ETHYL 1-BENZYL-2-(4-METHYLPHENYL)-1*H*-PYRROLO[2,3-*b*]QUINOXALINE-3-CARBOXYLATE AND ETHYL 6,7-DIMETHYL-1,2-DIPHENYL-1*H*-PYRROLO[2,3-*b*]QUINOXALINE-3-CARBOXYLATE: SYNTHESIS AND STUDY ON NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

ETHYL 1-BENZYL-2-(4-METHYLPHENYL)-1*H*-PYRROLO[2,3-*b*]QUINOXALINE-3-CARBOXYLATE VÀ ETHYL 6,7-DIMETHYL-1,2-DIPHENYL-1*H*-PYRROLO[2,3-*b*] QUINOXALINE-3-CARBOXYLATE: TỔNG HỢP VÀ PHÂN TÍCH PHỔ CỘNG HƯỞNG TỪ HẠT NHÂN

Vo Viet Dai, Bui Bich Loc, Nguyen Tran Nguyen*

The University of Danang - University of Science and Education, Vietnam

*Corresponding author: ntnguyen@ued.udn.vn

(Received: February 21, 2025; Revised: April 02, 2025; Accepted: April 04, 2025)

DOI: 10.31130/ud-jst.2025.094E

Abstract - Synthetic pyrrolo[2,3-*b*]quinoxalines have been confirmed to possess valuable biological activities and pharmacokinetic properties. However, the presence of heavy metal catalysts in synthesizing these heterocycles has restricted the application of those methods in pharmaceutical manufacturing. In this study, two pyrrolo[2,3-*b*]quinoxalines have been synthesized *via* the nucleophilic addition reaction between 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrrolin-2-ones and *o*-phenylenediamine or 4,5-dimethyl-*o*-phenylenediamine as nucleophiles in glacial acetic acid. In the acidic medium of acetic acid, 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-ones could be tautomerized to keto tautomers, also known as 2,3-dioxopyrrolidine derivatives. More importantly, the structure of two desired pyrrolo[2,3-*b*]quinoxalines has been approved *via* nuclear magnetic resonance spectroscopy (1D NMR, 2D NMR) and high-resolution mass spectrometry (HRMS).

Key words - 1,5-disubstituted-3-hydroxy-3-pyrroline-2-ones; pyrrolo[2,3-*b*]quinoxalines; quinoxaline derivatives; multi-component reaction; *γ*-lactam ring

Tóm tắt - Nhiều dẫn xuất pyrrolo[2,3-*b*]quinoxaline đã được tổng hợp và qua khảo sát cho thấy chúng có hoạt tính sinh học, dược động học có giá trị. Tuy nhiên, các phương pháp sử dụng xúc tác kim loại nặng trong quá trình tổng hợp đã làm hạn chế việc ứng dụng các phương pháp này trong công nghiệp hoá dược. Trong nghiên cứu này, hai dẫn xuất pyrrolo[2,3-*b*]quinoxaline đã được tổng hợp thông qua phản ứng cộng nucleophile giữa hai dẫn xuất 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one và tác nhân nucleophile là *o*-phenylenediamine hoặc 4,5-dimethyl-*o*-phenylenediamine trong dung môi acetic acid khan. Trong môi trường acid của acetic acid, các hợp chất 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one có thể bị tautomer hoá thành dạng keto, còn được gọi là các dẫn xuất 2,3-dioxopyrrolidine. Ngoài ra, cấu trúc của hai dẫn xuất pyrrolo[2,3-*b*]quinoxaline cũng đã được phân tích và chứng minh dựa vào phổ cộng hưởng từ hạt nhân và phổ khối phân giải cao.

Từ khóa - 1,5-disubstituted-3-hydroxy-3-pyrroline-2-ones; pyrrolo[2,3-*b*]quinoxalines; quinoxaline derivatives; multi-component reaction; *γ*-lactam ring

1. Introduction

Numerous quinoxaline derivatives have been synthesized and explored their biological activities and pharmacokinetic properties [1], [2]. For instance, XK469 (**1**) exhibited successful inhibition of neuroblastoma tumor growth, and the structure-activity relationship study showed the well-fitted quinoxaline core of XK469 into the hydrophobic pocket of tumor cells [3]. 2-Amino-1-(5-methoxy-2-methylphenyl)-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxamide (**2**) was evaluated for its pharmacokinetic properties in mice, which displayed the cytostatic activity *in vivo* assays of human breast cancer xenograft [4]. Pyrrolo[1,2-*a*]quinoxalines (**3**) have been identified as potent inhibitors toward the ATP binding site of cyclin-dependent protein kinase 2 (CDK2) in cancer treatment (Figure 1) [5]. It is undoubtedly true that quinoxaline derivatives have attracted great attention due to promising biological activities that ensure them a bright future in the pharmaceutical industry. Additionally, quinoxalines have also been applied in agriculture as insecticides, fungicides, herbicides [6], and some other fields, such as dyes [7], electroluminescent materials [8], and organic semiconductors [9].

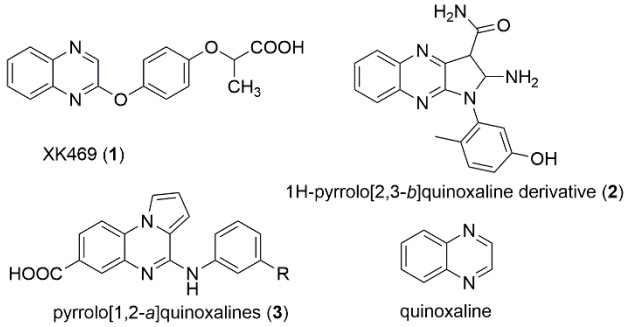

***Figure 1**. Biologically active compounds containing quinoxaline moiety*

A simple quinoxaline core has been synthesized based on the condensation between *o*-phenylenediamine and 1,2-diketone containing compounds at high temperatures, and an acid catalyst is required [1]. Many non-natural

pyrrolo[2,3-*b*]quinoxaline derivatives have been synthesized and proven as potential drug candidates in anticancer treatment [10], antioxidants [11], and antibiotics [12]. Consequently, numerous efforts have been made to explore the green synthetic pathways towards pyrrolo[2,3-*b*]quinoxalines instead of using palladium-based catalysts [13], [14]. Recently, there have been several ethyl 1,2-disubstituted-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylate synthesized *via* the condensation between *o*-phenylenediamine and 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-ones in glacial acetic acid without any toxic metal catalyst, and their antioxidant activities were also evaluated [11]. In this manuscript, the synthesis of two pyrrolo[2,3-*b*]quinoxalines based on the known method [11] will be reported and their nuclear magnetic resonance spectra will also be characterized.

2. Experimental section

2.1. General experimental methods

^{1}H NMR, ^{13}C NMR, COSY, HSQC, and HMBC spectra were acquired on Bruker Avance II+ 600 MHz spectrometer and 500 MHz spectrometer. Chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal reference or internal deuterated solvent signal. Electrospray ionization – High resolution mass spectra (ESI – HRMS) were recorded on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Silica gel 60 (0.063-0.200 mm) was used as the stationary phase for column chromatography. The melting points were measured by Büchi Melting Point B-545 apparatus. All chemicals were purchased from Sigma Aldrich, Acros, or Merck without further purification.

2.2. Synthetic procedure for ethyl 1-benzyl-2-(4-methylphenyl)-1H-pyrrolo[2,3-b]quinoxaline-3-carboxylate (6) like reference [11]

To a screw-capped reaction tube equipped with a magnetic stirring bar was added 1-benzyl-5-(4-methylphenyl)-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (**4**) (50.0 mg, 0.142 mmol, 1 equiv.), *o*-phenylenediamine (**5**) (46.2 mg, 0.427 mmol, 3 equiv.) and glacial acetic acid (0.5 mL). The resulting mixture was stirred vigorously at 90 °C for 2 hours. The crude product was purified *via* column chromatography (silica gel, hexane: ethylacetate = 8: 1.5) to obtain a pure product.

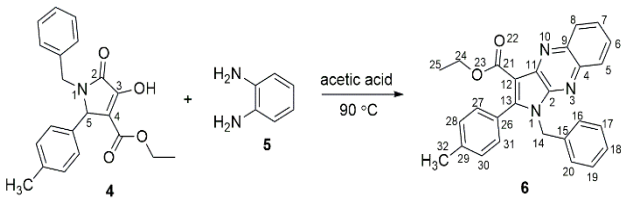

***Figure 2**. Synthesis of ethyl 1-benzyl-2-(4-methylphenyl)-1H-pyrrolo[2,3-b]quinoxaline-3-carboxylate (6)*

2.3. Synthetic procedure for ethyl 6,7-dimethyl-1,2-diphenyl-1H-pyrrolo[2,3-b]quinoxaline-3-carboxylate (9) like reference [11]

To a screw-capped reaction tube equipped with a magnetic stirring bar was added 1,5-diphenyl-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (**7**) (50.0 mg, 0.155 mmol, 1 equiv.), 4,5-dimethyl-*o*-phenylenediamine (**8**) (63.2 mg, 0.464 mmol, 3 equiv.) and glacial acetic acid (0.5 mL). The resulting mixture was stirred vigorously at 90 °C for 7 hours. The crude product was purified *via* column chromatography (silicagel, hexane: ethylacetate = 8: 2.25) to obtain a pure product.

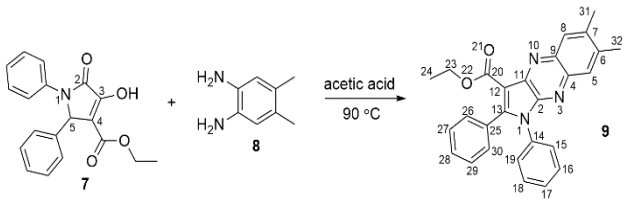

***Figure 3**. Synthesis of ethyl 6,7-dimethyl-1,2-diphenyl-1H-pyrrolo[2,3-b]quinoxaline-3-carboxylate (9)*

3. Results and discussion

1-Benzyl-5-(4-methylphenyl)-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (**4**) and 1,5-diphenyl-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-one (**7**) were synthesized *via* multicomponent reaction of amine, aldehyde, and sodium diethyl oxalacetate in the presence of citric acid as the catalyst [15]. There is no doubt that the enol forms of 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-ones **4**, **7** could be interconverted to keto tautomers **4'**, **7'**, respectively, in polar protic solvent CH_3COOH (Figure 4) [11], [16], [17]. In the enol tautomers **4** and **7**, a lone pair of electrons on the oxygen atom of hydroxyl group (–OH) at the 3-position is in conjugation with the C–C π bond at 3,4-positions which can donate towards the ring leading to new C–O π bond. Subsequently, the pair of electrons of the C–C π bond at 3,4-positions moves over to become a lone pair of electrons on the carbon atom at the 4-position. Consequently, there are positive charge and negative charge located on the oxygen atom and carbon atom, respectively, in the intermediate **10**. The negative charge on the carbon atom will be neutralized by the acidic proton of acetic acid and its conjugated base will then take a hydrogen atom attaching to a positively charged oxygen atom which results in the keto tautomers **4'**, **7'** (Figure 4).

Keto tautomers **4'**, **7'** are 2,3-dioxopyrrolidine derivatives which react with *o*-phenylenediamine (**5**), 4,5-dimethyl-*o*-phenylenediamine (**8**), respectively, in glacial acetic acid at high temperature (90 °C) to yield pyrrolo[2,3-*b*]quinoxalines **6** and **9** (Figure 2, Figure 3). For the synthesis of ethyl 6,7-dimethyl-1,2-diphenyl-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylate (**9**), for instance, a lone pair of electrons on nitrogen atom of amino group (NH_2) of 4,5-dimethyl-*o*-phenylenediamine (**8**) will be used to make a new sigma bond with carbonyl carbon atom at the 3-position of keto form **7'** to yield the intermediate **12**. Subsequently, there is the intramolecular hydrogen transfer from positively charged nitrogen to negatively charged oxygen, which results in the intermediate **13**. The oxygen atom of a hydroxyl group (–OH) in **13** will then be protonated by the acidic proton of acetic acid, leaving the positive charge on the oxygen atom of intermediate **14**.

Due to the difference in electronegativity between oxygen and carbon atoms, the sigma bond between the carbon atom and positively charged oxygen atom in **14** will be weakened as compared to the original bond in **13**. The abstraction of a secondary amino proton (NH) by acetate anion in combination with the heterolytic cleavage of carbon – positively charged oxygen sigma bond in **14** will bring about the imine intermediate **15**. There is the imine **15** and enamine **16** tautomerization in which the equilibrium favors the more stable enamine tautomer **16** side. In the intermediate **16**, the lone pair of electrons on the secondary amino nitrogen atom (NH) is in conjugation with both C–C π bond at the 3,4-positions and C–O π bond of ethoxycarbonyl group attached to the 4-position of the 2-pyrrolidinone core. The intramolecular nucleophilic addition reaction between the primary amino nitrogen atom and carbonyl carbon atom in the enamine intermediate **16** will lead to cyclization in the intermediate **17**. The positive charge and negative charge on nitrogen and oxygen atoms of the intermediate **17**, respectively, will then be neutralized *via* the intramolecular hydrogen transfer to reach the compound **18**. Afterward, acetic acid plays a role as the catalyst for the dehydration of intermediate **18** to yield the kinetic product **20**. Lastly, oxidation by O_2 molecules will be responsible for the dehydrogenation of compound **20** which results in final thermodynamic product, ethyl 6,7-dimethyl-1,2-diphenyl-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylate (**9**) (Figure S1, see Supporting Information) [11].

Ethyl 1-benzyl-2-(4-methylphenyl)-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylate (**6**) was obtained as a light yellow solid (27.9 mg, 46.5%), melting point: 133-134°C. HRMS (ESI-quadrupole) *m/z* $[M + H]^+$ calcd for $C_{27}H_{23}N_3O_2$: 422.1869; found: 422.1850 $[M + H]^+$ (Figure S2, see Supporting Information)

In the ^{1}H NMR spectrum of compound **6**, there are resonance signals in the chemical shift range of 6.9 – 8.5 ppm corresponding to thirteen (13) hydrogen atoms of three benzene rings. In addition, there are quartet and triplet resonance signals at 4.27 and 1.17 ppm represented two methylene hydrogen atoms H24, and methyl hydrogen atoms H25, respectively, of ethoxycarbonyl group. Furthermore, there are two siglets at 5.48 ppm and 2.45 ppm correlated with protons H14 of methylene group at 14-position and those of methyl group H32 at 32-position, respectively (Figure S3). The ^{13}C NMR spectrum of pyrrolo[2,3-*b*]quinoxaline **6** has exhibited twenty-three (23) resonance signals representing twenty-seven (27) carbon atoms in the structure of ethyl 1-benzyl-2-(4-methylphenyl)-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylate (**6**) (Figure S4, Figure S5, see Supporting Information).

To determine the exact resonance signals of carbon and hydrogen atoms in pyrrolo[2,3-*b*]quinoxaline derivative **6**, its 2D NMR spectra were also recorded. In the ^{1}H – ^{13}C HSQC spectrum (Figure 5), protons H25, H32, H24 and H14 exhibited cross peaks with carbon atoms resonance at 14.39, 21.80, 46.33, and 60.39 ppm, respectively. Thus, these ^{13}C resonance signals correspond to C25, C32, C24 and C14, accordingly. In addition, aromatic hydrogen atoms' resonance signals at 8.41, 8.13, 7.25, 7.22 and 6.93 ppm represented cross peaks with carbon atoms resonance at 130.24, 128.65, 129.07, 129.91, and 127.52 ppm, respectively. Two aromatic protons resonating at 7.72 ppm correlated with two carbon atoms at 128.51 and 127.63 ppm. More importantly, multiplet resonance signal, in the range of 7.19 ppm to 7.14 ppm, for three aromatic protons showed correlation signals with ^{13}C atoms resonance at 128.74 and 127.86 ppm (Figure 5).

The ^{1}H – ^{1}H COSY spectrum of **6** confirmed that hydrogen atoms resonance at 8.40 ppm and 8.13 ppm, respectively, were coupled to protons resonating at 7.72 ppm as a multiplet. However, there were no cross-peaks observed between the two protons resonance at 8.40 ppm and 8.13 ppm. Therefore, resonance signals at 8.40 ppm, 8.13 ppm correspond to H5, H8, and multiplet signals at 7.72 ppm will belong to H6 and H7. It can be seen that two aromatic protons resonance at 7.25 ppm as a doublet were coupled with those represented by a doublet signal at 7.22 ppm (Figure 6). Consequently, these two doublet peaks have arisen from four hydrogen atoms of 1,4-disubstituted benzene ring in the structure of ethyl 1-benzyl-2-(4-methylphenyl)-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylate (**6**).

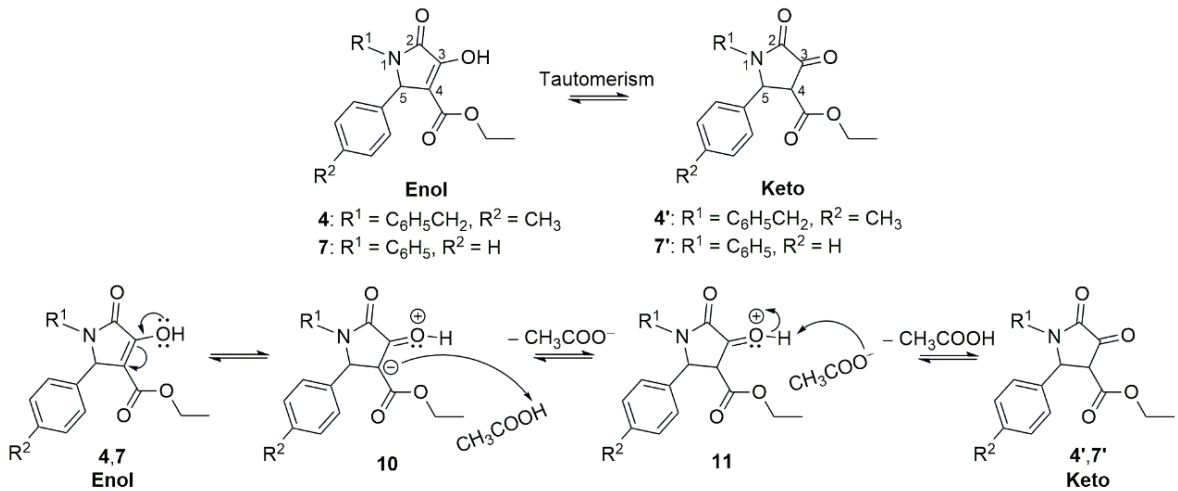

Figure 4. *Mechanism of enol – keto tautomerism of two 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-ones in glacial acetic acid*

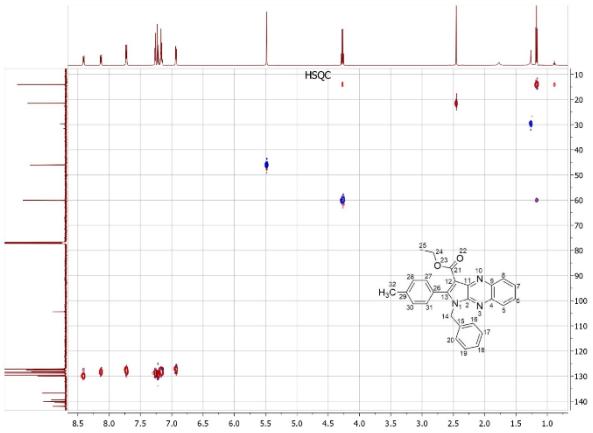

Figure 5. *$^{1}H - ^{13}C$ HSQC spectrum of ethyl 1-benzyl-2-(4-methylphenyl)-1H-pyrrolo[2,3-b]quinoxaline-3-carboxylate (**6**)*

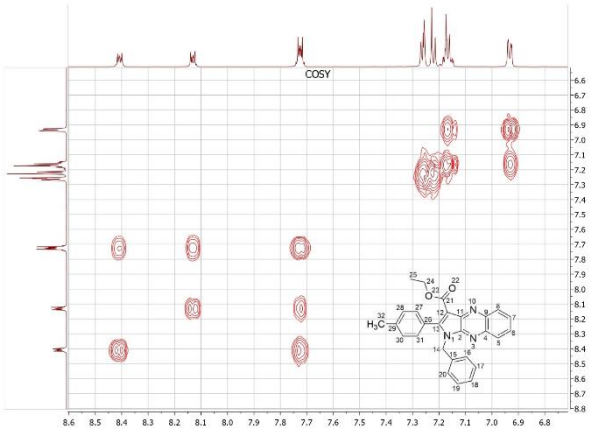

Figure 6. *$^{1}H - ^{1}H$ COSY spectrum of ethyl 1-benzyl-2-(4-methylphenyl)-1H-pyrrolo[2,3-b]quinoxaline-3-carboxylate (**6**)*

The $^{1}H - ^{13}C$ HMBC spectrum of ethyl 1-benzyl-2-(4-methylphenyl)-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylate (**6**) (Figure S6, see Supporting Information) appeared cross signal corresponding to the correlation between methylene protons H24 at 4.27 ppm as a quartet in ^{1}H NMR and carbon at 163.44 ppm in ^{13}C NMR. It is undeniable that the resonance signal at 163.44 ppm in ^{13}C NMR is associated with carbonyl carbon atom C21 at 21-position of pyrrolo[2,3-*b*]quinoxaline **6**. Both low-intensity signals at 140.30 ppm and higher ones at 129.07 ppm in ^{13}C NMR all showed cross peaks with the same hydrogen atoms of methyl group (CH_3) at 32-position. Therefore, resonance peaks at 140.30 ppm and 129.07 ppm in ^{13}C NMR spectrum represent carbon atom C29 and two chemically equivalent atoms C28 + C30, respectively. In combination with COSY and HSQC spectra, it could be approved that doublet signals at 7.25 ppm, 7.22 ppm in ^{1}H NMR and resonance signal at 129.91 ppm in ^{13}C NMR will belong to chemically equivalent protons H28 + H30, H27 + H31, and chemically equivalent carbons C27 + C31, respectively. Two methylene protons H14 and two chemically equivalent atoms H27 + H31 all displayed correlation signals with the same carbon atom resonance at 156.80 ppm and thus, carbon atom C13 resonated at 156.80 ppm in ^{13}C NMR spectrum. In addition, two chemically equivalent atoms H28 + H30 representing by a doublet peak at 7.25 ppm exhibited cross-coupling signal with low intensity carbon signal at 127.41 ppm and consequently, the resonance peak at 127.41 ppm in ^{13}C NMR must be that of carbon C26. There was a cross signal resulting from the correlation between carbon C14 resonance at 46.33 ppm and two protons representing by a doublet of doublets at 6.93 ppm (^{3}J(H,H) = 7.8 Hz, ^{4}J(H,H) = 1.5 Hz). Furthermore, HMBC spectrum showed that two hydrogen atoms at 6.93 ppm in ^{1}H NMR were also coupled with the carbon atom's low-intensity signal at 127.86 ppm in ^{13}C NMR. However, there has no spin – spin coupling appeared between two methylene protons (CH_2) at 14-position and carbon resonance at 127.86 ppm. It could be concluded that doublet of doublets peak at 6.93 ppm in ^{1}H NMR and resonance signal at 127.86 ppm in ^{13}C NMR must be those of two chemically equivalent protons H16 + H20, and carbon C18, respectively. Moreover, HSQC spectrum appeared cross peak corresponding to the correlation between hydrogens H16 + H20 and intense resonance signal at 127.52 ppm. Thus, it is undeniable that the carbon peak at 127.52 ppm stands for C16 + C20.

The $^{1}H - ^{1}H$ COSY spectrum of ethyl 1-benzyl-2-(4-methylphenyl)-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylate (**6**) has determined that there was a cross signal derived from the correlation between chemically equivalent protons H16 + H20 at 6.93 ppm and protons resonance at 7.17 ppm as a multiplet. It means that the multiplet signal at 7.17 ppm in ^{1}H NMR must be those of two chemically equivalent protons H17 + H19 and proton H18. In addition, HSQC 2D spectrum has a cross peak resulted from the spin – spin coupling between protons at 7.17 ppm in ^{1}H NMR and carbons showing by a high intensity signal at 128.74 ppm in ^{13}C NMR. Therefore, high intensity peak at 128.74 ppm in ^{13}C NMR will belong to two chemically equivalent carbon atoms C17 + C19. Furthermore, HMBC spectrum exhibited the cross peak showing the interaction between two protons H16 + H20 and carbon atom at 127.86 ppm in which the signal's intensity at 127.86 ppm is approximately one-half as compared to the one at 128.74 ppm for C17 + C19. It could be confirmed that the signal at 127.86 ppm must be that of carbon C18. More importantly, hydrogen atoms H14, H16 + H20, H17 + H19 all appeared cross signals with the same carbon atom resonance at 137.09 ppm as a low-intensity signal. Thus, it could be concluded that carbon atom C15 has resonated at 137.09 ppm in ^{13}C NMR measurement.

It is reported that four carbon atoms directly attached to two nitrogen atoms of quinoxaline molecule have resonated at higher frequencies, corresponding to approximately 142 ppm in ^{13}C NMR spectrum, than the remaining carbons at around 130 ppm [18]. HMBC spectrum of ethyl 1-benzyl-2-(4-methylphenyl)-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylate (**6**) has an intense cross peak which exhibited the spin-spin coupling between protons H14 and carbon atom resonance at 142.35 ppm. Thus, the resonance peak at 142.35 ppm in ^{13}C NMR represents carbon atom C2. HSQC spectrum of compound **6** has shown correlation signals between H5 (or H8, *can not be determined exactly*) and carbon at 130.24 ppm, H8

(or H5, *can not be determined exactly*) and carbon at 128.65 ppm, H6 (or H7, *can not be determined exactly*) and carbon at 127.63 ppm, H7 (or H6, *can not be determined exactly*) and carbon at 128.51 ppm. In addition, hydrogen atoms H6 (or H7, *can not be determined exactly*) and H5 (or H8, *can not be determined exactly*) all showed correlation peaks with one carbon resonating at 142.30 ppm and thus, C4 (or C9, *can not be determined exactly*) has resonated at the chemical shift of 142.30 ppm in ^{13}C NMR. Moreover, carbon atom resonance at 139.75 ppm in ^{13}C NMR spectrum showed cross peaks with two protons H7 (or H6, *can not be determined exactly*) and H8 (or H5, *can not be determined exactly*) and consequently, resonance signal at 139.75 ppm in ^{13}C NMR must be that of carbon C9 (or C4, *can not be determined exactly*). Lastly, resonance signals at 140.82 ppm and 104.70 ppm must be those of carbon atoms C11 and C12, respectively. All spectroscopic data of ethyl 1-benzyl-2-(4-methylphenyl)-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylate (**6**) have been summarized in Table 1.

Table 1. *^{1}H NMR, ^{13}C NMR spectroscopic data of ethyl 1-benzyl-2-(4-methylphenyl)-1H-pyrrolo[2,3-b]quinoxaline-3-carboxylate (**6**) (600/150 MHz, $CDCl_3$)*

Position	δ_C (ppm)	δ_H (ppm)	Position	δ_C (ppm)	δ_H (ppm)
2	142.35	---	**17 and 19**	128.74	7.17 (m, overlapped, 3H; Ar-H)
4 and 9	142.30, 139.75	---	**18**	127.86	
5 and 8	130.24, 128.65	8.40 (m, overlapped, 1H; Ar-H), 8.13 (m, overlapped, 1H; Ar-H)	**21**	163.44	---
6 and 7	127.63, 128.51	7.72 (m, overlapped, 2H; Ar-H)	**24**	60.39	4.27 (q, ^{3}J(H,H) = 7.14 Hz, 2H; OCH_2)
11	140.82	---	**25**	14.39	1.17 (t, ^{3}J(H,H) = 7.14 Hz, 3H; CH_3)
12	104.70	---	**26**	127.41	
13	156.80	---	**27 and 31**	129.91	7.22 (d, ^{3}J(H,H) = 8.14 Hz, 2H; Ar-H)
14	46.39	5.48 (s, 2H; CH_2)	**28 and 30**	129.07	7.25 (d, ^{3}J(H,H) = 7.69 Hz, 2H; Ar-H)
15	137.09	---	**29**	140.30	---
16 and 20	127.52	6.93 (dd, ^{3}J(H,H) = 7.8 Hz, ^{4}J(H,H) = 1.5 Hz, 2H; Ar-H)	**32**	21.80	2.45 (s, 3H; CH_3)

Ethyl 6,7-dimethyl-1,2-diphenyl-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylate (**9**) was obtained as a light yellow solid (44.6 mg, 68.4%), melting point: 192-195 ^{o}C. HRMS (ESI-quadrupole) *m/z* $[M + H]^+$ calcd for $C_{27}H_{23}N_3O_2$: 422.1869; found: 422.1858 $[M + H^+]$, 444.1679 $[M + Na]^+$ (Figure S7, see Supporting Information). The proton and carbon nuclear magnetic resonance spectroscopic measurement could be summarized as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H, H5 or H8), 7.79 (s, 1H, H8 or H5), 7.35 (m, 9H; Ar-H), 7.25 (m, 1H; Ar-H), 4.31 (q, ^{3}J(H,H) = 7.06 Hz, 2H; OCH_2), 2.52 (s, 3H; CH_3), 2.47 (s, 3H; CH_3), 1.19 ppm (t, ^{3}J(H,H) = 7.13 Hz, 3H; CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.53, 153.95, 142.63, 141.34, 139.83, 139.15, 138.72, 138.13, 135.09, 130.74, 130.35, 129.52, 129.15, 128.96, 128.79, 128.29, 127.84, 127.64, 105.23, 60.44, 20.45, 20.43, 14.21 ppm.

In the structure of ethyl 6,7-dimethyl-1,2-diphenyl-1*H*-pyrrolo[2,3-*b*]quinoxaline-3-carboxylate (**9**), there are two methyl groups attached to two carbon atoms C6 and C7 of pyrrolo[2,3-*b*]quinoxaline core and thus, hydrogen atoms H5 and H8 have resonated as two separated singlet signals at 8.14 ppm and 7.79 ppm in ^{1}H NMR spectrum. Similar to pyrrolo[2,3-*b*]quinoxaline derivative **6**, two methylene hydrogen atoms and three methyl hydrogen atoms exhibited as quartet and triplet resonance peaks at 4.31 ppm and 1.19 ppm, respectively. In addition, ten aromatic protons of two monosubstituted benzene rings are represented by multiple signals in the chemical shift range of 7.24 – 7.39 ppm. Furthermore, protons H31 and H32 have been shown by two singlets at 2.52 ppm and 2.47 ppm (Figure S8, see Supporting Information).

4. Conclusions

There is the enol – keto tautomerism of starting material, two 1,5-disubstituted-4-ethoxycarbonyl-3-hydroxy-3-pyrroline-2-ones, in polar protic solvent glacial acetic acid. Consequently, these two 3-hydroxy-3-pyrroline-2-ones could play the role of 1,2-diketone derivatives which then react with *o*-phenylenediamine, 4,5-dimethyl-*o*-phenylenediamine as nucleophiles *via* nucleophilic addition reaction. Acetic acid is not only the solvent but also the catalyst for the imine intermediate formation and then the intramolecular cyclization will result in desired pyrrolo[2,3-*b*]quinoxalines. The structure of two pyrrolo[2,3-*b*]quinoxalines has been approved *via* one-dimensional 1D and two-dimensional 2D nuclear magnetic resonance spectroscopy (^{1}H NMR, ^{13}C NMR, COSY, HSQC, HMBC), and high-resolution mass spectrometry.

REFERENCES

[1] J. A. Pereira *et al.*, "Quinoxaline, its derivatives and applications: A State of the Art review", *European Journal of Medicinal Chemistry*, vol. 97, no. 5, pp. 664-672, 2015. https://doi.org/10.1016/j.ejmech.2014.06.058

[2] M. Montana, F. Mathias, T. Terme, and P. Vanelle, "Antitumoral activity of quinoxaline derivatives: A systematic review", *European journal of medicinal chemistry*, vol. 163, no. 1, pp. 136-147, 2019. https://doi.org/10.1016/j.ejmech.2018.11.059

[3] Q. -H. Xia *et al.*, "Design, synthesis, biological evaluation and molecular docking study on peptidomimetic analogues of XK469", *European journal of medicinal chemistry*, vol. 124, no. 29, pp. 311-325, 2016. https://doi.org/10.1016/j.ejmech.2016.08.010

[4] A. Unzue, J. Dong, K. Lafleur, H. Zhao, E. Frugier, A. Caflisch, and C. Nevado, "Pyrrolo [3,2-*b*] quinoxaline derivatives as types $I_{1/2}$ and II Eph tyrosine kinase inhibitors: structure-based design, synthesis, and *in vivo* validation", *Journal of medicinal chemistry*, vol. 57, no. 15, pp. 6834-6844, 2014. https://doi.org/10.1021/jm5009242

[5] J. Guillon *et al.*, "Synthesis and biological evaluation of novel substituted pyrrolo[1,2-*a*]quinoxaline derivatives as inhibitors of the human protein kinase CK2", *European Journal of Medicinal Chemistry*, vol. 65, pp. 205-222, 2014. https://doi.org/10.1016/j.ejmech.2013.04.051

[6] G. Sakata, K. Makino, and Y. Kurasawa, "Regent progress in the quinoxaline chemistry. synthesis and biological activity", *Heterocycles*, vol. 27, no. 10, pp. 2481-2515, 1988.

[7] J. -Y. Jaung, "Synthesis and halochromism of new quinoxaline fluorescent dyes", *Dyes and Pigments*, vol. 71, no. 3, pp. 245-250, 2006. https://doi.org/10.1016/j.dyepig.2005.07.008

[8] K. R. J. Thomas, M. Velusamy, J. T. Lin, C. -H. Chuen, and Y. -T. Tao, "Chromophore-labeled quinoxaline derivatives as efficient electroluminescent materials", *Chemistry of Materials*, vol. 17, no. 7, pp. 1860-1866, 2005. https://doi.org/10.1021/cm047705a

[9] D. O'Brien, M. S. Weaver, D. G. Lidzey, and D. D. C. Bradley, "Use of poly(phenyl quinoxaline) as an electron transport material in polymer light-emitting diodes", *Applied Physics Letter*, vol. 69, no. 7, pp. 881-883, 1996. https://doi.org/10.1063/1.117975

[10] B. Prasad *et al.*, "$AlCl_3$ induced C–N bond formation followed by Pd/C–Cu mediated coupling–cyclization strategy: synthesis of pyrrolo[2,3-*b*]quinoxalines as anticancer agents", *Tetrahedron Letters*, vol. 53, no. 45, pp. 6059-6066, 2012. https://doi.org/10.1016/j.tetlet.2012.08.119

[11] N. T. Nguyen, V. V. Dai, A. Mechler, L. Van Meervelt, N. T. Hoa, and Q. V.Vo, "Synthesis and computational evaluation of the antioxidant activity of pyrrolo[2,3-*b*]quinoxaline derivatives", *RSC advances*, vol. 14, no. 34, pp. 24438-24446, 2024. DOI: 10.1039/D4RA03108C

[12] R. Chemboli *et al.*, "Pyrrolo[2,3-*b*]quinoxalines in attenuating cytokine storm in COVID-19: their sonochemical synthesis and *in silico*/*in vitro* assessment", *Journal of Molecular Structure*, 2021, vol. 1230, no. 15, pp. 129868, 2021. https://doi.org/10.1016/j.molstruc.2020.129868

[13] P. V. Babu *et al.*, "Ligand/PTC-free intramolecular Heck reaction: synthesis of pyrroloquinoxalines and their evaluation against PDE4/luciferase/oral cancer cell growth *in vitro* and zebrafish *in vivo*", *Organic & Biomolecular Chemistry*, vol. 11, no. 39, pp. 6680-6685, 2013. https://doi.org/10.1039/C3OB41504J

[14] S. K. Kolli *et al.*, "Ligand-free Pd-catalyzed C–N cross-coupling/cyclization strategy: An unprecedented access to 1-thienyl pyrroloquinoxalines for the new approach towards apoptosis", *European Journal of Medicinal Chemistry*, vol. 86, no. 30, pp. 270-278, 2014. https://doi.org/10.1016/j.ejmech.2014.08.057

[15] 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, no. 38, pp. 24579-24588, 2022. DOI: 10.1039/D2RA04640G

[16] F. A. Rashid, M. Mohammat, F. Bouchamma, Z. Shaameri, and A. Hamzah, "Facile Reduction of *β*-Enamino Oxopyrrolidine Carboxylates Mediated by Heterogeneous Palladium Catalyst". *Russian Journal of Organic Chemistry*, vol. 56, no. 6, pp. 1082-1088, 2020. https://doi.org/10.1134/S1070428020060184

[17] A. G. Cook and P. M. Feltman, "Determination of Solvent Effects on Keto-Enol Equilibria of 1,3-Dicarbonyl Compounds Using NMR", *Journal of chemical education*, vol. 84, no. 11, pp. 1827, 2007. https://doi.org/10.1021/ed084p1827

[18] H. McNab, "^{13}C Nuclear Magnetic Resonance Spectra of Quinoxaline Derivatives", *Journal of the Chemical Society, Perkin Transactions 1*, pp. 357-363, 1982. https://doi.org/10.1039/P19820000357

SUPPORTING INFORMATION

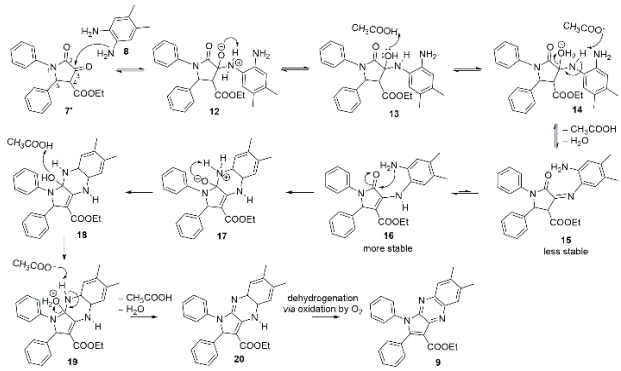

Figure S1. *Mechanism for the synthesis of ethyl 6,7-dimethyl-1,2-diphenyl-1H-pyrrolo[2,3-b]quinoxaline-3-carboxylate (**9**) [11]*

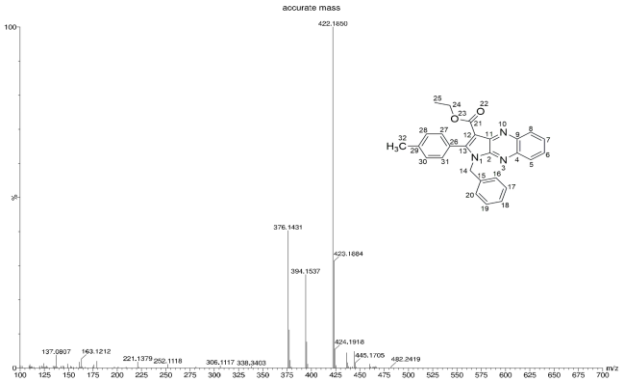

Figure S2*. HRMS spectrum of ethyl 1-benzyl-2-(4-methylphenyl)-1H-pyrrolo[2,3-b]quinoxaline-3-carboxylate (**6**)*

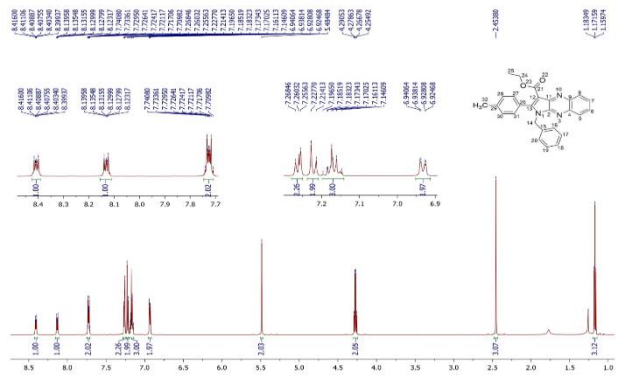

Figure S3*. ^{1}H NMR spectrum of ethyl 1-benzyl-2-(4-methylphenyl)-1H-pyrrolo[2,3-b]quinoxaline-3-carboxylate (**6**)*

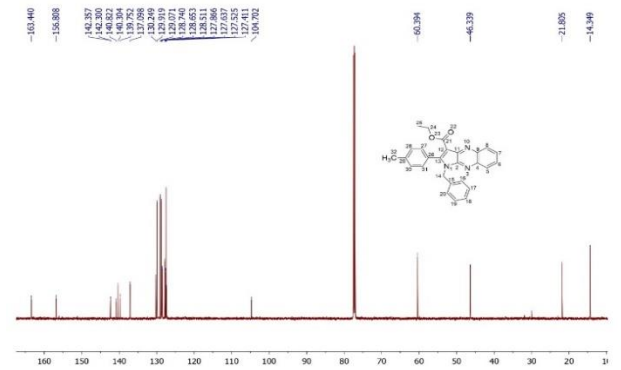

Figure S4*. ^{13}C NMR spectrum of ethyl 1-benzyl-2-(4-methylphenyl)-1H-pyrrolo[2,3-b]quinoxaline-3-carboxylate (**6**)*

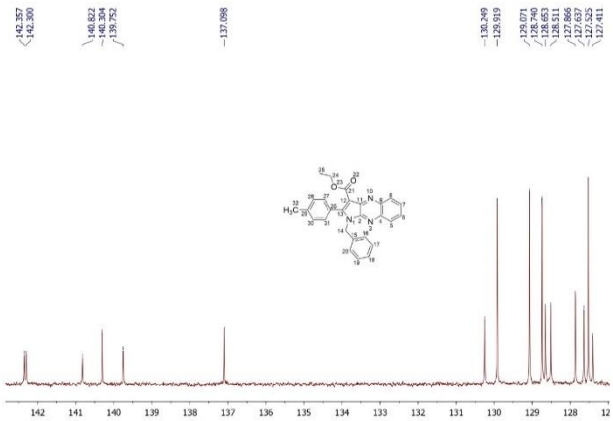

Figure S5. *^{13}C NMR spectrum of ethyl 1-benzyl-2-(4-methylphenyl)-1H-pyrrolo[2,3-b]quinoxaline-3-carboxylate (**6**) in the chemical shift region of 142-127 ppm*

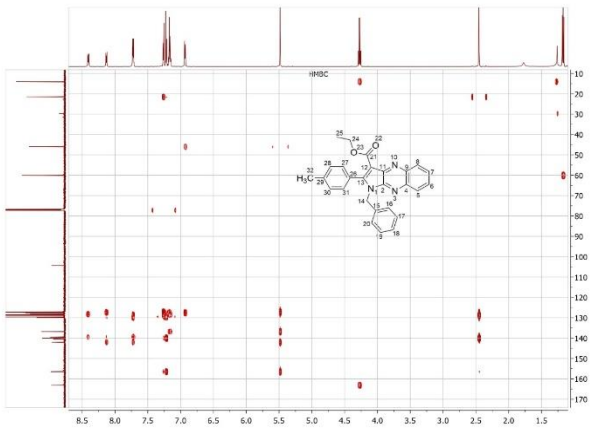

Figure S6. *HMBC spectrum of ethyl 1-benzyl-2-(4-methylphenyl)-1H-pyrrolo[2,3-b]quinoxaline-3-carboxylate (**6**)*

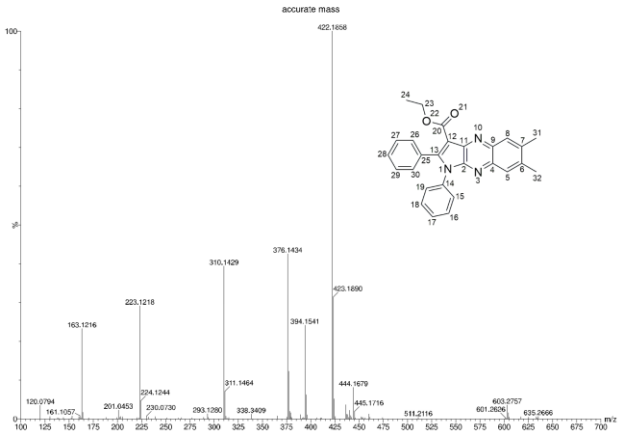

Figure S7. *HRMS spectrum of ethyl 6,7-dimethyl-1,2-diphenyl-1H-pyrrolo[2,3-b]quinoxaline-3-carboxylate (**9**)*

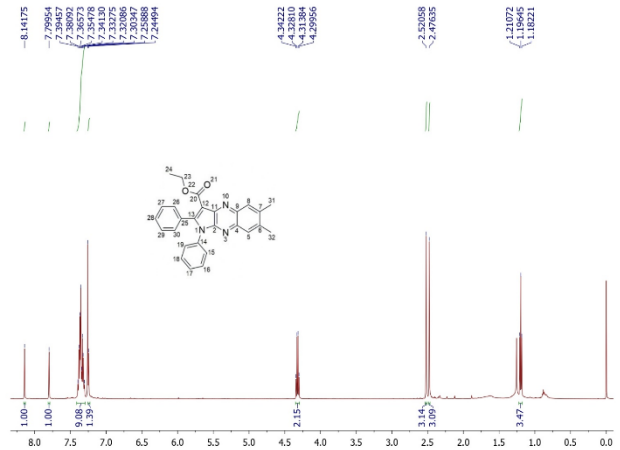

Figure S8. *^{1}H NMR spectrum of ethyl 6,7-dimethyl-1,2-diphenyl-1H-pyrrolo[2,3-b]quinoxaline-3-carboxylate (**9**)*