SYNTHESIS AND STRUCTURAL DETERMINATION OF SOME 1,5-DISUBSTITUTED-4-ETHOXYCARBONYL-3-HYDROXY-3-PYRROLINE-2-ONE DERIVATIVES CONTAINING NITRO GROUP

TỔNG HỢP VÀ XÁC ĐỊNH CẤU TRÚC CỦA MỘT SỐ DẪN XUẤT 1,5-DISUBSTITUTED-4-ETHOXYCARBONYL-3-HYDROXY-3-PYRROLINE-2-ONE CHỨA NHÓM NITRO

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(Received: October 31, 2023; Revised: December 22, 2023; Accepted: December 29, 2023)

Abstract - 2-Pyrrolidinone is a *γ*-lactam heterocycle consisting of four carbon atoms and one nitrogen atom. In the family of 2-pyrrolidinone heterocycles, 3-pyrroline-2-ones, also named as 1,5-dihydro-2*H*-pyrrol-2-ones are important substructures of various natural products with promising biological activities. In addition, this *γ*-lactam heterocyclic ring also exists in synthetic medicinal compounds. In this manuscript, multi-component reactions (MCRs) were applied to synthesize three 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-ones containing nitro group from aromatic aldehydes, 4-nitroaniline and sodium diethyl oxalacetate in absolute ethanol. Furthermore, the molecular structure of products has been proven *via* modern spectroscopic methods: nuclear magnetic resonance spectroscopy (^{1}H NMR, ^{13}C NMR) and electrospray ionization-high resolution mass spectrometry (ESI – HRMS).

Key words - Multi-component reaction; *γ*-lactam ring; 2-pyrrolidinone; 3-pyrroline-2-one; 1,5-dihydro-2*H*-pyrrol-2-one

Tóm tắt - 2-Pyrrolidinone là một dị vòng *γ*-lactam chứa bốn nguyên tử carbon và một nguyên tử nitrogen. Trong nhóm các dẫn xuất 2-pyrrolidinone, 1,5-dihydro-2*H*-pyrrol-2-one, còn được gọi là các dẫn xuất 3-pyrroline-2-one là những đơn vị cấu trúc quan trọng trong nhiều hợp chất thiên nhiên có hoạt tính sinh học. Hơn nữa, dị vòng *γ*-lactam này còn có mặt trong cấu trúc của một số loại dược phẩm. Trong nghiên cứu này, ba dẫn xuất của 4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one chứa nhóm nitro (–NO_2) đã được tổng hợp dựa vào phản ứng nhiều thành phần (MCR) từ aldehyde thơm, 4-nitroaniline và sodium diethyl oxalacetate trong dung môi ethanol. Ngoài ra, cấu trúc của các sản phẩm đã được chứng minh dựa vào các phương pháp phổ hiện đại như phổ cộng hưởng từ hạt nhân (^{1}H NMR, ^{13}C NMR) và phổ khối phân giải cao (ESI – HRMS)

Từ khóa - Multi-component reaction; *γ*-lactam ring; 2-pyrrolidinone; 3-pyrroline-2-one; 1,5-dihydro-2*H*-pyrrol-2-one

1. Introduction

2-Pyrrolidinone is a *γ*-lactam nitrogen-containing heterocyclic scaffold that occurs in numerous biologically active compounds of natural origin and non-natural medicinal compounds [1], [2], [3]. Azaspirene, for example, was isolated from the fungus Neosartorya sp. which exhibited the endothelial migration induced by the vascular endothelial growth factor [4]. Cynometrine, an *γ*-lactam containing alkaloid, was found in the sterm bark of Cynometra hankei [5] which has been used as an antitussive and analgesic (for dental pain and rheumatism) [2], [6]. Doxapram, a non-natural compound, has been used to form doxapram hydrochloride which helps to increase the respiratory rate [7] (Figure 1).

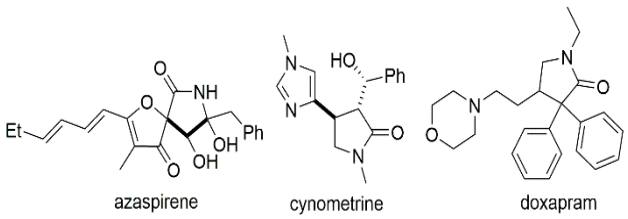

Figure 1. *Structure of some naturally occurring and synthetic 2-pyrrolidinone derivatives*

In the family of 2-pyrrolidinones, 3-pyrroline-2-ones, also known as 1,5-dihydro-2*H*-pyrrol-2-ones are important substructures in numerous naturally occurring compounds. Pyrrocidine A, for instance, was derived from Acremonium zeae, a fungal endophyte, and this natural origin compound presents biological activity against Gram-positive bacteria [8]. Ascosali pyrrolidinone A was isolated from a marine fungus named Ascochyta salicornae which shows antimalarial activity [9] (Figure 2).

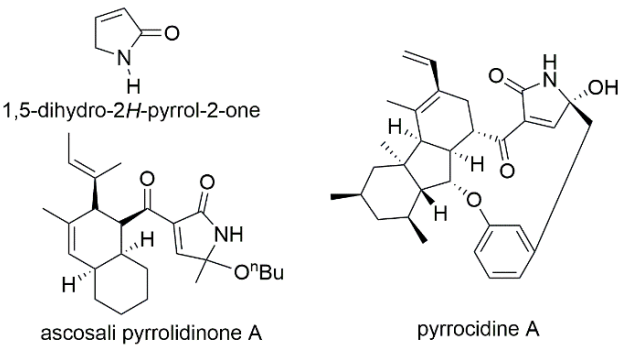

Figure 2. *Natural compounds containing 1,5-dihydro-2H-pyrrol-2-one subunit*

Along with compounds of natural origin, non-natural polysubstituted 3-pyrroline-2-ones have been synthesized and evaluated for their biological and pharmacological activities such as antioxidant [10], [11], [12], antibacterial [13], [14], anticancer [15], [16], [17], as well as anti-HIV-1 [18] and inflammatory [19]. Therefore, there has been increasing attention to the synthesis of polysubstituted 3-pyrroline-2-ones, and especially 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-ones [20].

Multi-component reactions (MCRs) are efficient synthetic strategies in which three or more starting materials react in a single flask to obtain new products containing important portions of all reactants [21]. 1,5-Disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-ones have been synthesized *via* MCRs of substituted benzaldehydes, amines, and diethyl acetylenedicarboxylate [22], [23], [24], [25]. In addition, 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-ones could also be synthesized *via* MCRs of substituted benzaldehydes, amines and sodium diethyl oxalacetate [26], [10]. However, the above-mentioned five-membered ring heterocycles containing nitro group (–NO_2) still need to be explored more by synthetic organic chemists. Thus, in this manuscript, MCRs of substituted benzaldehydes, 4-nitroaniline and sodium diethyl oxalacetate to obtain nitro group (–NO_2) containing 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-ones will be reported. Furthermore, the molecular structure of three products will be determined *via* nuclear magnetic resonance spectroscopy (^{1}H NMR, ^{13}C NMR) and electrospray ionization-high resolution mass spectrometry (ESI – HRMS).

2. Experimental section

2.1. General experimental methods

All chemicals were received from Merk, Sigma Aldrich and Acros without further purification. Silica gel 60 (0.063-0.200 mm) was used as the stationary phase for column chromatography. All NMR spectra were acquired on Bruker Avance II+ spectrometer at 600 MHz for proton and 150 MHz for carbon. The chemical shifts were reported in ppm (part per million) relative to tetramethylsilane (TMS) or internal deuterated solvent signals ($CDCl_3$ or DMSO-d6). Büchi Melting Point B-545 apparatus was used to determine the melting points of products. Electrospray ionization - High-resolution mass spectra (ESI – HRMS) were recorded with SCIEX X500 QTOF instrument.

2.2. Preparation and purification of 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-ones [10]

To a round-bottom flask of 10 mL equipped with a mechanical stirrer was added substituted benzaldehyde (1 mmol, 1 equiv.), 4-nitroaniline (1 mmol, 1 equiv.), citric acid (2 mmol, 2 equiv.), absolute ethanol (1.5 mL) and toluene (0.5 ml). The mixture was stirred at room temperature for 1 hour under Ar atmosphere. Then, sodium diethyl oxalacetate (2 mmol, 2 equiv.) was added, the resulting mixture was stirred vigorously at room temperature for 12 hours under Ar atmosphere. The formation 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-ones was checked by thin layer chromatography (TLC) (Hexane/Ethyl acetate = 5: 1 and Hexane/Ethyl acetate = 5: 3.5). Then, dichloromethane (CH_2Cl_2) and HCl (5%) were added to the flask, and the mixture was stirred at room temperature for 15 minutes. Two layers were separated and the organic layer was washed three times with distilled water, and dried over $MgSO_4$. The crude product was recrystallized in the solvent mixture of CH_2Cl_2 and absolute ethanol or CH_2Cl_2 and ethyl acetate to yield a pure product.

3. Results and discussion

The optimal reaction conditions for the synthesis of 1,5-diphenyl-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one [10] were applied to yield nitro group containing 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline -2-ones (Figure 3, Table 1). Furthermore, due to low solubility of nitro group containing aromatic compounds in absolute ethanol, toluene was also added to the reaction mixture to dissolve all starting material containing nitro group (–NO_2).

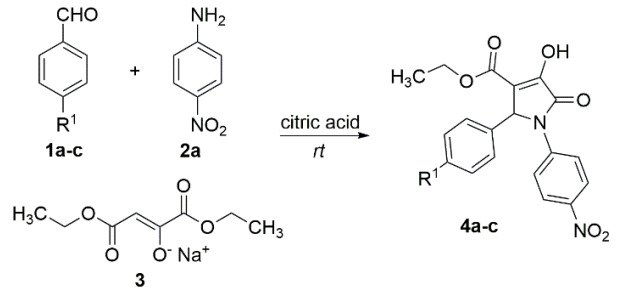

Figure 3. *The overall reaction for the synthesis of 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-ones (**4a-c**)*

Table 1. *Synthesis of 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-ones (**4a-c**)*

Entry	R^1	Product	Yield (%)
1	H	**4a**	38
2	CH_3	**4b**	31
3	NO_2	**4c**	48

The initial step in MCRs to synthesize 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-ones (**4a-c**) takes place *via* the reaction between substituted benzaldehyde (**1a-c**) and 4-nitroaniline (**2a**) to yield imine (**5**) [27] (Figure 4). Therefore, the presence of substituent groups attached to the benzene ring in the structure of starting materials will affect both the rate and the yield of imine formation reaction [10].

Nitro group (NO_2), an electron-withdrawing group, in 4-nitroaniline (**2a**) results in the decrease in the nucleophilicity of the amino group (–NH_2) [28]. Therefore, the imine formation reaction rate between benzaldehyde (**1a**) and 4-nitroaniline (**2a**) is slower than that between benzaldehyde (**1a**) and aniline [27], [29]. Consequently, there was a dramatic decrease in the yield of 1-(4-nitrophenyl)-5-phenyl-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (**4a**), 38% (Table 1), as compared to the synthesis of 1,5-diphenyl-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one, 86% [10]. Moreover, the yields of **4b** and **4c** were also lower than that of 1,5-diphenyl-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one [10].

The existence of substituents in substituted benzaldehydes will affect the electrophilicity of the carbonyl carbon atom (C=O). Methyl (CH_3) is an electron-donating group which brings about the decrease in the electrophilicity of carbonyl carbon atom in

4-methylbenzaldehyde (**1b**) as compared to benzaldehyde (**1a**). The formation of the imine between **1b** and **2a** is slower than that between **1a** and **2a**, and consequently, the yield of **4b** is lower than that of **4a**. In contrast, the presence of nitro group (NO_2) in reactant **1c** leads to the increase in the electrophilicity of the carbonyl carbon atom [27], [28], [29]. As a consequence, the yield of **4c** is higher than that of **4a** and **4b** (Table 1).

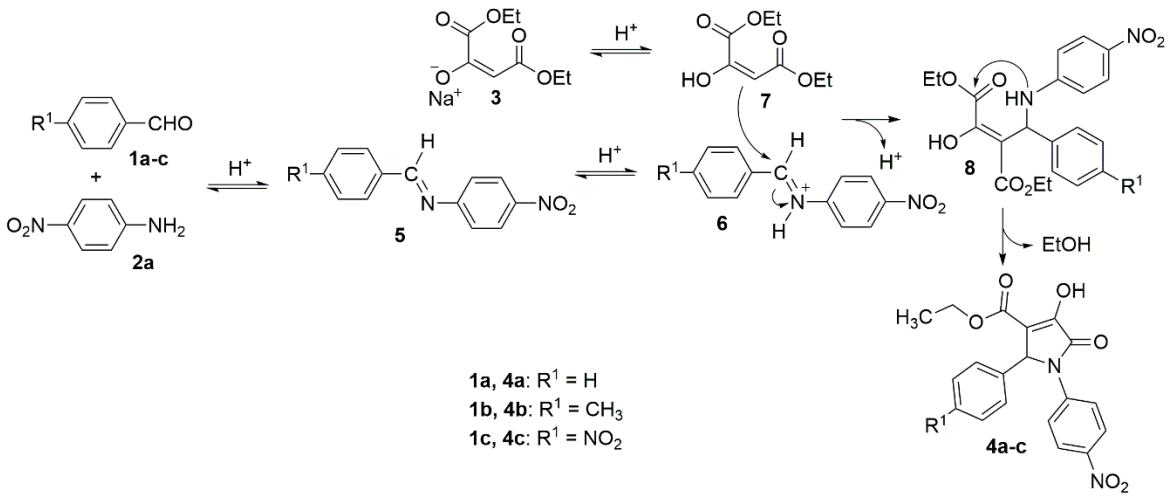

Figure 4. *Mechanism for the synthesis of 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-ones [10]*

1-(4-Nitrophenyl)-5-phenyl-4-ethoxycarbonyl-3-hydroxy -3-pyrroline-2-one (**4a**) was obtained as an off-white solid, melting point: 180 – 182°C. HRMS (ESI-TOF MS/MS) m/z: found 369.1076 $[M + H]^+$, 391.0908 $[M + Na]^+$ (calculated: 369.1087 $[M + H]^+$, 391.0906 $[M + Na]^+$). ^{1}H NMR (600 MHz, DMSO-d6) δ 11.85 (s_{br}, 1H; −OH), 8.13 (d, ^3J(H,H) = 9.29 Hz, 2H; Ar-H), 7.90 (d, ^3J(H,H) = 9.29 Hz, 2H; Ar-H), 7.31 (d, ^3J(H,H) = 6.95 Hz, 2H; Ar-H), 7.23 (t, ^3J(H,H) = 7.34 Hz, 2H; Ar-H), 7.17 (m, 1H; Ar-H); 6.17 (s, 1H), 4.04 (dq, ^3J(H,H) = 7.03 Hz, ^2J(H,H) = 10.8 Hz, 1H; $-OCH_2-$), 3.99 (dq, ^3J(H,H) = 7.07 Hz, ^2J(H,H) = 10.9 Hz, 1H; $-OCH_2-$), 1.07 ppm (t, 3H; CH_3). ^{13}C NMR (DMSO-d6, 150 MHz) δ 164.69, 161.75, 151.83, 143.52, 142.06, 135.94, 128.37, 128.17, 127.73, 124.34, 121.59, 113.22, 60.34, 59.88, 13.94 ppm.

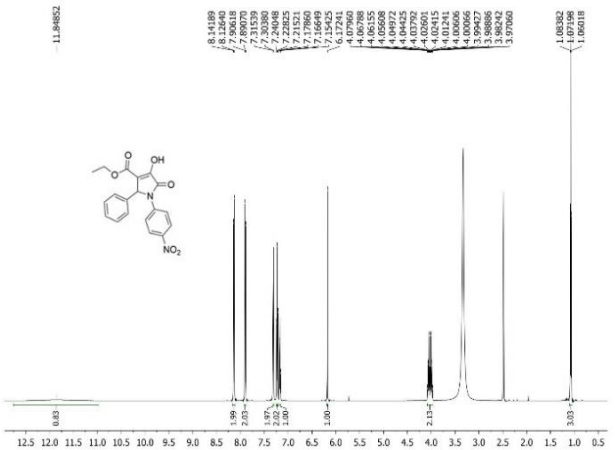

Figure 5. *^{1}H NMR spectrum of 1-(4-nitrophenyl)-5-phenyl-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (**4a**)*

The ^{1}H NMR spectrum of **4a** exhibited a broad and low intensity peak representing for hydrogen atom of the hydroxyl group (–OH) at a high chemical shift, 11.85 ppm, which is due to intramolecular hydrogen bond. Four hydrogen atoms of 1,4-disubstituted benzene ring linked to nitrogen atom at 1-position of the 3-pyrroline-2-one heterocyclic ring were showed by two doublets at 8.13 and 7.90 ppm. In addition, the spectrum also exhibited peaks in the range of 7.15 – 7.31 ppm representing five hydrogen atoms of the monosubstituted benzene ring (Figure 5). Two protons of methylene group ($-CH_2$) of ethoxycarbonyl ($-C(O)OCH_2CH_3$) moiety were characterized by two doublets of quartets (dq) at 3.99 and 4.04 ppm (see supporting information). Undoubtedly, two methylene hydrogen atoms are diastereotopic, they will not only couple with each other but also show spin-spin coupling with methyl hydrogen atoms (CH_3) [30], [31].

5-(4-Methylphenyl)-1-(4-nitrophenyl)-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (**4b**) was obtained as an off-white solid, melting point: 205 – 207°C. The existence of strong electron-withdrawing group in 4-nitroaniline (**2a**) brought about a sharp decrease in the yield of **4b** as compared to 5-(4-methylphenyl)-1-phenyl-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one, 72% [10].

HRMS (ESI-TOF MS/MS) m/z: found 383.1238 $[M + H]^+$, 405.1089 $[M + Na]^+$ (calculated: 383.1243 $[M + H]^+$, 405.1063 $[M + Na]^+$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.06 (s_{br}, 1H; −OH), 8.12 (d, ^3J(H,H) = 9.29 Hz, 2H; Ar-H), 7.79 (d, ^3J(H,H) = 9.34 Hz, 2H; Ar-H), 7.12 (d, ^3J(H,H) = 8.27 Hz, 2H; Ar-H), 7.09 (d, ^3J(H,H) = 8.05 Hz, 2H; Ar-H), 5.76 (s, 1H), 4.22 (m, 2H; CH_2), 2.27 (s, 3H; CH_3), 1.22 ppm (t, ^3J(H,H) = 7.09, 3H; CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.11, 163.37, 155.76, 144.30, 142.31, 139.11, 131.31, 129.82, 127.30, 124.79, 120.76, 114.31, 61.78, 61.14, 21.27, 14.08 ppm.

Similarly to compound **4a**, the ^{1}H NMR spectrum of **4b** also appeared resonance signal of proton of hydroxyl group (–OH) as a broad and low-intensity peak at the chemical shift of 9.06 ppm. There were four doublets located at 8.12, 7.79, 7.12 and 7.09 ppm representing eight protons of two 1,4-disubstituted benzene rings which attached to 1,5-positions of the 3-pyrroline-2-one heterocyclic ring. In

addition, the spectrum exhibited two singlet resonance signals at 5.76 and 2.27 ppm corresponding to hydrogen atom at the 5-position and methyl group protons, respectively (Figure 6). Furthermore, resonance signals of two methylene protons and three methyl protons of ethoxycarbonyl (−C(O)OCH$_2$CH$_3$) group were characterized by a multiplet and a triplet at 4.22 and 1.22 ppm, respectively.

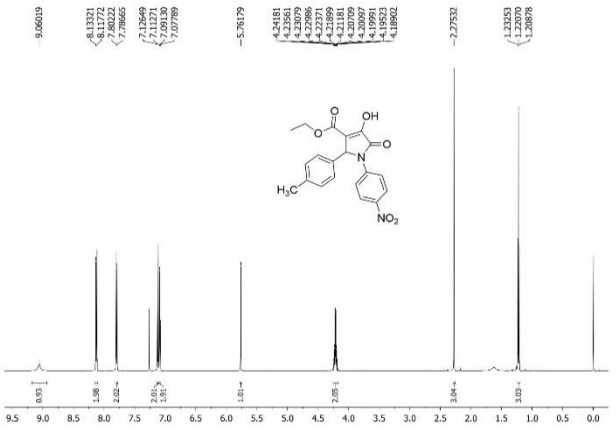

Figure 6. *^{1}H NMR spectrum of 5-(4-methylphenyl)-1-(4-nitrophenyl)-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (**4b**)*

1-(4-Nitrophenyl)-5-(4-nitrophenyl)-4-ethoxycarbonyl -3-hydroxy-3-pyrroline-2-one (**4c**) was obtained as a slightly yellow off-white solid, melting point: 200 – 202°C. The yield of **4c** had roughly halved to 48%, as compared to 5-(4-nitrophenyl)-1-phenyl-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one, 91% [10].

HRMS (ESI-TOF MS/MS) m/z: found 412.0777 [M - H]$^-$, (calculated: 412.0781 [M - H]$^-$). ^{1}H NMR (600 MHz, DMSO-d6) δ 8.11 (d, ^3J(H,H) = 9.28 Hz, 2H; Ar-H), 8.04 (d, ^3J(H,H) = 8.90 Hz, 2H; Ar-H), 7.87 (d, ^3J(H,H) = 9.28 Hz, 2H; Ar-H), 7.63 (d, ^3J(H-H) = 8.78 Hz, 2H; Ar-H), 6.33 (s, 1H), 4.01 (dq, ^3J(H,H) = 7.05 Hz, ^2J(H,H) = 10.82 Hz, 1H; −OCH$_2$−), 3.97 (dq, ^3J(H,H) = 7.09 Hz, ^2J(H,H) = 10.93 Hz, 1H; −OCH$_2$−), 1.05 ppm (t, ^3J(H,H) = 7.06, 3H; CH$_3$). ^{13}C NMR (DMSO-d6, 150 MHz) δ 164.67, 161.71, 152.83, 147.31, 144.09, 143.76, 141.78, 129.38, 124.53, 123.51, 121.65, 111.97, 60.06, 59.47, 14.00 ppm.

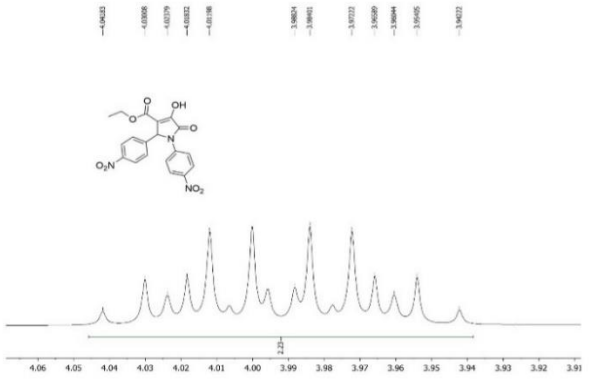

Figure 7. *Peaks of doublet of quartet (dq) of two diastereotopic methylene protons (−CH$_2$) in compound **4c***

3-Pyrroline-2-one derivative **4c** was dissolved in the solvent of DMSO-d6 for ^{1}H NMR measurement. 8 Protons of two 1,4-disubstituted benzene rings in the structure of compound **4c** were characterized by four doublets at 8.11, 8.04, 7.86, and 7.62 ppm. In addition, the spectrum exhibited singlet resonance signal at 6.33 ppm corresponding to hydrogen atom at 5-position of the heterocyclic ring. It is undoubtedly that the plane of five-membered heterocyclic ring and ethoxycarbonyl moiety (−C(O)OCH$_2$CH$_3$) is co-planar [30], [31]. Two methylene protons (CH$_2$) in compound **4c** are not chemically equivalent and therefore, represented by two doublets of quartets (dq) at 4.01 and 3.97 ppm (Figure 7).

4. Conclusions

Three polysubstituted 3-pyrroline-2-ones containing nitro group (−NO$_2$) were synthesized successfully *via* three-component reactions (MCRs) of 4-nitroaniline, substituted benzaldehydes and sodium diethyl oxalacetate. The presence of electron-withdrawing or electron-donating groups bonded to the benzene ring in the structure of both aromatic amine and aromatic aldehyde will affect the yield of heterocyclic products **4a-c**. The molecular structure of three polysubstituted 1,5-dihydro-2*H*-pyrrol-2-ones was determined by ^{1}H NMR, ^{13}C NMR spectroscopy and electrospray ionization - high resolution mass spectrometry (ESI-HRMS).

Acknowledgment: [Vo Viet Dai] was funded by the Master, PhD scholarship Programme of Vingroup Innovation Foundation (VinIF), code [VINIF.2022.ThS.021].

REFERENCES

[1] A. Harreus, R. Backes, J. Eichloer, R. Feuerhake, C. Jakel, U. Mahn, R. Pinkos, and R. Vogelsang, *2-Pyrrolidone*, 6th edition. NJ: Wiley-VCH Verlag GmbH & Co., 2011.

[2] J. Caruano, G. Muccioli, and R. Robiette, "Biologically active γ-lactams: synthesis and natural sources", *Organic and biomolecular chemistry*, vol. 14, no. 43, pp. 10134-10156, 2016. https://doi.org/10.1039/C6OB01349J

[3] G. Li Petri, M. V. Raimondi, V. Spanò, R. Holl, P. Barraja, and A. Montalbano, "Pyrrolidine in drug discovery: a versatile scaffold for novel biologically active compounds", *Topics in Current Chemistry*, vol. 379, no. 34, pp. 1-46, 2021. https://doi.org/10.1007/s41061-021-00347-5

[4] Y. Asami, H. Kakeya, R. Onose, A. Yoshida, H. Matsuzaki, and H. Osada, "Azaspirene: A Novel Angiogenesis Inhibitor Containing a 1-Oxa-7-azaspiro[4.4]non-2-ene-4,6-dione Skeleton Produced by the Fungus Neosartorya sp.", *Organic letters*, vol. 4, no. 17, pp. 2845-2848, 2002. https://doi.org/10.1021/ol020104

[5] P. G. Waterman and D. F. Faulkner, "Imidazole alkaloids from Cynometra hankei", *Phytochemistry*, vol. 20, no.12, pp. 2765-2767, 1981. https://doi.org/10.1016/0031-9422(81)85283-1

[6] C. W. Fishwick, R. J. Foster, and R. E. Carr, "A short dipolar cycloaddition approach to γ-lactam alkaloids from cynometra hankei", *Tetrahedron letters*, vol. 37, no.22, pp. 3915-3918, 1996. https://doi.org/10.1016/0040-4039(96)00688-0

[7] P. Singh, V. Dimitriou, R. Mahajan, and A. Crossley, "Double-blind comparison between doxapram and pethidine in the treatment of postanaesthetic shivering", *BJA: British Journal of Anaesthesia*, vol. 71, no. 5, pp. 685-688, 1993. https://doi.org/10.1093/bja/71.5.685

[8] H. He, H. Y. Yang, R. Bigelis, E. H. Solum, M. Greenstein, and G. T. Carter, "Pyrrocidines A and B, new antibiotics produced by a filamentous fungus", *Tetrahedron Letters*, vol. 43, no. 9, pp. 1633-1636, 2002. https://doi.org/10.1016/S0040-4039(02)00099-0

[9] C. Osterhage, R. Kaminsky, G. M. König, and A. D. Wright, "Ascosalipyrrolidinone A, an Antimicrobial Alkaloid, from the Obligate Marine Fungus *Ascochyta salicorniae*", *The Journal of*

Organic Chemistry, vol. 65, no.20, pp. 6412-6417, 2000. https://doi.org/10.1021/jo000307g

[10] N. T. Nguyen, V. V. Dai, A. Mechler, N. T. Hoa, and Q. V. Vo, "Synthesis and evaluation of the antioxidant activity of 3-pyrroline-2-ones: experimental and theoretical insights", *RSC advances*, vol. 12, 2022. DOI: 10.1039/d2ra04640g

[11] J. Whitt, S. M. Shipley, D. J. Newman, and K. M. Zuck, "Tetramic Acid Analogues Produced by Coculture of Saccharopolyspora erythraea with Fusarium pallidoroseum", *Journal of natural products*, vol. 77, no. 1, 2014, pp. 173-177. https://doi.org/10.1021/np400761g

[12] S. Zykova *et al*., "Predictive and experimental determination of antioxidant activity in the series of substituted 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diphenyl-1,5-dihydro-2*H*-pyrrol-2-ones", *Journal of Pharmaceutical Sciences and Research*, vol. 10, no. 1, pp. 164-166, 2018.

[13] A. Q. Cusumano and J. G. Pierce, "3-Hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones as novel antibacterial scaffolds against methicillin-resistant Staphylococcus aureus", *Bioorganic & medicinal chemistry letters*, vol. 28, no. 16, pp. 2732-2735, 2018. https://doi.org/10.1016/j.bmcl.2018.02.047

[14] A. López-Pérez *et al.*, "Discovery of Pyrrolidine-2,3-diones as Novel Inhibitors of P. aeruginosa PBP3", *Antibiotics*, vol. 10, no. 5, pp. 529, 2021. https://doi.org/10.3390/antibiotics10050529

[15] X. Del Corte *et al.*, "A Multicomponent Protocol for the Synthesis of Highly Functionalized γ-Lactam Derivatives and Their Applications as Antiproliferative Agents", *Pharmaceuticals*, vol. 14, no. 8, pp. 782, 2021. https://doi.org/10.3390/ph14080782

[16] E. Surmiak *et al.*, "A Unique Mdm2-Binding Mode of the 3-Pyrrolin-2-one- and 2-Furanone-Based Antagonists of the p53-Mdm2 Interaction", *ACS chemical biology*, vol. 11, no. 12, pp. 3310-3318, 2016. https://doi.org/10.1021/acschembio.6b00596

[17] N. Joksimović *et al.*, "Synthesis, characterization, anticancer evaluation and mechanisms of cytotoxic activity of novel 3-hydroxy-3-pyrrolin-2-ones bearing thenoyl fragment: DNA, BSA interactions and molecular docking study", *Bioorganic Chemistry*, vol. 88, pp. 102954, 2019. https://doi.org/10.1016/j.bioorg.2019.102954

[18] K. Ma, P. Wang, W. Fu, X. Wan, L. Zhou, Y. Chu, and D. Ye, "Rational design of 2-pyrrolinones as inhibitors of HIV-1 integrase", *Bioorganic & medicinal chemistry letters*, vol. 21, no. 22, pp. 6724-6727, 2011. https://doi.org/10.1016/j.bmcl.2011.09.054

[19] N. V. Ortiz Zacarías *et al.*, "Pyrrolone Derivatives as Intracellular Allosteric Modulators for Chemokine Receptors: Selective and Dual-Targeting Inhibitors of CC Chemokine Receptors 1 and 2", *Journal of Medicinal Chemistry*, vol. 61, no. 20, pp. 9146-9161, 2018. https://doi.org/10.1021/acs.jmedchem.8b00605

[20] E. M. de Marigorta, J. M. de los Santos, A. M. O. de Retana, J. Vicario, and F. Palacios, "Multicomponent Reactions in the Synthesis of γ-Lactams", *Synthesis*, vol. 50, no. 23, pp. 4539-4554, 2018. DOI:10.1055/s-0037-1611014

[21] K. L. Ameta and A. Dandia, *Multicomponent reactions: Synthesis of bioactive heterocycles*, CRC Press, 2017

[22] R. Ghorbani-Vaghei, N. Sarmast, and J. Mahmoodi, "One-pot synthesis of polysubstituted pyrrolidinones using novel magnetic nanoparticles as an efficient and reusable catalyst", *Applied Organometallic Chemistry*, vol. 31, no. 8, pp. e3681, 2017. https://doi.org/10.1002/aoc.3681

[23] S. Esmaeilzadeh and D. Setamdideh, "Synthesis and characterization of Fe_3O_4/PEG-400/oxalic acid magnetic nanoparticles as a heterogeneous catalyst for the synthesis of pyrrolin-2-ones derivatives", *Journal of the Serbian Chemical Society*, vol. 86, no. 11, pp. 1039-1052, 2021. https://doi.org/10.2298/JSC210521059E

[24] A. Saha, S. Payra, and S. Banerjee, "In-water facile synthesis of poly-substituted 6-arylamino pyridines and 2-pyrrolidone derivatives using tetragonal nano-ZrO_2 as reusable catalyst", *RSC advances*, vol. 6, pp. 101953-101959, 2016. https://doi.org/10.1039/C6RA24367C

[25] A. Dutta, M. A. Rohman, R. Nongrum, A. Thongni, S. Mitra, and R. Nongkhlaw, "Visible light-promoted synthesis of pyrrolidinone derivatives *via* Rose Bengal as a photoredox catalyst and their photophysical studies", *New Journal of Chemistry*, vol. 45, no. 18, pp. 8136-8148, 2021. https://doi.org/10.1039/D1NJ00343G

[26] S. Manta *et al.*, "A novel and easy two-step, microwave-assisted method for the synthesis of halophenyl pyrrolo[2,3-*b*]quinoxalines via their pyrrolo precursors. Evaluation of their bioactivity", *Tetrahedron Letters*, vol. 55, no. 11, pp. 1873-1876, 2014. https://doi.org/10.1016/j.tetlet.2014.01.106

[27] N. T. Nguyen, V. V. Dai, N. N. Tri, L. Van Meervelt, N. T. Trung, and W. Dehaen, "Experimental and theoretical studies on the synthesis of 1,4,5-trisubstituted pyrrolidine-2,3-diones", *Beilstein Journal of Organic Chemistry*, vol. 18, pp. 1140-1153, 2022. https://doi.org/10.3762/bjoc.18.118

[28] A. K. Chakraborti, S. Bhagat, and S. Rudrawar, "Magnesium perchlorate as an efficient catalyst for the synthesis of imines and phenylhydrazones", *Tetrahedron letters*, vol. 45, no. 41, pp. 7641-7644, 2004. https://doi.org/10.1016/j.tetlet.2004.08.097

[29] B. Mostafa, S. M. Habibi-Khorassani, and M. Shahraki, "An experimental investigation of substituent effects on the formation of 2,3-dihydroquinazolin-4(1H)-ones: a kinetic study", *Journal of Physical Organic Chemistry*, vol. 30, no. 3, pp. e3616, 2017. https://doi.org/10.1002/poc.3616

[30] H. Ahankar, A. Ramazani, K. Ślepokura, T. Lis, and S. W. Joo, "Synthesis of pyrrolidinone derivatives from aniline, an aldehyde and diethyl acetylenedicarboxylate in an ethanolic citric acid solution under ultrasound irradiation", *Green Chemistry*, vol.18, pp. 3582-3593, 2016. DOI: 10.1039/C6GC00157B

[31] Z. Hosseinzadeh, A. Ramazani, H. Ahankar, K. Ślepokura, and T. Lis, "Sulfonic Acid-Functionalized Silica-Coated Magnetic Nanoparticles as a Reusable Catalyst for the Preparation of Pyrrolidinone Derivatives Under Eco-Friendly Conditions", *Silicon*, vol. 11, pp. 2933-2943, 2019. https://doi.org/10.1007/s12633-019-0087-2

SUPPORTING INFORMATION

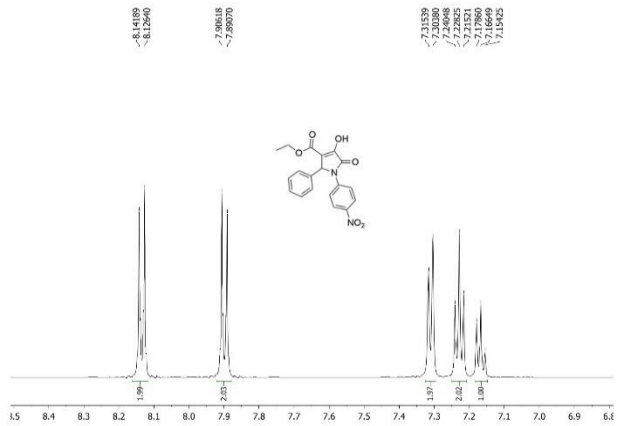

Figure S1. *^{1}H NMR spectrum of 1-(4-nitrophenyl)-5-phenyl-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (**4a**) in the chemical shift range of 7.0 – 8.4 pmm*

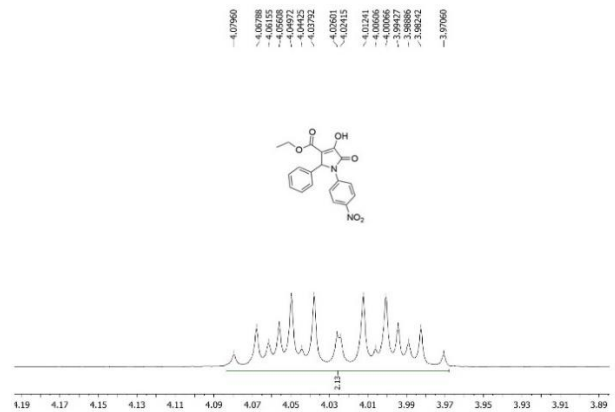

Figure S2. *Peaks of doublet of quartet (dq) of two diastereotopic methylene protons (−CH_2) in compound **4a***

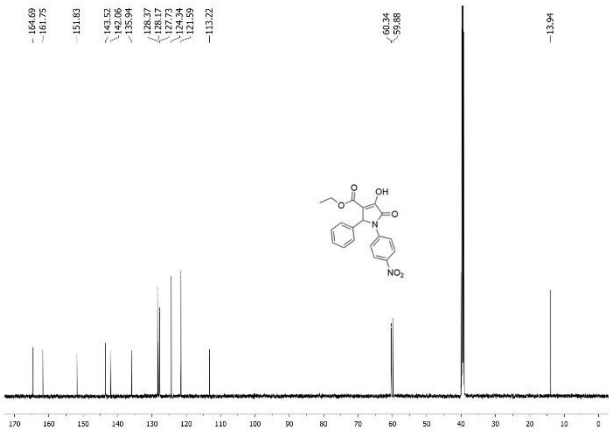

Figure S3. *^{13}C NMR spectrum of 1-(4-nitrophenyl)-5-phenyl-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (**4a**)*

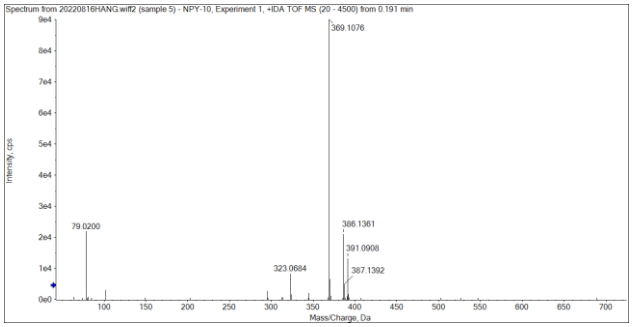

Figure S4. *ESI – HRMS spectrum of 1-(4-nitrophenyl)-5-phenyl-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (**4a**)*

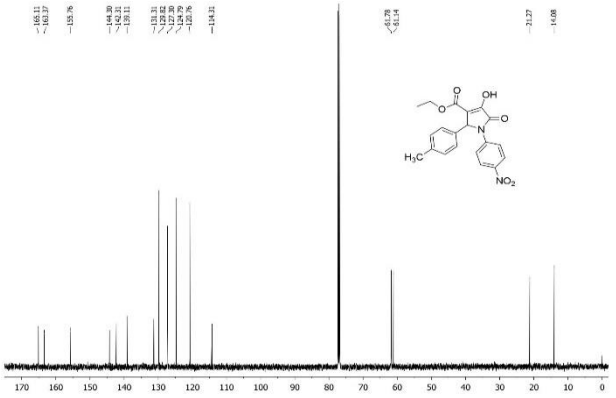

Figure S5. *^{13}C NMR spectrum of 5-(4-methylphenyl)-1-(4-nitrophenyl)-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (**4b**)*

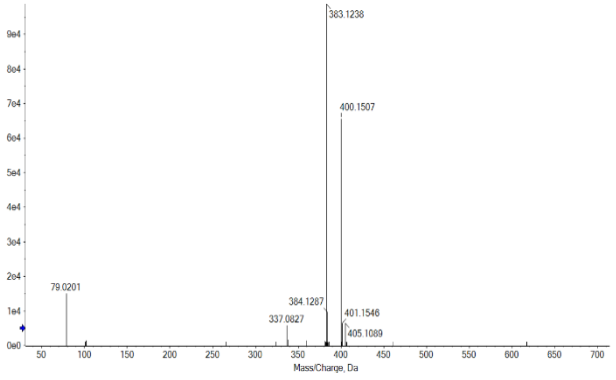

Figure S6. *ESI – HRMS spectrum of 5-(4-methylphenyl)-1-(4-nitrophenyl)-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (**4b**)*

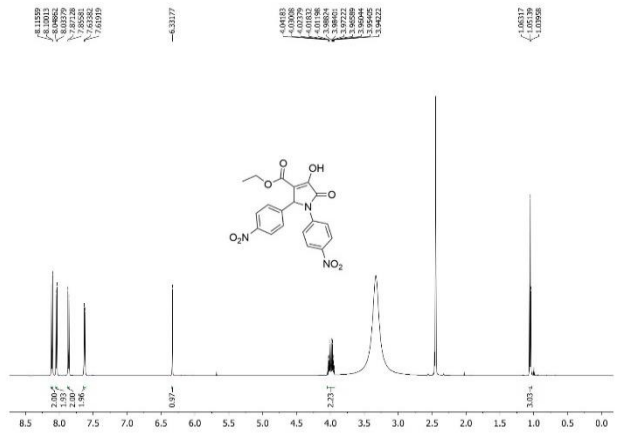

Figure S7. *^{1}H NMR spectrum of 1-(4-nitrophenyl)-5-(4-nitrophenyl)-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (**4c**)*

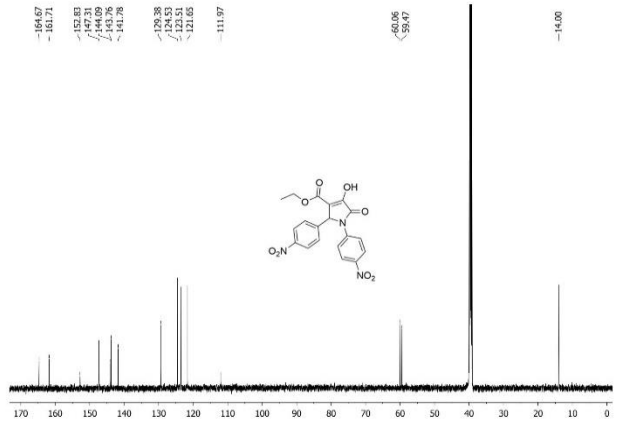

Figure S8. *^{13}C NMR spectrum of 1-(4-nitrophenyl)-5-(4-nitrophenyl)-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (**4c**)*

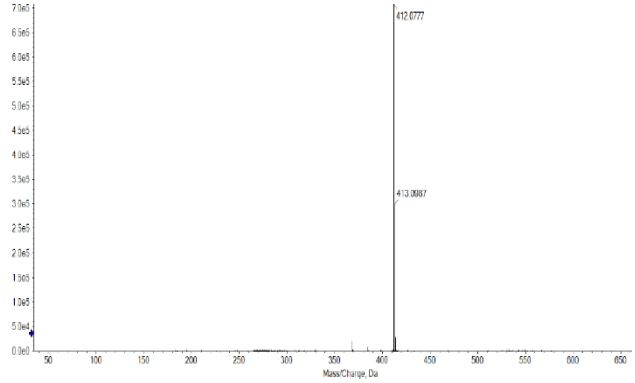

Figure S9. *ESI – HRMS spectrum of 1-(4-nitrophenyl)-5-(4-nitrophenyl)-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (**4c**)*