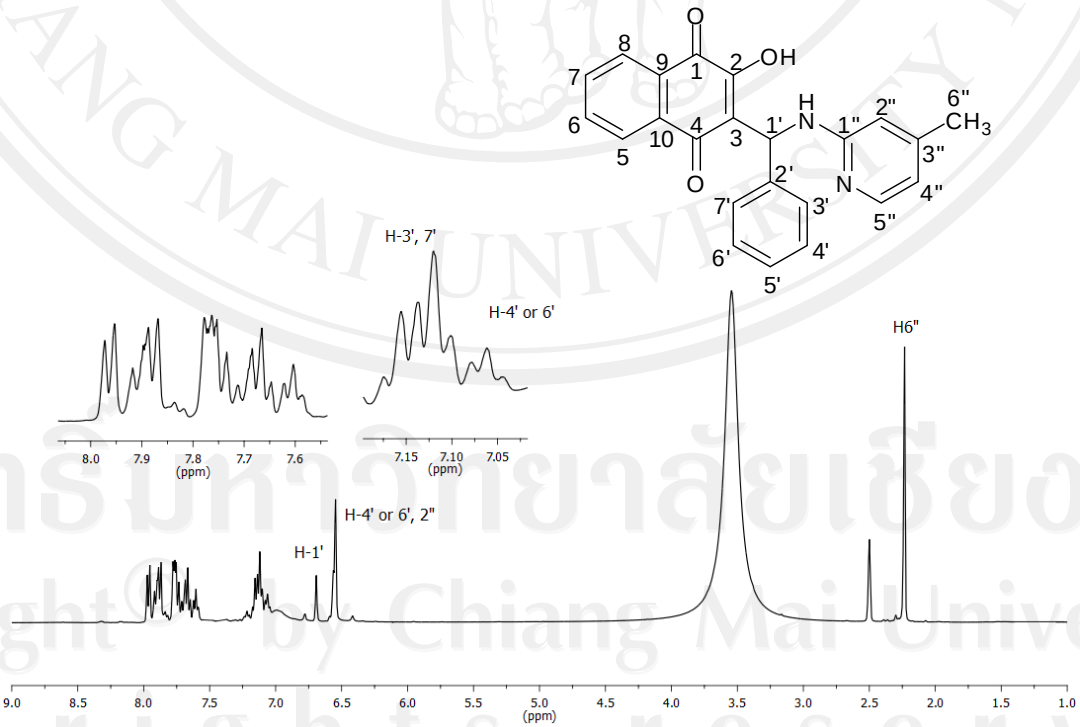
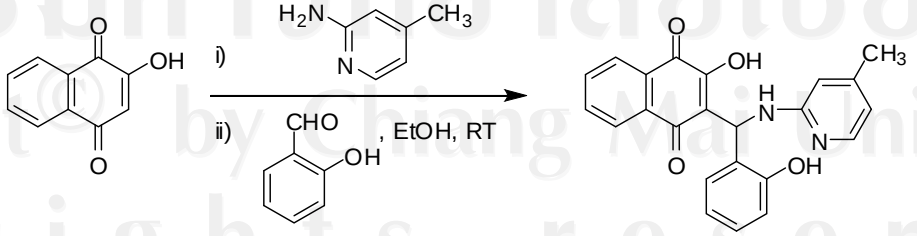


Figure 3.16 ^{1}H NMR spectra of compound **117**

3.1.17. Synthesis of 2-hydroxy-3-((2-hydroxyphenyl)(4-methyl pyridin-2-ylamino)methyl)naphthalene-1,4-dione (118)

The procedure was carried out as described in preparation **2.2.1.1** using 2-hydroxy-1,4-naphthoquinone (153.0 mg, 0.879 mmol) and 4-methyl-2-aminopyridine (104.6 mg, 0.967 mmol) as starting material and salicylaldehyde (0.10 ml, 0.967 mmol) was then added with stirring vigorously. The pure product was obtained as an orange precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **118** (272.9 mg, 80.43 % yield) as orange solids from CH_2Cl_2/hexane, m.p. 170.0-171.3 ^oC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 387.1337 $(M+H)^+$, corresponding to a molecular formula $C_{23}H_{19}N_2O_4$. FT-IR spectrum showed absorption band at ν_{max} 3315 cm^{-1} (O-H and N-H), 3012 cm^{-1} (C-H of aromatic), 2951 cm^{-1}(C-H of CH_3) and 1665 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **118** in DMSO-d_6 showed four signals of aromatic protons of naphthoquinone at δ 7.66 (*t, J* = 8.0 Hz), 7.73 (*t, J* = 8.0 Hz), 7.86 (*d, J* = 7.4 Hz) and 7.94 (*d, J* = 7.8 Hz) ppm. The methyl protons were observed at δ 2.21 (*s*) ppm. The reaction was shown in Scheme 3.18 and ^{1}H-NMR was shown in Figure 3.17. For the reaction mechanism was similar to Scheme 3.2.



7 **118**

Scheme 3.18 Synthesis of compound **118**

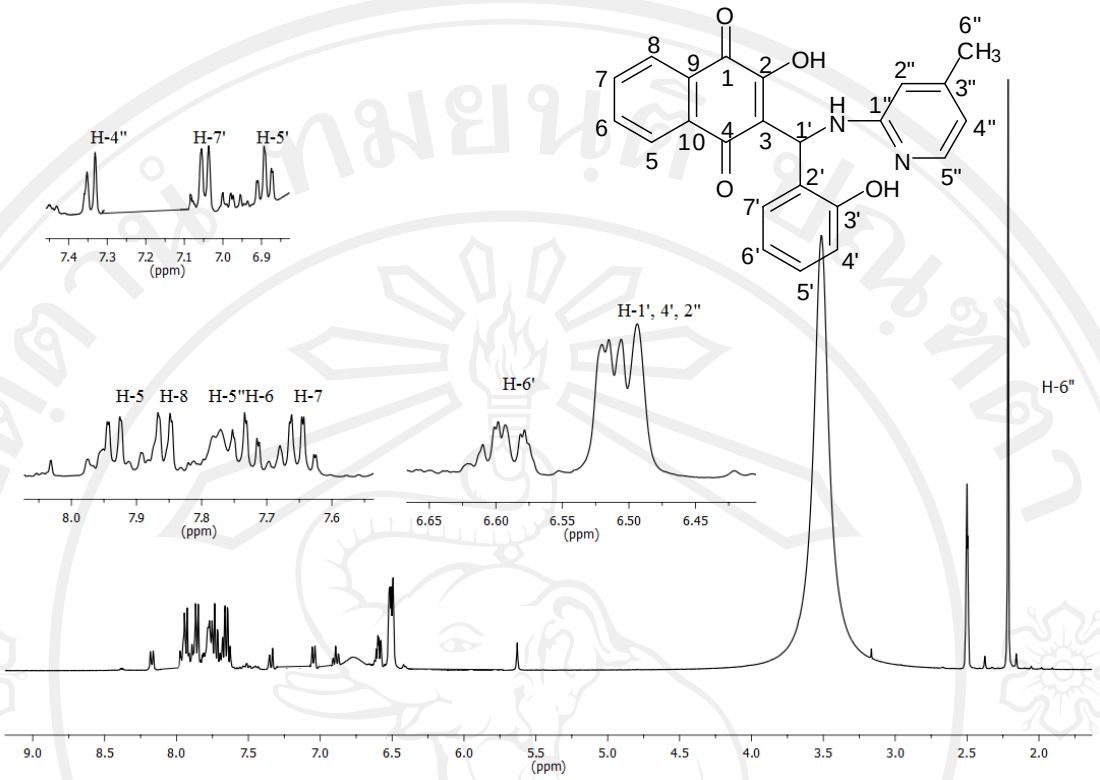
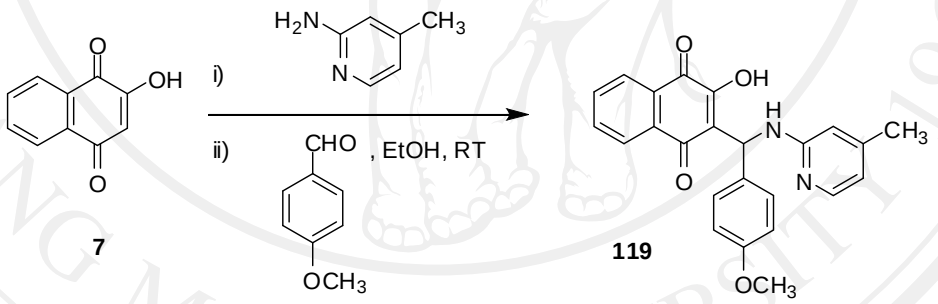


Figure 3.17 ^{1}H NMR spectra of compound **118**

3.1.18. Synthesis of 2-hydroxy-3-((4-methoxyphenyl)(4-methyl pyridin-2-ylamino)methyl)naphthalene-1,4-dione (119)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (153.9 mg, 0.884 mmol) and 4-methyl-2-aminopyridine (105.2 mg, 0.973 mmol) as starting material and *p*-methoxybenzaldehyde (0.12 ml, 0.973 mmol) was then added with stirring vigorously. The pure product was obtained as a red precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **119** (95.3 mg, 26.95 % yield) as red solids from CH_2Cl_2/hexane, m.p. 162.0-164.0 ºC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 401.1502 $(M+H)^+$, corresponding to a molecular formula $C_{24}H_{21}N_2O_4$. FT-IR spectrum showed absorption band at ν_{max} 3397 cm^{-1} (O-H and N-H), 3085 and 3060 cm^{-1} (C-H of aromatic), 2983 and 2952 cm^{-1}(C-H of CH_3) and 1676 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **119** in DMSO-d_6 showed four signals of aromatic protons of naphthoquinone at δ 7.67 (*t*, *J* = 7.4 Hz), 7.76 (*dd*, *J* = 10.5, 6.7 Hz), 7.88 (*d*, *J* = 6.9 Hz) and 7.96 (*d*, *J* = 7.6 Hz) ppm. The signal at δ 3.67 (*s*) ppm was assigned to methoxy group. The methyl protons were observed at δ 2.23 (*s*) ppm. The reaction was shown in Scheme 3.19 and ^{1}H-NMR was shown in Figure 3.18. For the reaction mechanism was similar to Scheme 3.2.



Scheme 3.19 Synthesis of compound **119**

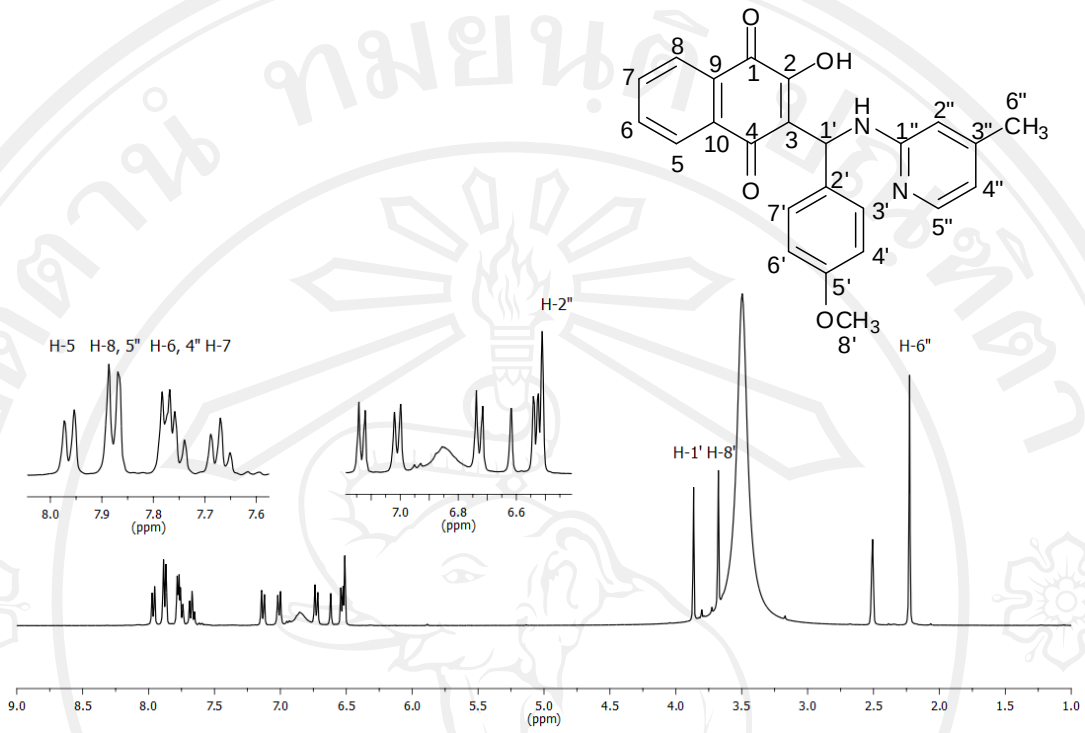
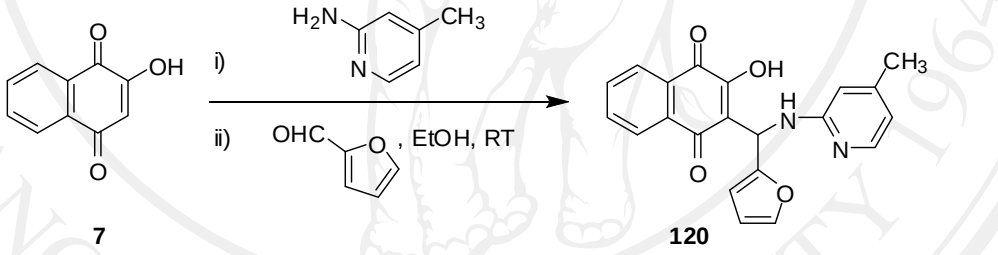


Figure 3.18 ^{1}H NMR spectra of compound **119**

3.1.19. Synthesis of 2-(furan-2-yl(4-methylpyridin-2-ylamino) methyl)-3-hydroxy naphthalene-1,4-dione (120)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (156.8 mg, 0.901 mmol) and 4-methyl-2-aminopyridine (107.2 mg, 0.991 mmol) as starting material and furfuraldehyde (0.08 ml, 0.991 mmol) was then added with stirring vigorously. The pure product was obtained as an orange precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **120** (115.8 mg, 35.70 % yield) as orange solids from CH_2Cl_2/hexane, m.p. 163.0-163.5 ^{o}C.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 361.1184 $(M+H)^+$, corresponding to a molecular formula $C_{21}H_{17}N_2O_4$. FT-IR spectrum showed absorption band at ν_{max} 3432 cm^{-1} (O-H and N-H), 3080 cm^{-1} (C-H of aromatic), 2929 cm^{-1}(C-H of CH_3) and 1674 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **120** in DMSO-d_6 showed four signals of aromatic protons of naphthoquinone at δ 7.67 (*t, J* = 10.7 Hz), 7.73-7.80 (*m*), 7.88 (*d, J* = 7.5 Hz) and 7.96 (*d, J* = 7.6 Hz) ppm. The signals at δ 5.97 (*m*), 6.25 (*m*) and 7.37 (*m*) ppm were assigned to protons of furan. The methyl protons were observed at δ 2.28 (*s*) ppm. The reaction was shown in Scheme 3.20 and ^{1}H-NMR was shown in Figure 3.19. For the reaction mechanism was similar to Scheme 3.2.



Scheme 3.20 Synthesis of compound **120**

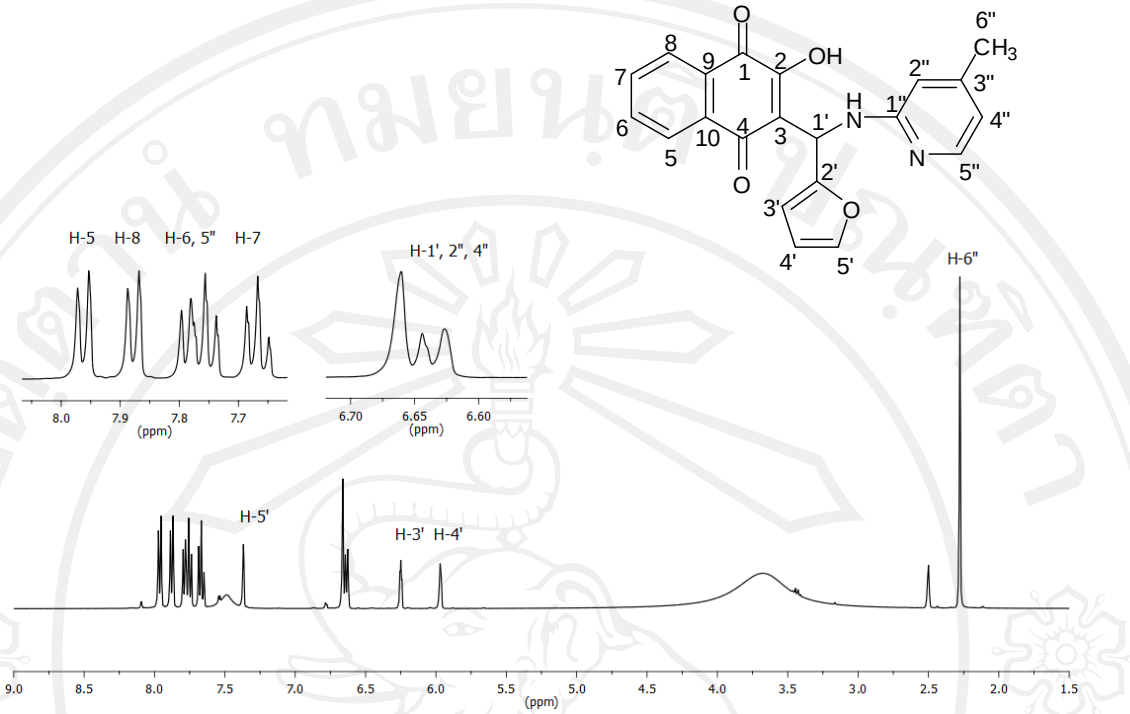


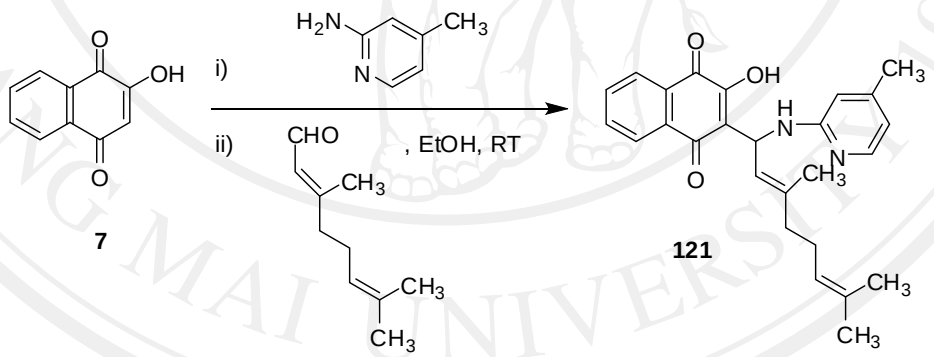
Figure 3.19 ^{1}H NMR spectra of compound **120**

3.1.20. Synthesis of (*E*)-2-(3,7-dimethyl-1-(4-methylpyridin-2-ylamino)octa-2,6-dienyl)-3-hydroxy naphthalene-1,4-dione (121)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (214.3 mg, 1.232 mmol) and 4-methyl-2-aminopyridine (146.5 mg, 1.355 mmol) as starting material and citral (0.23 ml, 1.355 mmol) was then added with stirring vigorously. The pure product was obtained as an orange precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **121** (195.3 mg, 38.15 % yield) as orange solids from CH_2Cl_2/hexane, m.p. 149.2-150.5 ^{o}C.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 417.2179 $(M+H)^+$, corresponding to a molecular formula $C_{26}H_{29}N_2O_3$. FT-IR

spectrum showed absorption band at ν_{max} 3364 cm^{-1} (O-H and N-H), 3187 and 3100 cm^{-1} (C-H of aromatic and double bond), 2963 and 2912 cm^{-1}(C-H of CH_2/CH_3) and 1680 cm^{-1}(C=O). ^{1}H-NMR (400 MHz) spectrum of compound **121** in DMSO-d_6 showed four signals of aromatic protons of naphthoquinone at δ 7.63 (*t*, *J* = 10.7 Hz), 7.72 (*t*, *J* = 7.6 Hz), 7.79-7.85 (*m*) and 7.93 (*d*, *J* = 7.7 Hz) ppm. The signals at δ 4.88-5.10 (*m*), 5.75 (*s*) and 6.02-6.08 (*m*) ppm were assigned to the methane protons at position 6', 1' and 2' respectively. The signal at δ 1.86-2.09 (*m*) ppm was assigned to methylene protons at position 4' and 5'. The protons of three methyl groups in side chain were observed at δ 1.30-1.43 (*m*), 1.43-1.50 (*m*) and 1.51-1.60 (*m*) ppm. The reaction was shown in Scheme 3.21 and ^{1}H-NMR was shown in Figure 3.20. For the reaction mechanism was similar to Scheme 3.2.



Scheme 3.21 Synthesis of compound **121**

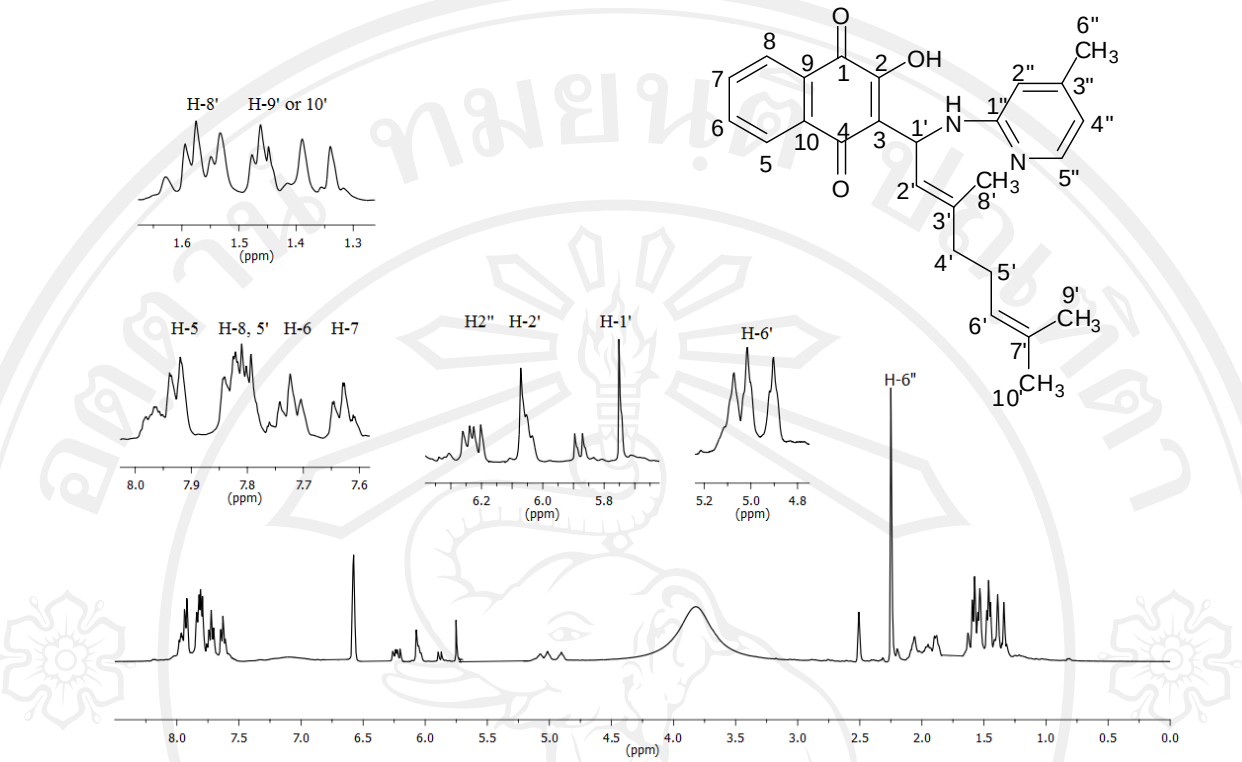
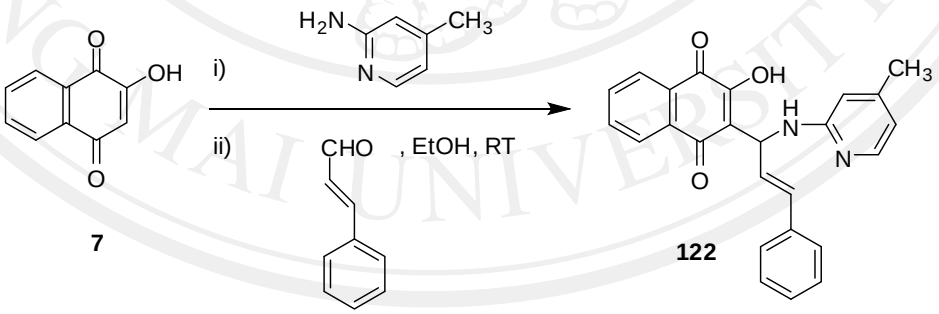


Figure 3.20 ^{1}H NMR spectra of compound **121**

3.1.21. Synthesis of (*E*)-2-hydroxy-3-(1-(4-methylpyridin-2-yl amino)-3-phenylallyl)naphthalene-1,4-dione (122)

The procedure was carried out as described in preparation **3.1.1** using 2-hydroxy-1,4-naphthoquinone (301.6 mg, 1.733 mmol) and 4-methyl-2-aminopyridine (206.2 mg, 1.907 mmol) as starting material and cinnamaldehyde (0.24 ml, 1.907 mmol) was then added with stirring vigorously. The pure product was obtained as an orange precipitale purified by preparative gel filtration chromatography (sephadex LH-20 methanol as eluent) to obtain compound **122** (260.5 mg, 38.01 % yield) as orange solids from CH_2Cl_2/hexane, m.p. 175.5-176.5 ^{o}C.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 397.1559 $(M+H)^+$, corresponding to a molecular formula $C_{25}H_{21}N_2O_3$. FT-IR spectrum showed absorption band at ν_{max} 3397 cm^{-1} (O-H and N-H), 3078 and 3031 cm^{-1} (C-H of aromatic and double bond), 2905 cm^{-1} (C-H of CH_3) and 1669 cm^{-1} (C=O). ^{1}H-NMR (400 MHz) spectrum of compound **122** in DMSO-d_6 showed four signals of aromatic protons of naphthoquinone at δ 7.66 (*t*, *J* = 7.5 Hz), 7.76 (*t* , *J* = 10.7 Hz), 7.88 (*d*, *J* = 7.5 Hz) and 7.95 (*d*, *J* = 7.6 Hz) ppm. The signals at δ 7.14 (*t*, *J* = 7.2 Hz), 7.24 (*t*, *J* = 7.6 Hz) and 7.32 (*d* (*J* = 7.6 Hz) ppm were assigned to aromatic protons at side chain. The signal at δ 1.86-2.09 (*m*) ppm was assigned to methylene protons at position 4' and 5'. The signals of two methine protons in side chain were observed at δ 6.29 (*dd*, *J* = 16.0, 1.5 Hz) and 6.65-6.73 (*m*) ppm. The reaction was shown in Scheme 3.22 and ^{1}H-NMR was shown in Figure 3.21. For the reaction mechanism was similar to Scheme 3.2.



Scheme 3.22 Synthesis of compound **122**

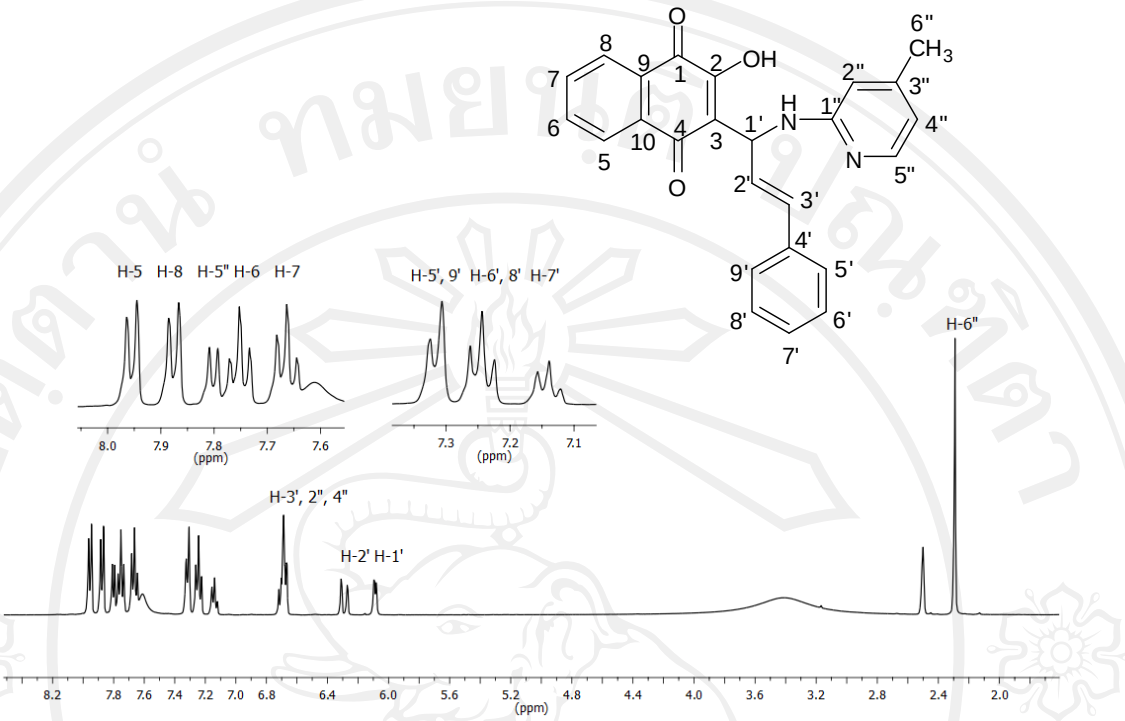
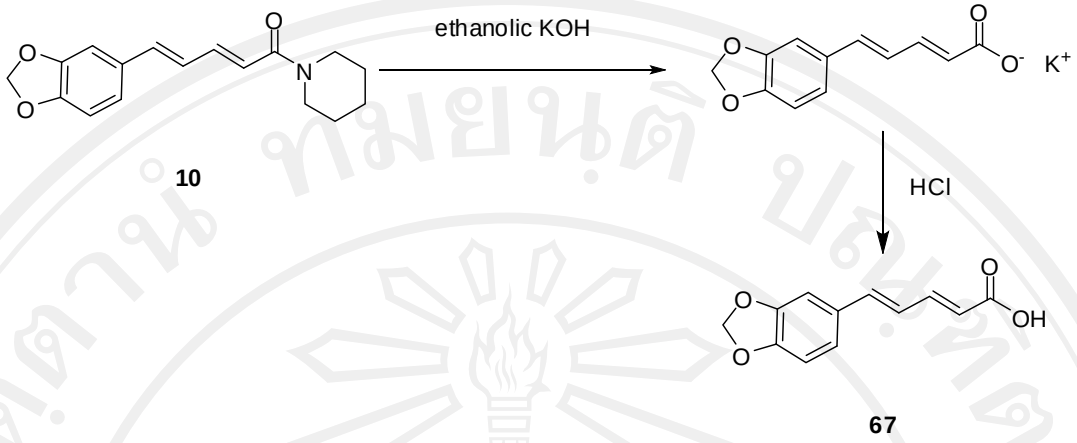


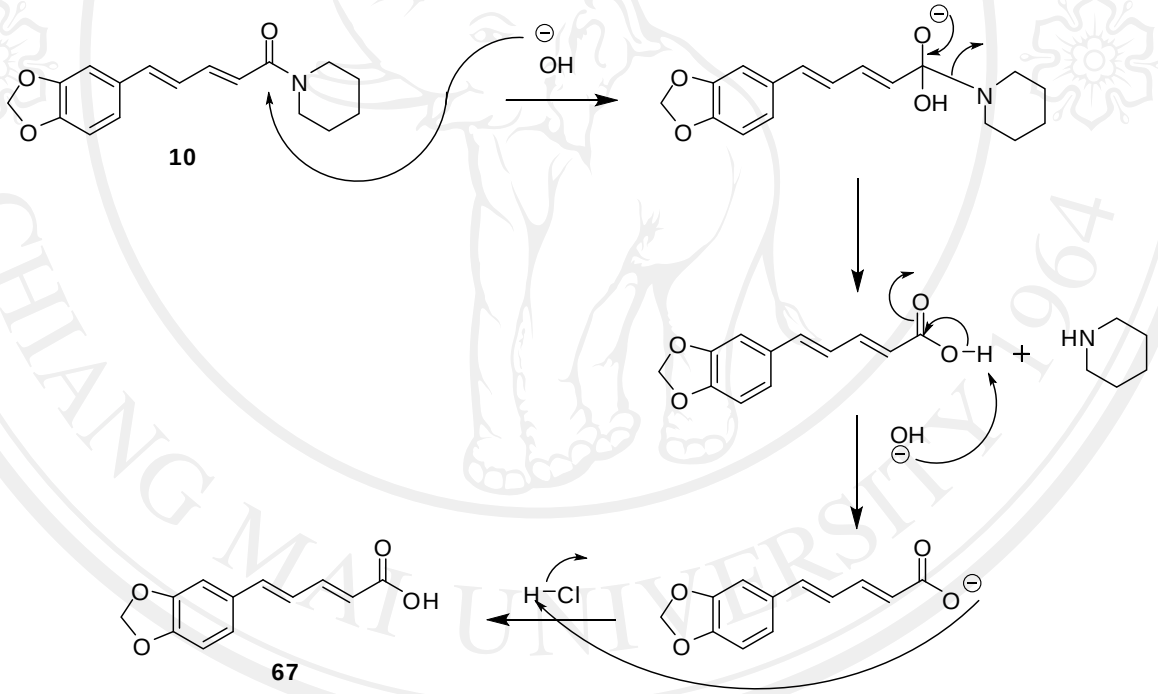
Figure 3.21 ^{1}H NMR spectra of compound **122**

3.2. General procedure for preparation of 5-(3,4-methylenedioxyphenyl)-2*E*,4*E*-pentadienoic acid (piperic acid) (67) from piperine (10)[48-50]

Piperine (2.8536 g, 10 mmol) was refluxed with ethanolic KOH (2 N, 10 ml) for 25 h. Ethanol was removed off by rotary evaporator to obtain the solid potassium salt of piperic acid, then follow by dissolved in hot water 50 ml, acidified with 35 % HCl to give the yellow precipitate and recrystallization with ethanol to obtain piperic acid (**67**) in 98.98 % yield as yellow solids. The reaction conditions for alkaline hydrolysis of piperic acid from piperine as shown in scheme 3.23. The reaction mechanism for preparation of piperic acid (**67**) from piperine (**10**) by addition of hydroxide ion to the carbonyl group of piperine (**10**), followed by elimination of the piperidine, after that abstraction of a proton from hydrochloric acid to obtain piperic acid (**67**), as shown in Scheme 3.24.[48]



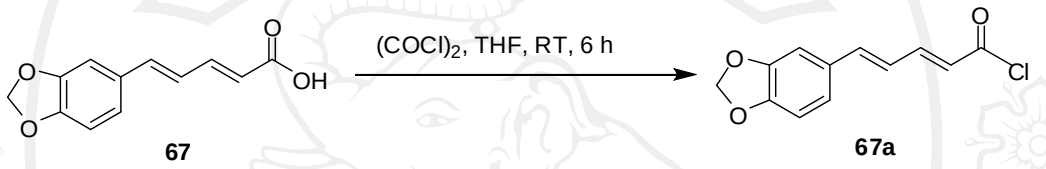
Scheme 3.23 Hydrolysis of piperic acid **67**



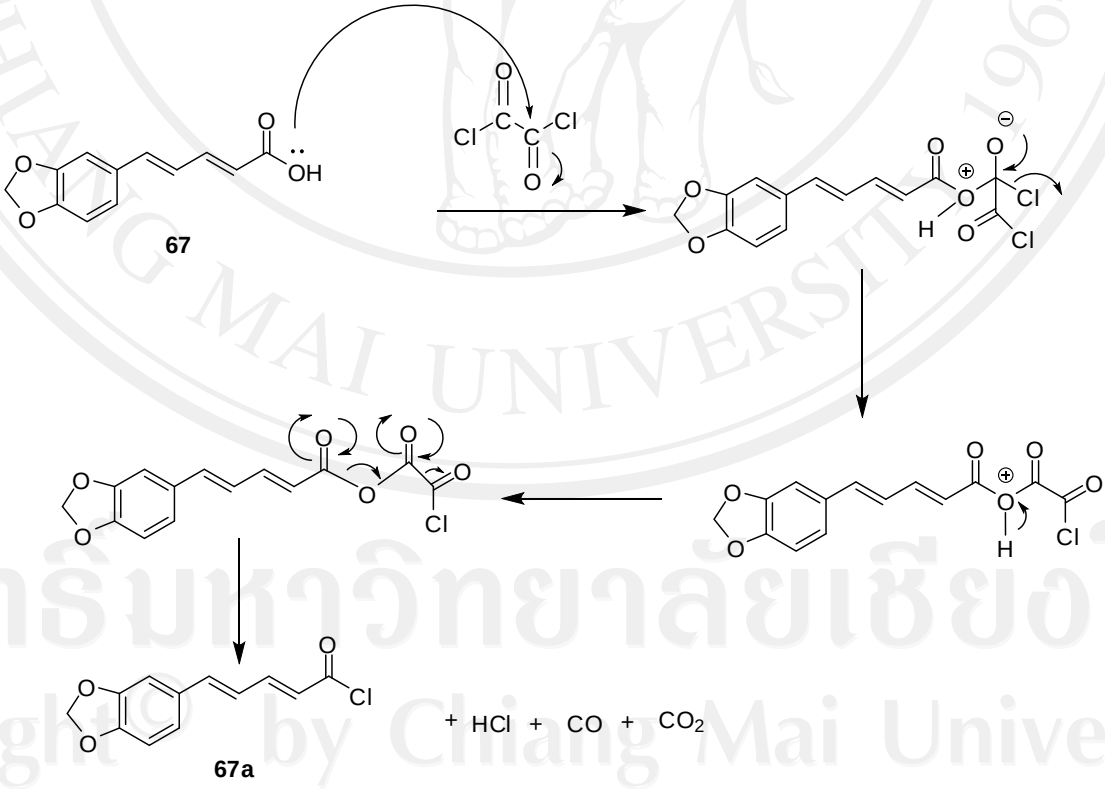
Scheme 3.24 Mechanism of piperic acid **67** from piperine **10**

Piperic acid (**67**) was dissolved in dried THF and kept under nitrogen atmosphere. Oxalyl chloride was added dropwise into the solution. The reaction mixture was stirred at room temperature for 6 h. Then, the excess oxalyl chloride was removed under reduced pressure to give acid chloride as an orange residue.

The purpose mechanism for preparation of piperic acid chloride (**67a**) from piperic acid (**67**) by addition of hydroxide ion of piperic acid (**67**) to the carbonyl group of oxalyl chloride, followed by elimination of chloride ion to obtain the intermediate, then elimination of carbon monoxide and carbon dioxide to obtain piperic acid chloride (**67a**). The preparation and reaction mechanism of piperic acid chloride were shown in Scheme 3.25 and 3.26 respectively.[48-51]



Scheme 3.25 Preparation of piperic acid chloride **67a**



Scheme 3.26 Mechanism of piperic acid chloride **67a**

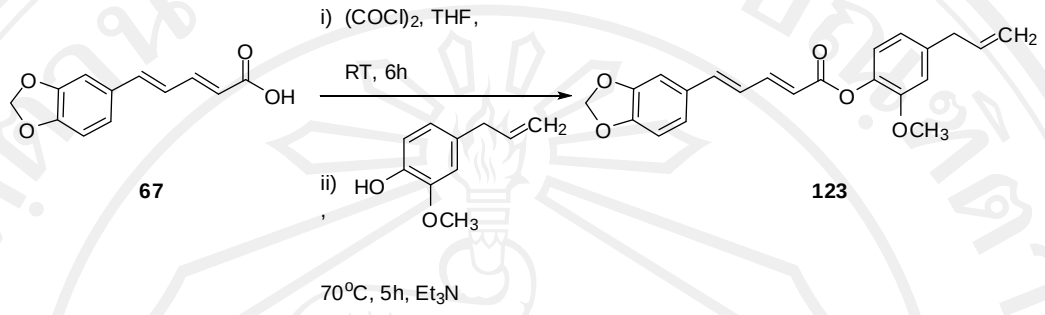
3.3. Synthesis of amides and ester derivatives of piperine (123-126)

3.3.1. Synthesis of (2*E*,4*E*)-4-allyl-2-methoxyphenyl-5-(benzo[*d*][1,3]dioxol-5-yl)penta-2,4-dienoate (123)

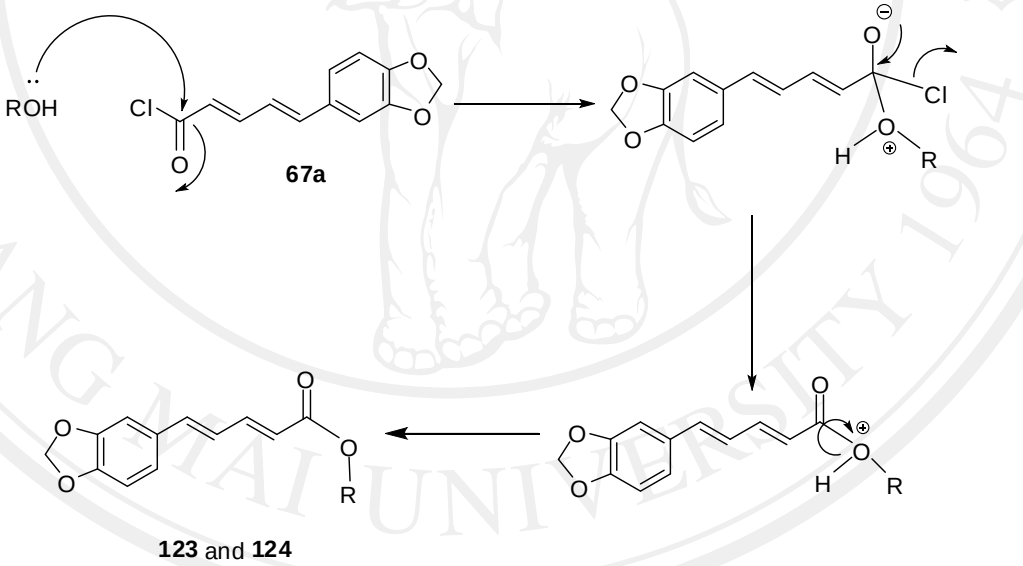
To a solution of piperic acid (0.5026 g, 2.3 mmol) in dried THF (4 ml) at room temperature under nitrogen atmosphere was added oxalyl chloride (1 ml, 11.5 mmol) and stirred at room temperature for 6 h. The reaction mixture was evaporated to give the crude piperic acid chloride as an orange residue. To the crude piperic acid chloride in dried THF (4 ml), was added the eugenol (0.35 ml, 2.3 mmol) in dried THF (3 ml) followed by triethylamine (0.48 ml, 3.5 mmol) and stirred at 70 ºC for 5 h. The reaction mixture was evaporated to give the yellow crude product and then purified by preparative thin layer column chromatography (silica gel; ethyl acetate in hexane, 1:4, as eluent) to obtain compound **123** (0.6393 g, 76.20 % yield) as yellow solids from CH_2Cl_2/hexane, m.p. 137.0-138.5 ºC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 387.1208 $(M+Na)^+$, corresponding to a molecular formula $C_{22}H_{20}O_5Na$. FT-IR spectrum showed absorption band at ν_{max} 3085 and 3010 cm^{-1} (C-H of aromatic and double bond), 2937 cm^{-1} (C-H of CH_3) and 1736 cm^{-1} (C=O). ^{1}H-NMR (400 MHz) spectrum of compound **123** in $CDCl_3$ showed signals of aromatic protons of piperine at δ 6.77-6.84 (*m*), 6.96 (*d*, *J* = 8.1 Hz) and 7.05 (*s*) ppm. The signals at δ 6.77-6.84 (*m*), 7.03 (*d*, *J* = 7.9 Hz) and 7.62 (*dd*, *J* = 15.2, 10.7 Hz) ppm were assigned to methine protons. The signals of two methylene protons at position 9' and 12 were observed at δ 5.08-5.20 (*m*) and 6.02 (*s*) ppm respectively. The signal at δ 3.84 (*s*) ppm was assigned to methoxy protons. The reaction and mechanism

were shown in Scheme 3.27 and 3.28 respectively and ^{1}H-NMR was shown in Figure 3.22.



Scheme 3.27 Synthesis of compound **123**



Scheme 3.28 Mechanism of compound **123** and **124**

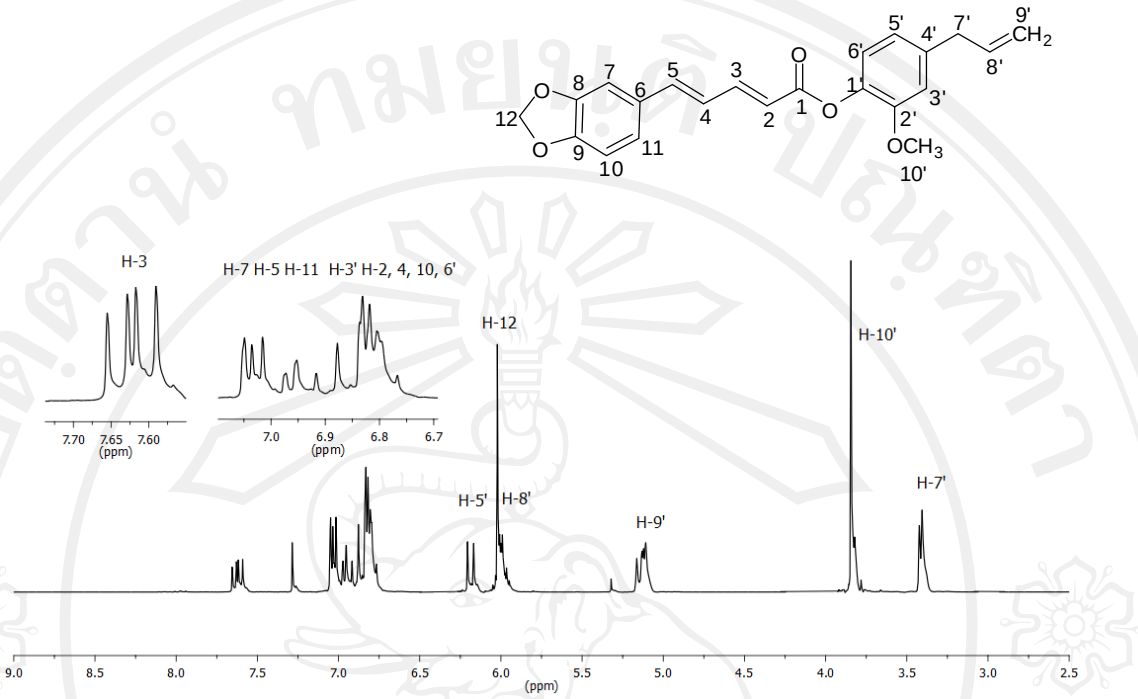
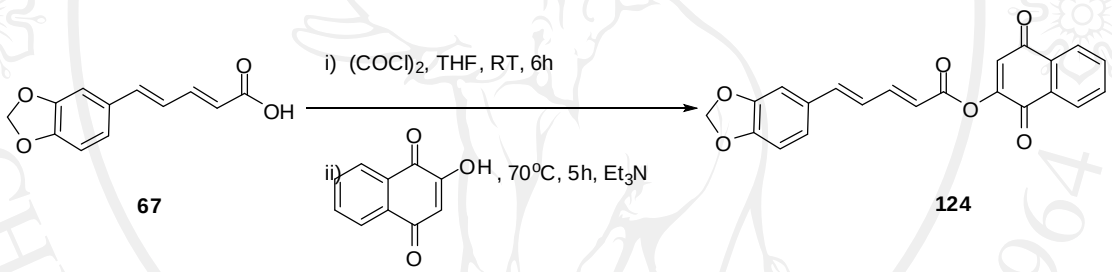


Figure 3.22 ^{1}H NMR spectra of compound **123**

3.3.2. Synthesis of (2*E*,4*E*)-1,4-dioxo-1,4-dihydronaphthalen-2-yl-5(benzo[*d*][1,3]dioxol-5-yl)penta-2,4-dienoate (124)

The procedure was carried out as described in preparation **3.3.1** a solution of piperic acid (0.0205 g, 0.940 mmol) was added oxalyl chloride (0.40 ml, 4.70 mmol) and stirred at room temperature for 6 h. and was added the solution of 2-hydroxy-1,4-naphthoquinone (0.0163 g, 0.940 mmol) in followed by triethylamine (0.19 ml, 1.41 mmol). The reaction mixture was evaporated to give the orange crude product and then purified by preparative thin layer column chromatography (silica gel; ethyl acetate in hexane, 1:4, as eluent) to obtain compound **124** (0.2013 g, 57.26 % yield) as light orange solids from CH_2Cl_2/hexane, m.p. 208.0-209.4 ºC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 397.0705 $(M+Na)^+$, corresponding to a molecular formula $C_{22}H_{14}O_6Na$. FT-IR spectrum showed absorption band at ν_{max} 3029 cm^{-1} (C-H of aromatic and double bond), 2948 cm^{-1} (C-H of CH_2) and 1742 cm^{-1} (C=O). ^{1}H-NMR (400 MHz) spectrum of compound **124** in DMSO-d_6 showed signals of aromatic protons of naphthoquinone at δ 7.90-7.95 (*m*) and 8.02-8.07 (*m*) ppm. The signal at δ 6.08 (*s*) ppm was assigned to methylene protons. The reaction and mechanism were shown in Scheme 3.29 and 3.28 respectively and ^{1}H-NMR was shown in Figure 3.23.



Scheme 3.29 Synthesis of compound **124**

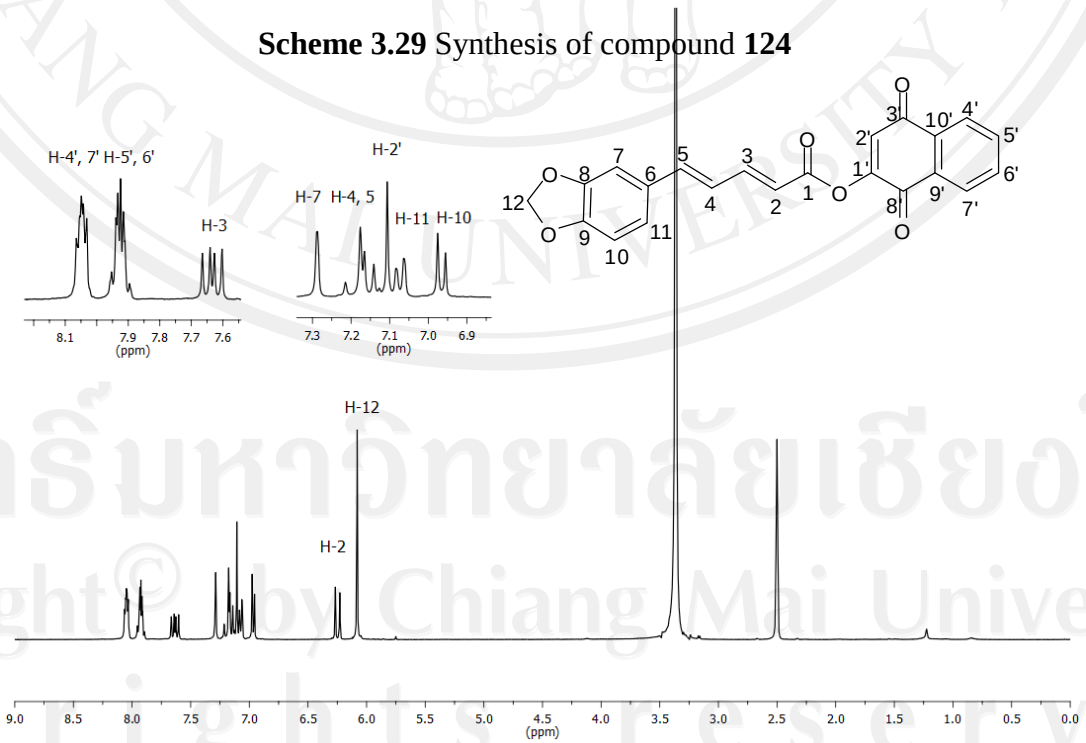
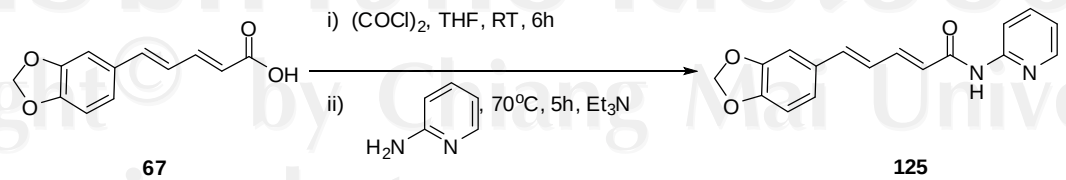


Figure 3.23 ^{1}H NMR spectra of compound **124**

3.3.3. Synthesis of (2*E*,4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)-*N*-(pyridin-2-yl)penta-2,4-dienamide (125)

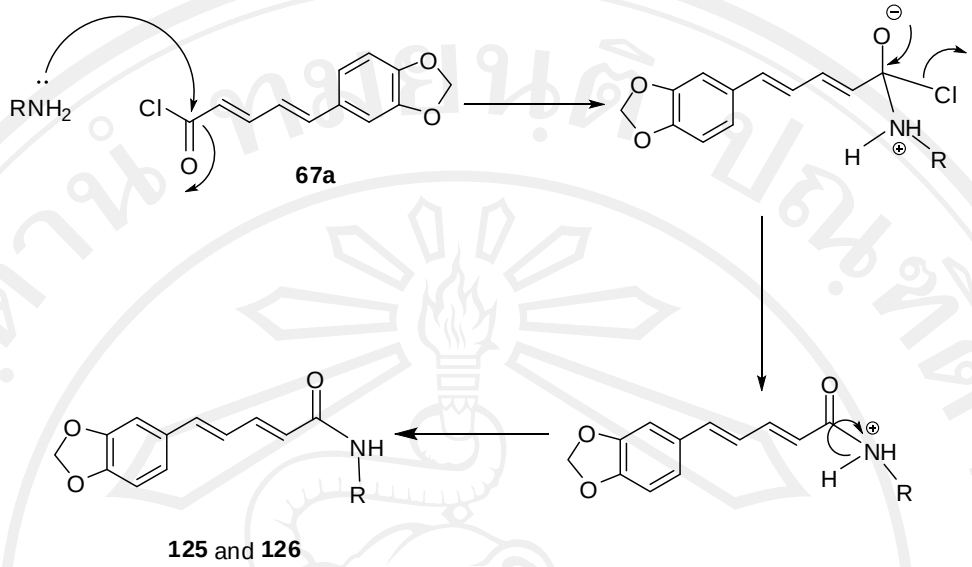
The procedure was carried out as described in preparation **3.3.1** a solution of piperic acid (0.2045 g, 0.938 mmol) was added oxalyl chloride (0.41 ml, 4.69 mmol) and stirred at room temperature for 6 h. and was added the solution of 2-aminopyridine (0.1424 g, 0.938 mmol) followed by triethylamine (0.20 ml, 1.40 mmol). The reaction mixture was evaporated to give the yellow crude product and then purified by preparative thin layer column chromatography (silica gel; ethyl acetate in hexane, 2:3, as eluent) to obtain compound **125** (0.0694 g, 25.17 % yield) as yellow solids from CH_2Cl_2/hexane, m.p. 185.0-186.5 ºC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 295.1080 $(M+H)^+$, corresponding to a molecular formula $C_{17}H_{15}N_2O_3$. FT-IR spectrum showed absorption band at ν_{max} 3370 cm^{-1} (N-H), 3010 cm^{-1} (C-H of aromatic and double bond), 2982 cm^{-1} (C-H of CH_2) and 1774 cm^{-1} (C=O). ^{1}H-NMR (400 MHz) spectrum of compound **125** in $CDCl_3$ showed four signals of aromatic protons of pyridine at δ 6.09 (*d*, *J* = 14.8 Hz), 7.73 (*t*, *J* = 7.0 Hz), 8.29 (*d*, *J* = 4.8 Hz) and 8.35 (*d*, *J* = 8.3 Hz) ppm. The signal at δ 5.98 (*s*) ppm was assigned to methylene protons. The reaction and mechanism were shown in Scheme 3.30 and 3.31 respectively and ^{1}H-NMR was shown in Figure 3.24.



67 **125**

Scheme 3.30 Synthesis of compound **125**



Scheme 3.31 Mechanism of compound **125** and **126**

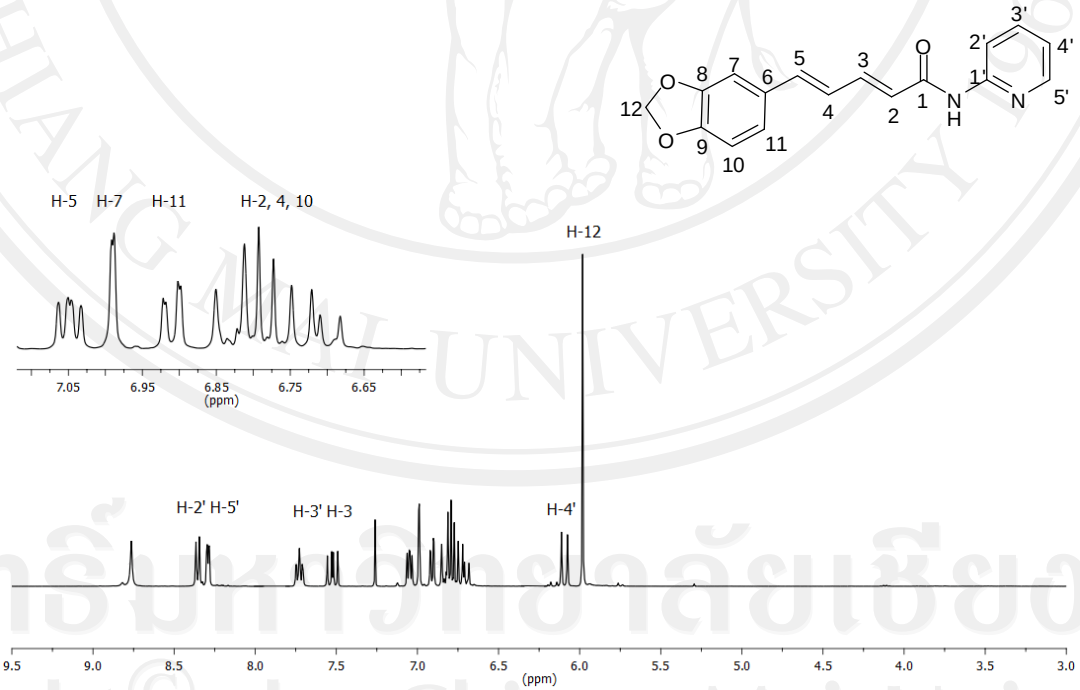
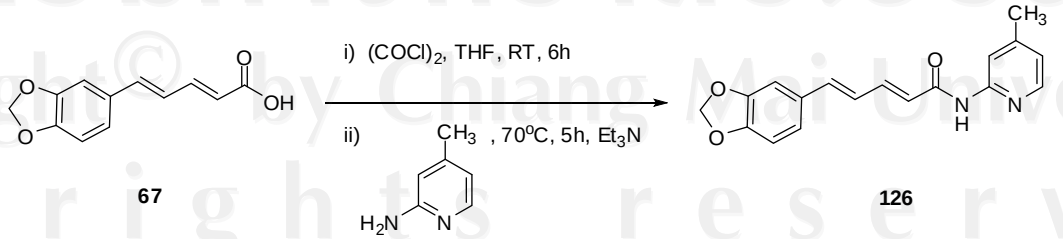


Figure 3.24 ^{1}H NMR spectra of compound **125**

3.3.4. Synthesis of (2*E*,4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)-4-methy-*N*-(pyridin-2-yl)penta-2,4-dienamide (126)

The procedure was carried out as described in preparation **3.3.1** a solution of piperic acid (0.2051 g, 0.941 mmol) was added oxalyl chloride (0.41 ml, 4.70 mmol) and stirred at room temperature for 6 h. and was added the solution of 4-methyl-2-aminopyridine (0.1017 g, 0.941 mmol) followed by triethylamine (0.20 ml, 1.40 mmol). The reaction mixture was evaporated to give the yellow crude product and then purified by preparative thin layer column chromatography (silica gel; ethyl acetate in hexane, 2:1, as eluent) to obtain compound **126** (0.0971 g, 33.50 % yield) as yellow solids from CH_2Cl_2/hexane, m.p. 177.0-178.5 ºC.

The HRMS analysis of this compound showed molecular ion adduct peak at m/z 309.1236 $(M+H)^+$, corresponding to a molecular formula $C_{18}H_{17}N_2O_3$. FT-IR spectrum showed absorption band at ν_{max} 3488 cm^{-1} (N-H), 3036 cm^{-1} (C-H of aromatic and double bond), 2896 cm^{-1} (C-H of CH_2) and 1716 cm^{-1} (C=O). ^{1}H-NMR (400 MHz) spectrum of compound **126** in $CDCl_3$ showed three signals of aromatic protons of pyridine at δ 6.08 (*d*, *J* = 14.8 Hz), 8.13 (*d*, *J* = 5.1 Hz) and 8.19 (*s*) ppm. The signal at δ 5.98 (*s*) ppm was assigned to methylene protons. The protons of methyl group were observed at δ 2.38 (*s*) ppm. The reaction and mechanism were shown in Scheme 3.32 and 3.31 respectively and ^{1}H-NMR was shown in Figure 3.25.



Scheme 3.32 Synthesis of compound **126**

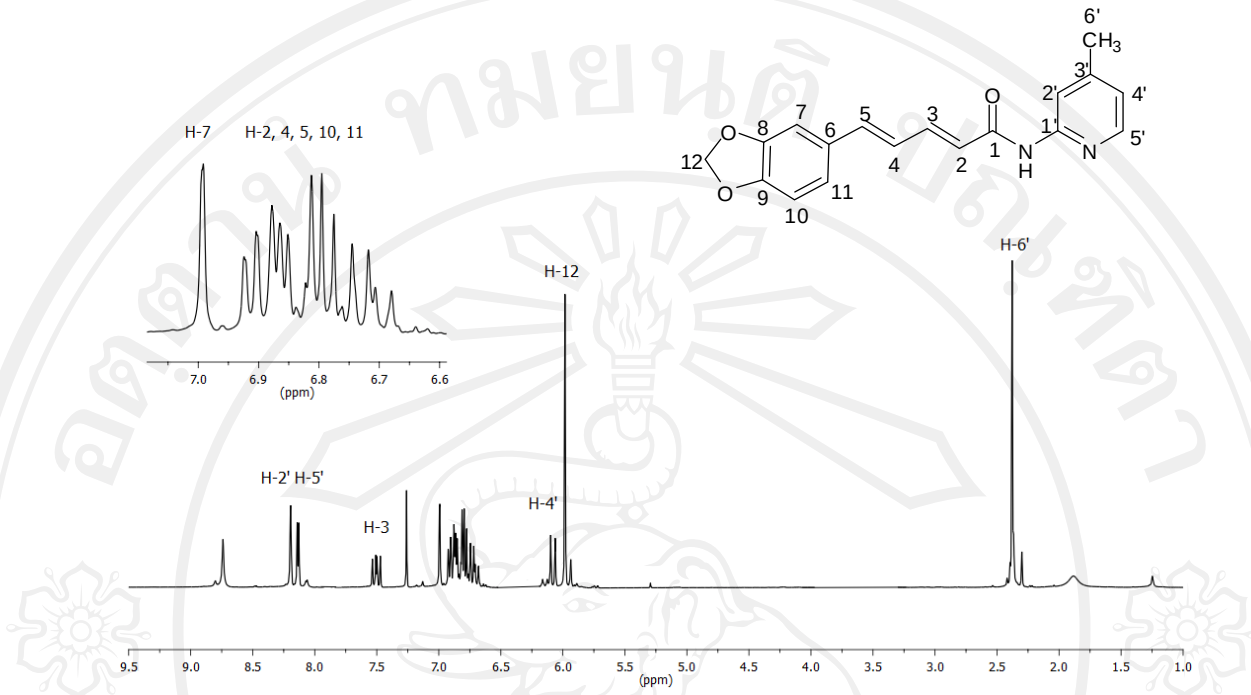


Figure 3.25 ^{1}H NMR spectra of compound **126**

3.4 Biological activities test

All of synthesized compounds were evaluated for in *vitro* anti-malaria, anti-*Mycobacterial tuberculosis* (Anti-TB), anti-cancer cell lines at National Center for Genetic Engineering and Biotechnology (BIOTEC) and antioxidant activities. For anti-malaria assay all of compounds were evaluated against *Plasmodium falciparum* the results showed that compounds **102**, **103**, **104**, **105**, **106**, **107**, **108**, **109**, **115**, **112**, **122** and **124** showed IC_{50} values of 0.77, 1.47, 3.21, 4.05, 3.28, 1.63, 3.49, 3.14, 3.92, 1.83, 3.15 and 7.79 µg/mL respectively, but from the results have five compounds **102**, **103**, **109**, **122** and **124** showed strong anti-malaria activity with IC_{50} values of 0.77, 1.47, 3.14, 3.15 and 7.79 µg/mL respectively and displayed non-cytotoxic. For the anti-*Mycobacterial tuberculosis* assay resulting that compounds **108**, **110**, **113**, **115**, **118**, **121** and **122** showed the MIC values of 25.00 and 50.00 µg/mL and was found that only compound **122** have the MIC value at 25.00 µg/mL and displayed non-cytotoxic. For tested *in vitro* cytotoxic activity against of breast cancer and lung cancer cell lines were found that compounds **106**, **107**, **108**, **113**, **114** and **124** showed the great IC_{50} values of 9.70, 6.34, 8.40, 8.93, 8.84 and 3.84 µg/mL respectively, but have only compound **124** exhibited anti-breast cancer with IC_{50} value of 3.84 µg/mL and displayed non-cytotoxic. For lung cancer cell lines twenty-three compounds were tested and the results showed that compounds **102**, **105**, **106**, **108**, **110**, **113**, **114**, **115**, **118**, **119**, **122** and **124** exhibited the good activity with the IC_{50} values of 7.94, 8.03, 3.96, 4.94, 4.24, 2.27, 9.24, 9.81, 5.95, 9.46, 9.22 and 2.24 µg/mL respectively, although five compounds **102**, **114**, **119**, **122** and **124** showed IC_{50} values of 7.94, 9.24, 9.46, 9.22 and 2.24 µg/mL with exhibited non-cytotoxicity. All of compounds were

evaluated for antioxidant activity by DPPH radical scavenging assay. The results showed that compounds **102**, **103**, **117**, **119**, **122**, **124** and **126** exhibited high antioxidant activity with IC_{50} values of 0.295, 0.175, 0.209, 0.281, 0.185, 0.223 and 0.326 mg/mL respectively and displayed non-cytotoxicity. The data of biological activities were shown in table 29, 30 and 31 respectively.

Table 29. Anti-malaria, anti-TB and cytotoxicity of compounds

Compounds	Anti-TB MIC (µg/mL)	Anti-malaria IC_{50} (µg/mL)	Cytotoxicity (*Vero cell*) IC_{50} (µg/mL)
102	inactive	0.77	non-cytotoxic
103	inactive	1.47	non-cytotoxic
104	inactive	3.21	26.30
105	inactive	4.05	12.11
106	inactive	3.28	8.13
107	inactive	1.63	8.78
108	25.00	3.49	7.03
109	inactive	3.14	non-cytotoxic
110	25.00	inactive	7.57
111	inactive	inactive	non-cytotoxic
112	inactive	inactive	non-cytotoxic
113	50.00	inactive	20.64
114	inactive	inactive	non-cytotoxic
115	50.00	3.92	8.50
116	inactive	inactive	non-cytotoxic
117	inactive	inactive	non-cytotoxic
118	25.00	inactive	16.49
119	inactive	inactive	non-cytotoxic
120	inactive	inactive	49.63
121	25.00	1.83	11.45

Table 29. Anti-malaria, anti-TB and cytotoxicity of compounds (continued)

Compounds	Anti-TB MIC (µg/mL)	Anti-malaria IC_{50} (µg/mL)	Cytotoxicity (*Vero cell*) IC_{50} (µg/mL)
122	25.00	3.15	non-cytotoxic
123	inactive	inactive	non-cytotoxic
124	inactive	7.79	non-cytotoxic
125	inactive	inactive	non-cytotoxic
126	inactive	inactive	non-cytotoxic
Rifampicina	0.003-0.012	-	-
Streptomycina	0.156-0.313	-	-
Isoniazida	0.023-0.046	-	-
Ofloxacina	0.391-0.781	-	-
Dihydroartemisinine	-	0.00153	-
Mefloquine	-	0.034	-
Ellipticine	-	-	1.671

(-) Not determined

Table 30. Anti-cancer (breast cancer MCF-7 and lung cancer cell lines NCI-H187) and cytotoxicity of compounds

Compounds	Cytotoxicity (IC_{50} µg/mL)		
	MCF-7	NCI-H187	*Vero cell*
102	inactive	7.94	non-cytotoxic
103	inactive	inactive	non-cytotoxic
104	inactive	30.87	26.30
105	18.24	8.03	12.11
106	9.70	3.96	8.13
107	6.34	11.14	8.78
108	8.40	4.94	7.03
109	24.28	17.27	non-cytotoxic
110	28.49	4.24	7.57
111	25.51	17.88	non-cytotoxic
112	inactive	13.70	non-cytotoxic
113	8.93	2.27	20.64
114	8.84	9.24	non-cytotoxic
115	17.72	9.81	8.50
116	inactive	21.39	non-cytotoxic
117	inactive	25.79	non-cytotoxic
118	10.67	5.95	16.49
119	inactive	9.46	non-cytotoxic
120	inactive	12.10	49.63
121	14.17	13.04	11.45
122	41.81	9.22	non-cytotoxic
123	inactive	inactive	non-cytotoxic
124	3.84	2.24	non-cytotoxic
125	36.92	NT	non-cytotoxic
126	inactive	NT	non-cytotoxic
Ellipticine	-	0.441 ± 0.195	1.671
Doxorubicin	1.29	0.094 ± 0.032	-

NT Not tested

(-) Not determined

Table 31. Antioxidant activity

Compounds	IC_{50} (mg/mL)
102	0.295
103	0.175
104	0.362
105	0.533
106	2.282
107	0.728
108	1.038
109	2.605
110	0.495
111	27.952
112	inactive
113	0.926
114	34.862
115	1.671
116	1.257
117	0.209
118	1.130
119	0.281
120	2.706
121	0.693
122	0.185
123	11.739
124	0.223
125	inactive
126	0.326
Vitamin C	0.002
Trolox	0.0022