SYNTHESIS AND STRUCTURAL DETERMINATION OF PYRROLIDINE-2,3-DIONE DERIVATIVES FROM 4-ACETYL-3-HYDROXY-5-PHENYL-1-(3-NITROPHENYL)-3-PYRROLINE-2-ONE

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Abstract - Numerous heterocyclic compounds containing 3-pyrroline-2-one or pyrrolidine-2,3-dione core have been found in nature and showed valuable biological activities. Therefore, the synthesis of 3-pyrroline-2-one derivatives and pyrrolidine-2,3-dione derivatives have attracted more and more attention from organic chemists and medicinal chemists. In this manuscript, 4-acetyl-3-hydroxy-1-(3-nitrophenyl)-5-phenyl-3-pyrroline-2-one has been prepared *via* three-component reaction and, besides, two 1,4,5-trisubstituted pyrrolidine-2,3-diones have also been synthesized *via* the reaction between the above 3-pyrroline-2-one derivative and aliphatic amine such as methylamine and 4-methoxybenzylamine. The structure of desired products have been confirmed *via* 1D NMR (^{1}H NMR, ^{13}C NMR), 2D NMR (HSQC, HMBC) and high resolution mass spectrometry (ESI – HRMS).

Key words - 2-pyrrolidinone; 3-pyrrolin-2-one; 1,4,5-trisubstituted pyrrolidine-2,3-dione; 1,5-dihydro-2H-pyrrol-2-one; multi-component reaction

1. Introduction

It is clear that nitrogen-containing heterocyclic compounds always play an important role in drug discovery [1], [2]. Heterocyclic compounds containing 2-pyrrolidinone core have attracted more and more attention due to their existence in various natural and non-natural biologically active compounds. For instance, Salinosporamide A (1) is a marine natural product produced by bacteria *Salinispora tropica* and *Salinispora arenicola* [3]. Flavoalkaloid with 2-pyrrolidinone ring (2) isolated from Xi-Gui green tea and showed protective effect against the senescence induced by high dose glucose on the HUVECs at 1.0 and 10 μM [4]. Non-natural macrocycle containing 2-pyrrolidinone moiety (3) exhibited strong Tyk2 inhibitory activity, along with excellent selectivity over the Jak family kinases (Figure 1) [5].

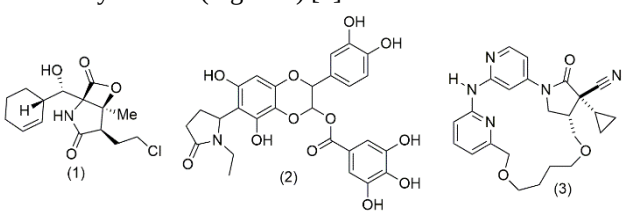

Figure 1. *Biologically active natural and non-natural compounds with 2-pyrrolidinone core*

Within the family of 2-pyrrolidinone derivatives, 1,5-dihydro-2*H*-pyrrol-2-ones, also named as 3-pyrroline-2-one, could be further modified and therefore, they are valuable building blocks in organic synthesis [6]. In addition, the structure of these unsaturated γ-lactam derivatives also occurs in numerous biologically active natural product. For example, oteromycin (4) has been isolated from fungus strains MF5810 an MF5811 which exhibited activity as a HIV-1 integrase inhibitor [7]. Equisetin (5) was isolated from the fungus Fusarium pallidoroseum which shows a very broad range of biological activities [8]. Cryptocin (6), derived from the endophytic fungus Cryptosporiopsis cf. quercina, is inactive against human pathogenic fungi but active against numerous plant pathogenic ones (Figure 2) [9]. Moreover, 1,5-dihydro-2*H*-pyrrol-2-one is also a key structural scaffold which could be found in many synthetic bioactive compounds [10].

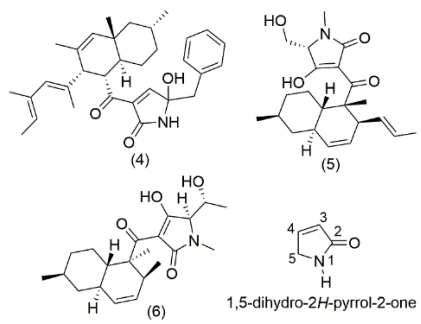

Figure 2. *Naturally occurring 1,5-dihydro-2H-pyrrol-2-ones derived from fungi*

One of the most common methodologies for the construction of the skeleton of substituted 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones is based on one-pot multi-component reactions of aromatic aldehydes, arylamines and acetylenedicarboxylate in the presence of an acid catalyst [11], [12], [13], [14]. However, 3-pyrroline-2-one derivatives obtained from this method contain alkoxycarbonyl group (−COOR) at the 4-position and therefore, these nitrogen-containing five-membered rings could only be functionalized with nucleophilic amine at the 3-position. The resulting compounds exist predominantly in the enamine form due to resonance stabilization *via* intramolecular hydrogen bonding (Figure 3) [15].

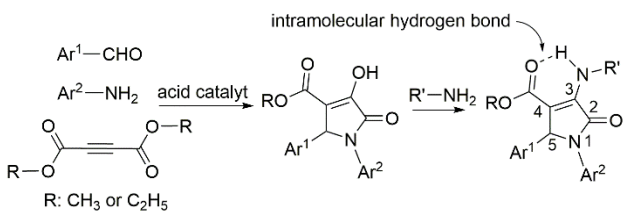

Figure 3. *Synthesis of substituted 3-hydroxy-1,5-dihydro-2H-pyrrol-2-ones based on three-component reaction and their reaction with amine (R'NH$_2$)*

In addition to alkoxycarbonyl group (−COOR), acetyl group (−$COCH_3$) could also be attached to the 4-position of the 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones to obtain 4-acetyl-3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones [16]. In this manuscript, the synthesis of 4-acetyl-3-hydroxy-1-(3-nitrophenyl)-5-phenyl-3-pyrroline-2-one *via* three-component reaction will be reported. Moreover, two pyrrolidine-2,3-dione derivatives have been synthesized *via* the reaction between 4-acetyl-3-hydroxy-1-(3-nitrophenyl)-5-phenyl-3-pyrroline-2-one and aliphatic amines in ethanol solvent. The structure of all products will be elucidated *via* modern spectroscopic methods.

2. Experimental section

2.1. General experimental methods

Bruker Avance II+ 600 MHz spectrometers, and chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (TMS) or the internal (NMR) solvent signals. High resolution mass spectra (HRMS) were recorded with SCIEX X500 QTOF instrument in which electrospray ionization (ESI) source in a positive mode was applied. The temperature of the source was set at 300°C. Curtain gas (25 psi) chambers were filled with high-purity nitrogen. The capillary voltage was constantly kept at 5500V. Collision energies was set at 10 V and zero collision energy spread. IDA mode was used to find mass in range 100 to 1000 amu. Melting points (not corrected) were determined with a Büchi Melting Point B-545 apparatus. For column chromatography, 70–230 mesh silica 60 was used as the stationary phase. Chemicals received from commercial sources were used without further purification.

2.2. Procedure for synthesis of 4-acetyl-3-hydroxy-1-(3-nitrophenyl)-5-phenyl-3-pyrroline-2-one [17]

Benzaldehyde (0.075 mL, 1.5 equiv., 0.75 mmol), 3-nitroaniline (69.0 mg, 1.0 equiv., 0.5 mmol) and glacial acetic acid (1.0 mL) were added to a round-bottom flask of 10 mL. The resulting mixture was magnetically stirred under Ar atmosphere for 1 hour. Subsequently, ethyl 2,4-dioxovalerate (0.07 mL, 1.0 equiv., 0.5 mmol) was added and the reaction was carried out at room temperature for 4 hours under Ar atmosphere. The crude product was recrystallized in the solvent mixture of dichloromethane and ethylacetate, dichloromethane was then evaporated on rotary evaporator to obtain pure product (76.5 mg, 45.1%) as off-white solid.

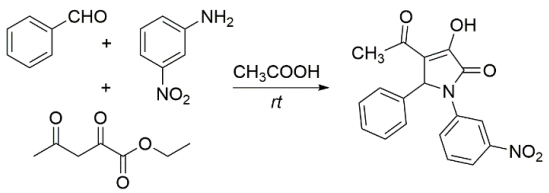

Figure 4. *Synthesis of 4-acetyl-3-hydroxy-1-(3-nitrophenyl)-5-phenyl-3-pyrroline-2-one*

2.3. Procedure for synthesis of 4-(1-methylamino)ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione [17]

To a glass reaction tube with screw cap equipped with a magnetic stirring bar was added 4-acetyl-3-hydroxy-1-(3-nitrophenyl)-5-phenyl-3-pyrroline-2-one (50.0 mg, 1.0 equiv., 0.148 mmol), methylamine (40% in water) (0.21 mL, 4.0 equiv., 0.590 mmol) and absolute ethanol (0.30 mL). The resulting mixture was stirred vigorously at 80°C for 7 hours and the reaction was followed by thin layer chromatography. The crude reaction mixture was then purified by column chromatography using dichloromethane and methanol as eluent to obtain 4-(1-methylamino)ethylene-5-phenyl-1-(3-nitrophenyl) pyrrolidine-2,3-dione as off-white solid (40.1 mg, 77.3%).

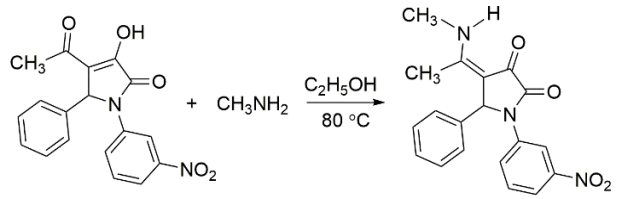

Figure 5. *Synthesis of 4-(1-methylamino)ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione*

2.4. Procedure for synthesis of 4-[1-(4-methoxybenzyl)amino]ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione [17]

To a glass reaction tube with screw cap equipped with a magnetic stirring bar was added 4-acetyl-3-hydroxy-1-(3-nitrophenyl)-5-phenyl-3-pyrrolin-2-one (50.0 mg, 1.0 equiv., 0.148 mmol), 4-methoxybenzylamine (0.078 mL, 4.0 equiv., 0.592 mmol) and absolute ethanol (0.30 mL). The resulting mixture was stirred vigorously at 80°C for 7 hours and the reaction was followed by thin layer chromatography. The crude reaction mixture was then purified by column chromatography using dichloromethane and methanol as eluent to obtain 4-[1-(4-methoxybenzyl)amino]ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione as light yellow solid (62.1 mg, 91.6%).

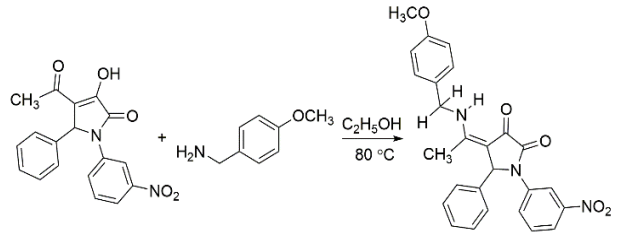

Figure 6. *Synthesis of 4-[1-(4-methoxybenzyl)amino]ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione*

3. Results and discussion

4-Acetyl-3-hydroxy-1-(3-nitrophenyl)-5-phenyl-3-pyrrolin-2-one was obtained as an off-white solid, melting point: 232 – 233 °C. HRMS (ESI-TOF MS/MS) m/z: found 339.0982 $[M + H]^+$, 361.0802 $[M + Na]^+$ (calculated: 339.0981 $[M + H]^+$, 361.0800 $[M + Na]^+$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (t, ^4J(H,H) = 2.16 Hz, 1H; Ar-H), 7.97 − 7.95 (m, 2H; Ar-H), 7.46 (t, ^3J(H,H) = 8.23 Hz, 1H; Ar-H), 7.25 – 7.32 (m, 5H; Ar-H), 5.88 (s, 1H), 2.17 ppm (s, 3H; CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.88, 163.86, 148.55, 137.29, 134.25, 130.10, 129.54, 129.50, 127.93, 127.82, 120.64, 120.32, 116.77, 62.17, 28.81 ppm.

The ^{1}H NMR spectrum of 4-acetyl-3-hydroxy-1-(3-nitrophenyl)-5-phenyl-3-pyrroline-2-one showed resonance signals in the chemical shift region of 7.97 – 7.95 ppm corresponding to nine protons of two benzene rings. In addition, the spectrum also exhibited two singlets at 5.88 and

2.17 ppm representing for proton at the 5-position of 3-pyrroline-2-one heterocyclic ring and three protons of methyl group (−CH_3), respectively (Figure 7). Moreover, the ^{13}C NMR spectrum of this compound in $CDCl_3$ was also recorded. Along with resonance signals of aromatic carbon atoms in the region of 148.55 – 116.77 pm, peaks of other characteristic carbon atoms were also observed in the spectrum. Peaks at 195.88 and 28.81 ppm represent for carbon atoms of carbonyl group (C=O) and methyl group (−CH_3), respectively, of acetyl moiety (−$COCH_3$) attached to the 4-position of the heterocyclic five-membered ring. Furthermore, carbons at the 2- and 5-positions of the heterocyclic ring were characterized by two resonance signals at the chemical shift of 163.86 and 62.17 ppm, respectively.

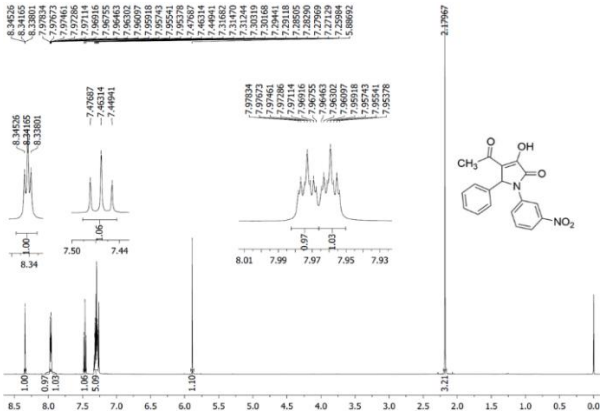

Figure 7. *^{1}H NMR spectrum of 4-acetyl-3-hydroxy-1-(3-nitrophenyl)-5-phenyl-3-pyrroline-2-one*

4-(1-Methylamino)ethylene-5-phenyl-1-(3-nitrophenyl) pyrrolidine-2,3-dione was obtained as an off-white solid, melting point: 250 – 252 °C. HRMS (ESI-TOF MS/MS) m/z: found 352.1291 $[M + H]^+$, 374.1115 $[M + Na]^+$ (calculated: 352.1297 $[M + H]^+$, 374.1117 $[M + Na]^+$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.44 (s_{br}, 1H; NH), 8.25 (t, ^4J(H,H) = 2.13 Hz, 1H; Ar-H), 8.06 (ddd, ^3J(H,H) = 8.15 Hz, ^4J(H,H) = 2.16 Hz, ^4J(H,H) = 2.19 Hz, 1H; Ar-H), 7.93 (ddd, ^3J(H,H) = 8.19 Hz, ^4J(H,H) = 2.18 Hz, ^4J(H,H) = 2.18 Hz, 1H; Ar-H), 7.44 (t, ^3J(H,H) = 8.19 Hz, 1H; Ar-H), 7.25 – 7.19 (m, 5H; Ar-H), 5.81 (s, 1H), 3.01 (d, ^3J(H,H) = 5.13 Hz, 3H; CH_3), 1.86 ppm (s, 3H; CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.34, 165.83, 164.78, 148.38, 138.11, 137.92, 129.83, 129.25, 129.23, 128.88, 128.03, 120.36, 117.30, 107.31, 61.13, 30.34, 15.35 ppm.

The ^{1}H NMR spectrum of 4-(1-methylamino)ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione appeared resonance signal of proton of secondary amino group (−NH−) at high chemical shift, 11.44 ppm, which is due to intramolecular hydrogen bond. In addition, the spin – spin coupling between protons of secondary amino group (−NH−) and methyl group (−CH_3) which separated by three sigma (σ) bonds was also observed and as a consequence, protons of methyl group was characterized by a doublet at 3.01 ppm. Furthermore, the spectrum showed two singlets at 5.81 and 1.86 ppm representing for one proton at the 5-position of the heterocyclic ring and three protons of the remaining methyl group, respectively (Figure 8). Besides, nine aromatic protons were exhibited by resonance signal in the chemical shift region of 8.26 – 7.19 ppm.

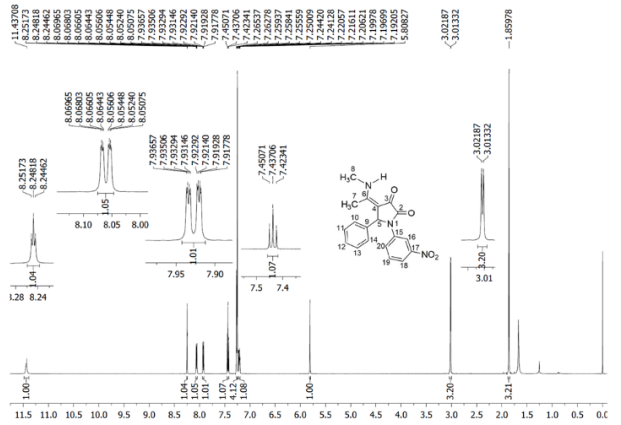

Figure 8. *^{1}H NMR spectrum of 4-(1-methylamino)ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione*

In addition to ^{1}H NMR and ^{13}C NMR, 2D NMR spectra of 4-(1-methylamino)ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione were also recorded. ^{1}H - ^{13}C HSQC spectrum showed that protons resonance at 1.86 ppm, 3.01 ppm, and 5.81 ppm correlate with carbons resonance at 15.35 ppm, 30.34 ppm, and 61.13 ppm, respectively. Therefore, peaks at 15.35 ppm, 30.34 ppm, and 61.13 ppm in ^{13}C NMR spectrum correspond to C7, C8, and C5, respectively. Besides, there were also other cross peaks resulted from the correlation between aromatic protons and aromatic carbons which are directly attached to each other (Figure 9).

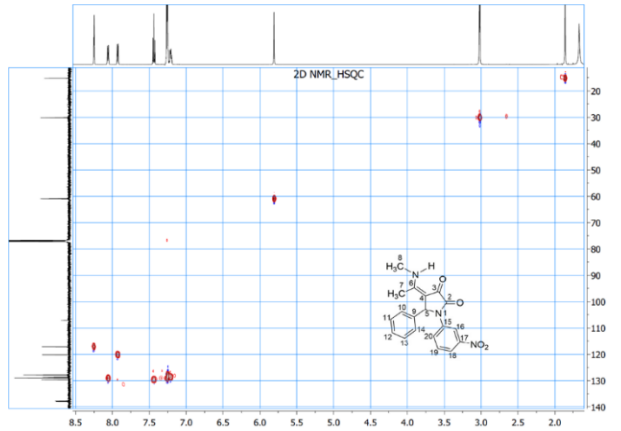

Figure 9. *^{1}H – ^{13}C HSQC spectrum of of 4-(1-methylamino) ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione*

In the 2D ^{1}H – ^{13}C HMBC spectrum of 4-(1-methylamino)ethylene-5-phenyl-1-(3-nitrophenyl) pyrrolidine-2,3-dione, protons H5, H8 and H7 resonance at 5.81 ppm, 3.01 ppm and 1.86 ppm, respectively, all showed cross peaks with the same carbon resonance at 165.83 ppm. Therefore, ^{13}C resonance signal at 165.83 ppm must be that of C6. In addition, the ^{13}C resonance at 107.31 ppm showed two cross peaks to H5 and H7 and this means that peak at 107.31 ppm belongs to C4. Besides, proton H5 resonance at 5.81 ppm exhibited cross peak to ^{13}C resonance at 138.11 ppm. Furthermore, there were cross peaks arised from the correlations between carbon signal at 138.11 ppm and hydrogens resonance at 8.25 ppm (triplet, ^4J(H,H) = 2.13 Hz), 8.06 ppm (doublet of doublet of doublet, ^3J(H,H) = 8.15 Hz, ^4J(H,H) = 2.16 Hz, ^4J(H,H) = 2.19 Hz) and 7.44 ppm (triplet, ^3J(H,H) = 8.19 Hz). Therefore, peaks at 138.11 ppm,

8.25 ppm, 8.06 ppm, and 7.44 ppm will correspond to C15, H16, H20, and H19, respectively. There were three cross peaks observed from the correlation of ^{13}C resonance signal at 148.38 ppm to H19, H16 and proton resonance at 7.93 ppm. Thus, peaks at 148.38 ppm and 7.93 ppm will represent for C17 and H18, respectively (Figure 10).

In 2D HSQC spectrum, there was a correlation between ^{13}C resonance at 128.88 ppm and proton resonance at 7.20 ppm as a multiplet. Therefore, resonance signals at 7.20 ppm, 128.88 ppm must be those of H12 and C12, respectively. In addition, in 2D HMBC spectrum, protons H5, H12 resonance at 5.81 ppm and 7.20 ppm, respectively, showed cross peaks to the same carbons resonance at 128.03 ppm. Thus, high intensity signal at 128.03 ppm was resulted from the resonance of two chemically equivalent carbon atoms C10 and C14. On the other hand, there were strong cross peaks in HSQC spectrum ensued from the correlation between four protons resonance at 7.26 – 7.24 ppm as a multiplet and carbons resonance at 129.23 ppm, 128.03 ppm. Hence, high intensity peak at 129.23 ppm could be assigned to two chemically equivalent carbon atoms C11, C13. In HMBC spectrum, ^{13}C resonance at 137.92 ppm showed cross peaks to not only four hydrogen atoms resonance at 7.26 – 7.24 ppm as a multiplet but also hydrogen atom H5. It is undoubtedly that resonance signal at 137.92 ppm will correspond to carbon atom C9. Lastly, based on HSQC spectrum, it could be confirmed that ^{13}C resonance signals at 117.30 ppm, 120.36 ppm, 129.25 ppm, 129.83 ppm represent for carbon atoms C16, C18, C20, C19, respectively. The spectroscopic data of 4-(1-methylamino)ethylene-5-phenyl-1-(3-nitrophenyl) pyrrolidine-2,3-dione could be summarized in Table 1.

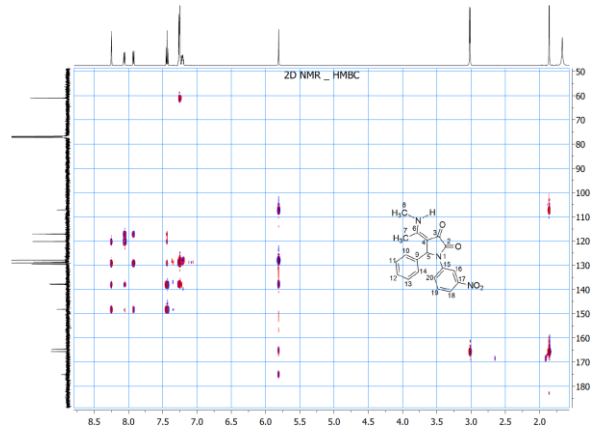

Figure 10

. *$^{1}H - ^{13}C$ HMBC spectrum of of 4-(1-methylamino) ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione*

Table 1. *^{1}H NMR, ^{13}C NMR spectroscopic data of 4-(1-methylamino)ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione (600/150 MHz, $CDCl_3$)*

Position	δ_C	δ_H	Position	δ_C	δ_H
2, 3	175.34, 164.78		12	128.88	7.20 (1H, m)
4	107.31		15	138.11	
5	61.13	5.81 (s, 1H)	16	117.30	8.25 (t, ^4J = 2.13 Hz)
6	165.83		17	148.38	
7	15.35	1.86 (s, 3H)	18	120.36	7.93 (ddd, ^3J = 8.19 Hz, ^4J = 2.18 Hz, ^4J = 2.18 Hz, 1H)
8	30.34	3.01 (d, ^3J = 5.13 Hz, 3H)	19	129.83	7.44 (t, ^3J= 8.19 Hz, 1H)
9	137.92		20	129.25	8.06 (ddd, ^3J = 8.15 Hz, ^4J = 2.16 Hz, ^4J = 2.19 Hz, 1H)
10, 14	128.03	7.26 – 7.24 (m, overlapped, 2H)			
11, 13	129.23	7.26 – 7.24 (m, overlapped, 2H)			

4-[1-(4-methoxybenzyl)amino]ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione was obtained as a light yellow solid, melting point: 233 – 236 °C. HRMS (ESI-TOF MS/MS) m/z: found 458.1716 $[M + H]^+$, 480.1535 $[M + Na]^+$ (calculated: 458.1716 $[M + H]^+$, 480.1535 $[M + Na]^+$). ^1H NMR (600 MHz, DMSO-d6) δ 11.46 (t, ^3J(H,H) = 5.85 Hz, 1H; NH), 8.56 (t, ^4J(H,H) = 2.21 Hz, 1H; Ar-H), 8.02 (ddd, ^3J(H,H) = 8.27 Hz, ^4J(H,H) = 2.21 Hz, ^4J(H,H) = 2.16 Hz, 1H; Ar-H), 7.94 (ddd, ^3J(H,H) = 8.25 Hz, ^4J(H,H) = 2.26 Hz, ^4J(H,H) = 2.28 Hz, 1H; Ar-H), 7.60 (t, ^4J(H,H) = 8.22 Hz, 1H; Ar-H), 7.35 (d, ^3J(H,H) = 8.35 Hz, 2H; Ar-H), 7.27 – 7.24 (m, 4H; Ar-H), 7.17 (t, ^3J(H,H) = 7.37 Hz, 1H; Ar-H), 6.95 (d, ^3J(H,H) = 8.65 Hz, 2H; Ar-H), 6.36 (s, 1H), 4.61 (dd, ^2J(H,H) = 6.03 Hz, ^3J(H,H) = 15.12 Hz, 1H; CH_2), 4.57 (dd, ^2J(H,H) = 5.73 Hz, ^3J(H,H) = 15.11 Hz, 1H; CH_2), 3.75 (s, 3H; OCH_3), 1.95 ppm (s, 3H; CH_3). ^{13}C NMR (150 MHz, DMSO-d6) δ 174.12, 164.81, 164.21, 158.84, 147.77, 138.67, 137.89, 130.01, 128.99, 128.71, 128.65, 128.34, 128.09, 127.83, 119.84, 116.73, 114.27, 107.53, 58.71, 55.13, 46.06, 15.36 ppm.

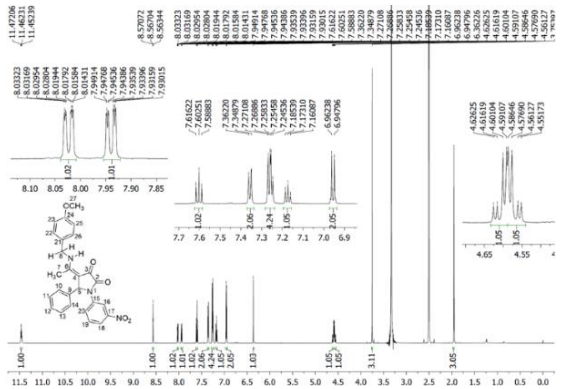

Figure 7. *^{1}H NMR spectrum of 4-[1-(4-methoxybenzyl) amino]ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione*

Similar to 4-(1-methylamino)ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione, the ^1H NMR spectrum of 4-[1-(4-methoxybenzyl)amino]ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione also exhibited resonance signals of secondary amino proton (−NH) at

high chemical shift due to intramolecular hydrogen bond, aromatic protons of two benzene rings attached to the 1- and 5-positions of heterocyclic ring. In addition, four protons of para-disubstituted benzene ring were showed by two doublets at the chemical shift of 7.35 ppm and 6.95 ppm. It is clear that three protons of methoxy group (−OCH_3) have lower shielding constant as compared to those of methyl group at the 7-position. Thus, singlet peaks at 3.75 ppm and 1.95 ppm must be that of protons of methoxy group and methyl group, respectively. Furthermore, two methylene protons at the 8-position are chemically non equivalent ones, also called diastereotopic protons, and they will couple with each other. Besides, each methylene proton will also couple with secondary amino proton (−NH) that are separated by three sigma bonds. As a consequence, the resonance of two methylene protons will correspond to two peaks of doublet of doublet at 4.61 ppm and 4.57 ppm.

4. Conclusions

4-Acetyl-3-hydroxy-1-(3-nitrophenyl)-5-phenyl-3-pyrroline-2-one was synthesized successfully *via* three-component reaction of *m*-nitroaniline, benzaldehyde and ethyl 2,4-dioxovalerate with the yield of 45.1%. The reaction between this 3-pyrroline-2-one derivative, containing acetyl group (−$COCH_3$) at the 4-position, with aliphatic amine such as methylamine and 4-methoxybenzylamine in absolute ethanol as green solvent will result in the formation of 1,4,5-trisubstituted pyrrolidine-2,3-diones. The structure of products was confirmed by nuclear magnetic resonance spectroscopy (1D and 2D NMR) and high resolution mass spectrometry (LC-ESI-TOF HRMS).

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SUPPORTING INFORMATION

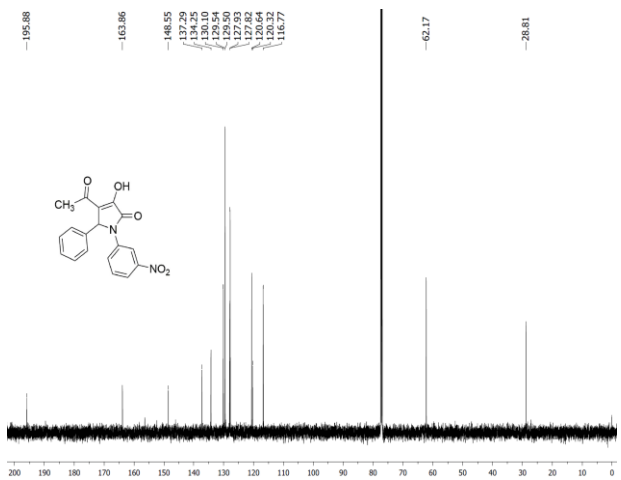

Figure S1. *^{13}C NMR spectrum of 4-acetyl-3-hydroxy-1-(3-nitrophenyl)-5-phenyl-3-pyrroline-2-one*

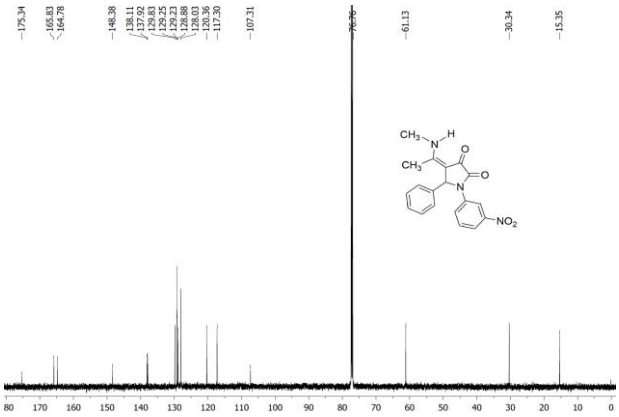

Figure S2. *^{13}C NMR spectrum of 4-(1-methylamino)ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione*

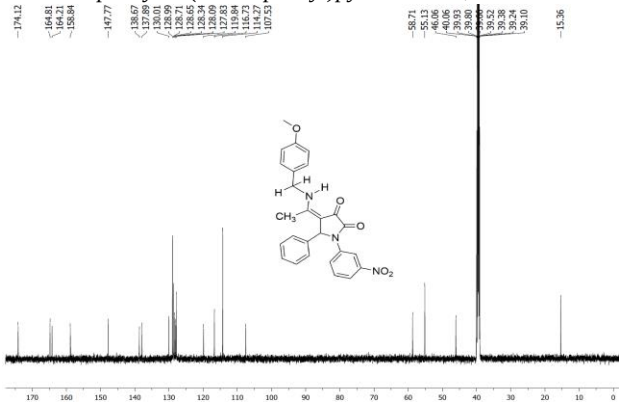

Figure S3. *^{13}C NMR spectrum of 4-[1-(4-methoxybenzyl)amino] ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione*

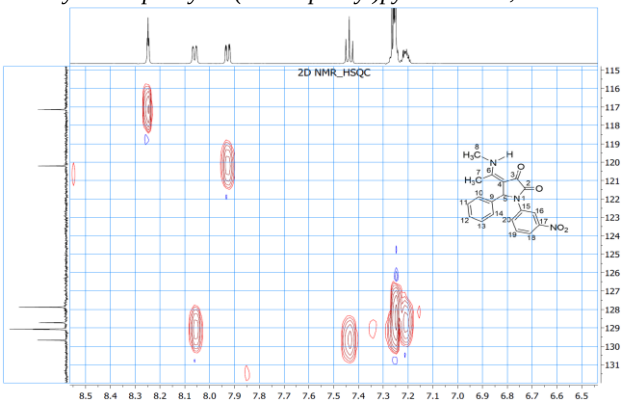

Figure S4. *HSQC spectrum of 4-(1-methylamino)ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione*

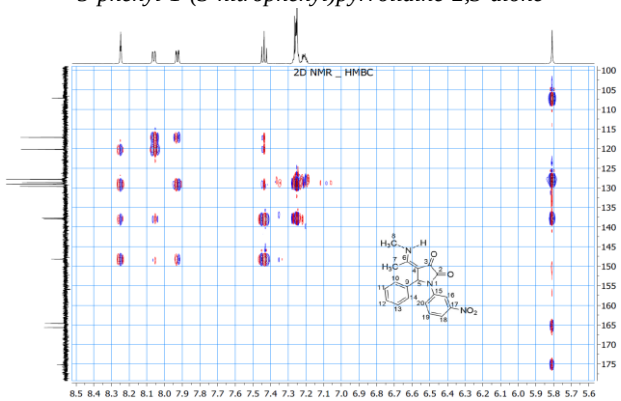

Figure S5. *HMBC spectrum of 4-(1-methylamino)ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione*

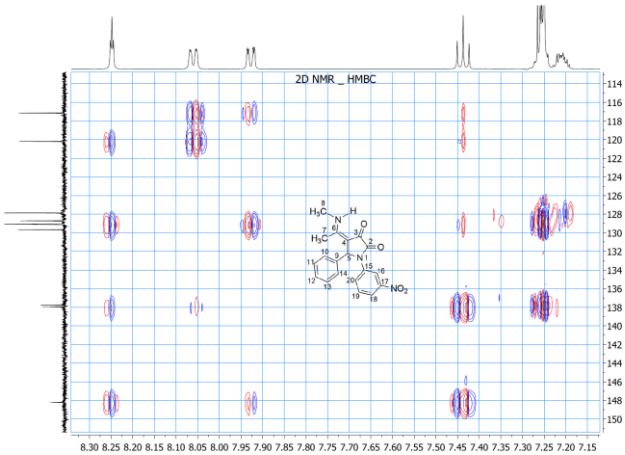

Figure S6. *HMBC spectrum of 4-(1-methylamino)ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione*

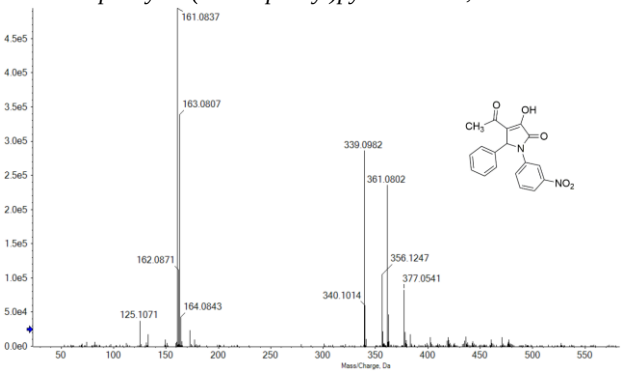

Figure S7. *ESI – HRMS spectrum of 4-acetyl-3-hydroxy-1-(3-nitrophenyl)-5-phenyl-3-pyrroline-2-one*

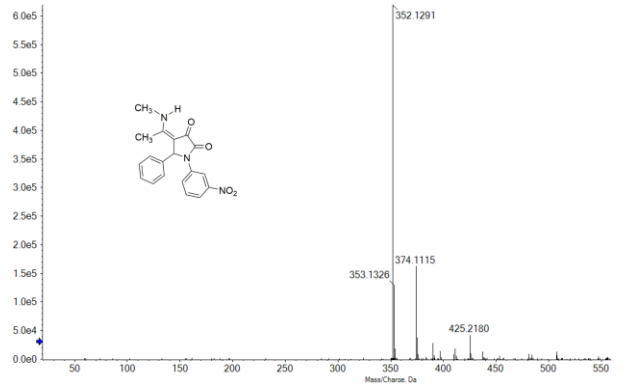

Figure S8. *ESI – HRMS spectrum of 4-(1-methylamino) ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione*

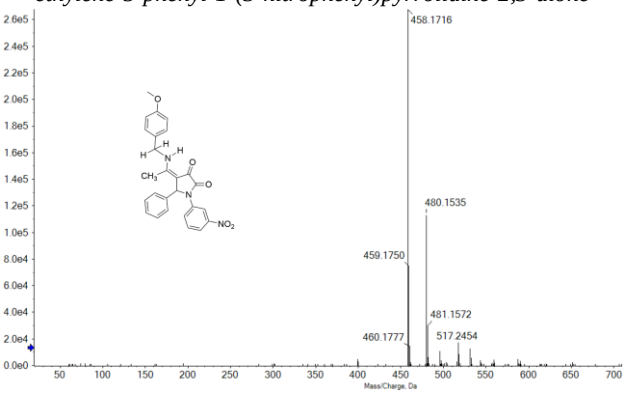

Figure S9. *ESI – HRMS spectrum of 4-[1-(4-methoxybenzyl)amino] ethylene-5-phenyl-1-(3-nitrophenyl)pyrrolidine-2,3-dione*