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# Synthesis of Quinoxalin-2(1H)-One Derivatives via the Novel Ugi 4CR-Palladium- Catalyzed Cyclization Process †

**Murali Venkata Basavanag Unnamatla [1,2], Rocio Gámez Montaño [3,*] and Laurent El Kaïm [4,*]**

[1] Centro Conjunto de Investigación en Quimica Sustentable, UAEM-UNAM, Unidad San Cayetano, km 14.5, Toluca, Estado de Mexico, Mexico; email1@email.com
[2] Facultad de Quimica, Universidad Autonoma del Estado de Mexico, Toluca, Estado de Mexico, Mexico
[3] Departamento de Química, Universidad de Guanajuato, Noria Alta S/N, Col. Noria Alta, Guanajuato C.P. 36050, Guanajuato, Mexico
[4] Unité de Chimie et Procédés, Synthèse Organique et Réactivité ENSTA Paris, Ecole Nationale Supérieure de Techniques Avancées 828, Boulevard des Maréchaux, 91120 Palaiseau, France
* Correspondence: rociogm@ugto.mx (R.G.M.); laurent.elkaim@ensta-paris.fr (L.E.K.)
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**Abstract**

A novel synthetic methodology has been developed for the efficient preparation of Quinoxalin-2(1H)-one derivatives through a strategically designed combination of Ugi four-component reaction (4CR) followed by metal-catalyzed cross-coupling reactions. This innovative approach demonstrates exceptional versatility in generating molecular diversity by systematically modulating the reactivity profiles of the initially formed Ugi adducts, thereby enabling access to a broad library of structurally diverse quinoxalinone compounds. The synthetic protocol consistently delivered the desired final products in good to moderate yields, demonstrating the reliability and practicality of this methodology for preparative applications. Comprehensive structural characterization of all synthesized derivatives was accomplished through a combination of advanced spectroscopic techniques, including proton nuclear magnetic resonance ($^{1}$H NMR), carbon-13 nuclear magnetic resonance ($^{13}$C NMR), and high-resolution mass spectrometry, ensuring unambiguous confirmation of product identities and purities. The methodological framework employs 2-iodoaniline and 2-chloroacetic acid as the fixed amine and carboxylic acid components, respectively, in the multicomponent Ugi reaction, providing a consistent synthetic foundation. Subsequently, the resulting Ugi adducts undergo palladium-catalyzed cross-coupling transformations under optimized reaction conditions, facilitating the crucial cyclization and functionalization steps necessary for the formation of the target Quinoxalin-2(1H)-one derivatives. This sequential approach represents a significant advancement in heterocyclic synthesis methodology.

**Keywords:** Ugi reaction; quinoxalin-2(1H)-one; palladium cross coupling reaction; IMCR

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## 1. Introduction

In recent years, the swift synthesis of intricate molecular architectures has been facilitated by the implementation of diversity-oriented synthetic methodologies alongside so-called complexity-generating reactions. Multicomponent reactions (MCRs) [1,2], which amalgamate a minimum of three fundamental building blocks within a single reaction

vessel, constitute an exceptionally potent framework for achieving both diversity and complexity while minimizing the number of reaction steps required. In this discourse, we delineate innovative modular reaction sequences predicated upon our earlier reported MCR chemistry in conjunction with cycloaddition reactions and transition-metal catalyzed cross-coupling processes [1]. Transformations catalyzed by palladium rank among the most robust and adaptable techniques in organic synthesis for the construction of C–C and C-heteroatom bonds [3], frequently providing unparalleled access to molecular frameworks that are otherwise challenging to synthesize.

In the context of our ongoing research initiative aimed at the identification of novel post-modifications [4,5] for compounds synthesized via multicomponent reactions (MCRs) [5], we sought to explore the potential of utilizing this cyclization with adducts generated through an Ugi reaction. From this perspective, we proposed a synthetic approach based on the Ugi reaction, which is subsequently followed by a sequential palladium-catalyzed cross-coupling reaction (Scheme 1) to yield Quinoxalin-2(1H)-one [6–9] derivatives.

Quinoxalinones represent a category of nitrogen-containing fused heterocyclic compounds that have garnered significant interest owing to their multifunctional scaffolds pertinent to pharmacological agents [10,11]. These compounds manifest a multitude of biological activities, including antimicrobial [12], antifungal [13], antidiabetic [14], antiviral [15], anticancer [16], and anti-inflammatory properties [17]. The exploration of quinoxalinone scaffolds constitutes an exceptionally compelling endeavor within the realm of drug discovery initiatives.

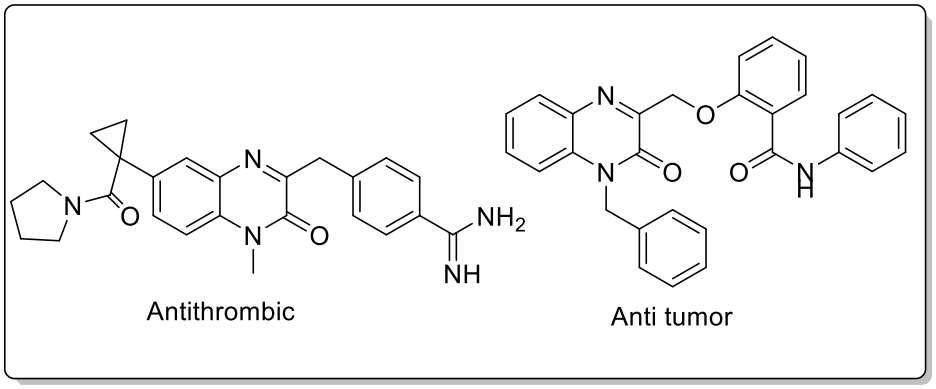
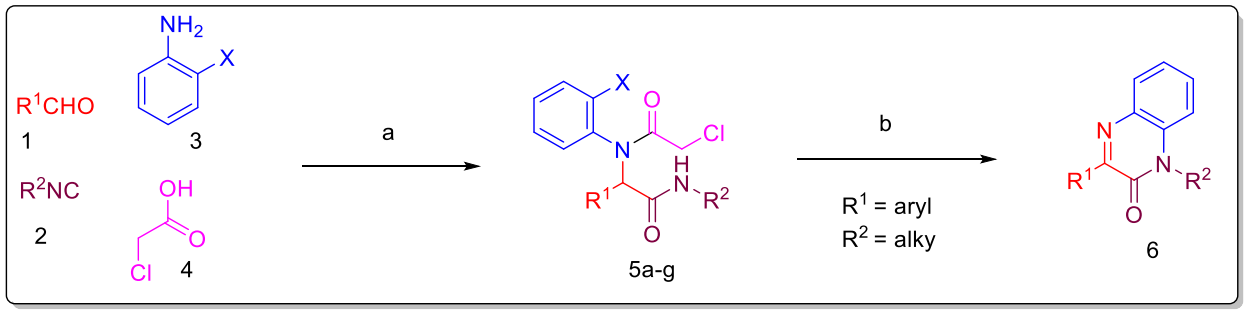



**Figure 1.** Structures of some pharmaceutically relevant quinoxalin-2(1H)-one derivatives.

To advance our research focus [18–20] on the establishment of resilient methodologies with substantial user adoption in the pharmaceutical industry, we herein elucidate our synthetic protocol to produce quinoxalin-2(1H)-ones through the Ugi four-component reaction coupled with metal-catalyzed cross-coupling processes.




**Scheme 1.** *Reagents and conditions*: (**a**) MeOH, rt, 24 h (**b**) 6 mol%$PdCl_2(CH_3CN)_2$, 12 mol% $C_{20}H_{27}P$, $Cs_2CO_3$, DMA, 120 °C.

In this synthesis, the classical Ugi 4-component reaction is employed, wherein the constituent elements are meticulously adjusted to achieve diverse structural points, specifically incorporating aldehyde (1), 2-halo aniline (2), 2-chloroacetic acid (4), and isocyanide (3). The compounds 2-chloroacetic acid and 2-halo aniline serve as critical agents for modulating the diversity points during the subsequent modification reaction. The Ugi multicomponent reaction was executed under conventional conditions, wherein equimolar amounts of aldehyde (1), 2-halo aniline (2), 2-chloroacetic acid (4), and isocyanide (3) were solubilized in 1M methanol and agitated at ambient temperature for 24 h, yielding Ugi adduct **5a–b** in satisfactory to moderate yields. (Figure 2: **5a–b**). The products obtained are characterized by $^{1}$H-NMR, $^{13}$C-NMR. The synthesized derivatives mentioned below with respective yields (Figure 2).

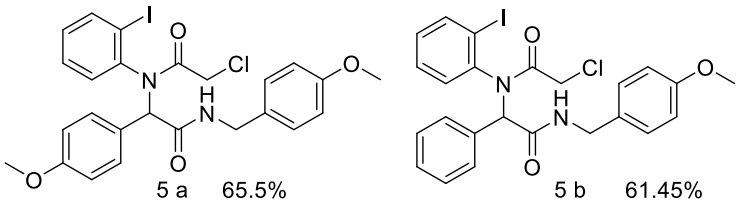



**Figure 2.** Ugi Adducts (**5a–b**).

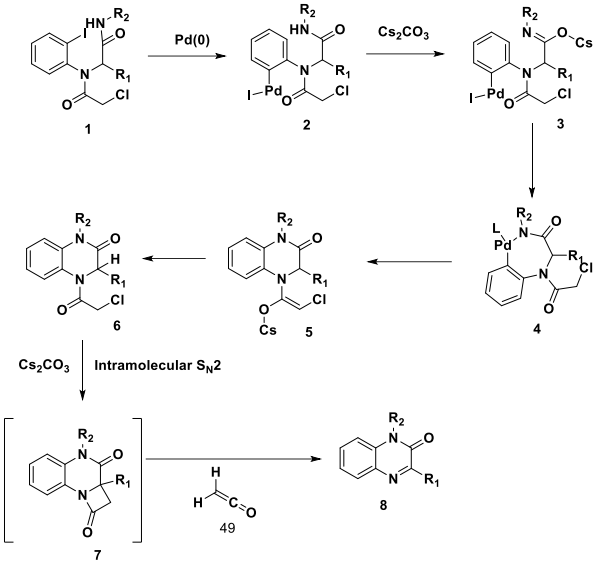
Following the synthesis of Ugi adducts **5a–b**, we advance to palladium-mediated cyclization as a subsequent modification of the Ugi adduct, specifically selecting Ugi adduct **5a** for the purpose of optimizing reaction conditions. The objective is to generate a diversity of products and modulate the reactivity of the Ugi adduct through the simultaneous formation of C-C and C-N bonds in a one-step process. Prior to initiating experimental procedures, we employed classical palladium catalysts and conducted a systematic screening of various catalysts and ligands. The efficacy of palladium-catalyzed reactions is largely contingent upon the judicious selection of appropriate ligands and catalysts, as well as the base utilized, which plays a crucial role in the overall reaction dynamics. The evaluation of various catalysts delineated in Table 1 substantiates the structural integrity through the application of 2D spectroscopic methodologies such as HMBC and HSQC, further corroborated by High-Resolution Mass Spectrometry (HRMS). The fundamental moiety of the resultant compound is identified as quinoxalin-2(1H)-one [1], which represents a significant category of heterocycles, holding substantial relevance in both biological and pharmaceutical contexts.

**Table 1.** Screening of catalysts and conditions for the Pd-catalyzed cyclization.

| Entry | Ugi Adduct | Catalyst (mol %) | Ligand (mol %) | Solvent | Base (1.5 Equiv) | %Yield 155a |
|---|---|---|---|---|---|---|
| 1 | 1equiv | 3 mol%$Pd(OAc)_2$ | 6 mol% $PPh_3$ | PhMe | $Cs_2CO_3$ | Not isolable |
| 2 | 1equiv | 5 mol%$Pd(OAc)_2$ | 10 mol% $PPh_3$ | PhMe | $Cs_2CO_3$ | Not isolable |
| 3 | 1equiv | 6 mol%$pd(OAc)_2$ | 12 mol% $PPh_3$ | PhMe | $Cs_2CO_3$ | 5 |
| 4 | 1equiv | 3 mol%$Pd(OAc)_2$ | 6 mol% $PPh_3$ | MeCN | $Cs_2CO_3$ | 24.2 |
| 5 | 1equiv | 6 mol%$Pd(OAc)_2$ | 12 mol% $PPh_3$ | DMF | $Cs_2CO_3$ | 36.58 |
| 6 | 1equiv | 6 mol%$Pd(OAc)_2$ | 12 mol% $(Cyc)_3P$ | PhMe | $Cs_2CO_3$ | 38 |
| 7 | 1equiv | 6 mol%$PdCl_2(CH_3CN)_2$ | 12 mol% $C_{20}H_{27}P$ | DMF | $Cs_2CO_3$ | 51.67 |
| **8** | **1equiv** | **6mol%$PdCl_2(CH_3CN)_2$** | **12 mol% $C_{20}H_{27}P$** | **DMA** | **$Cs_2CO_3$** | **55.67** |

The product formed is confirmed by NMR. The proposed mechanism mentioned in (Scheme 2). By this reaction, we observed that the whole process of first formation of diketopiperazine, which leads to product. The following mechanism explains the product formation. The reaction mechanism followed by formation of Buchwald hart wig product

**6** which is not isolable undergoes base catalysed intramolecular substitution nucleophilic reaction results beta-lactam intermediate **7** which is unstable where retro cycloaddition reaction occurs and elimination of ketene **8** leads to formation of substituted **quinoxalin-2(1H)-ones.**




**Scheme 3.** Proposed palladium catalyzed cyclization mechanism.

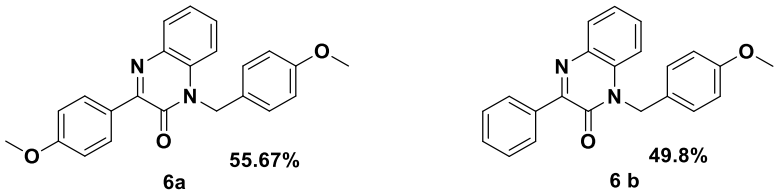
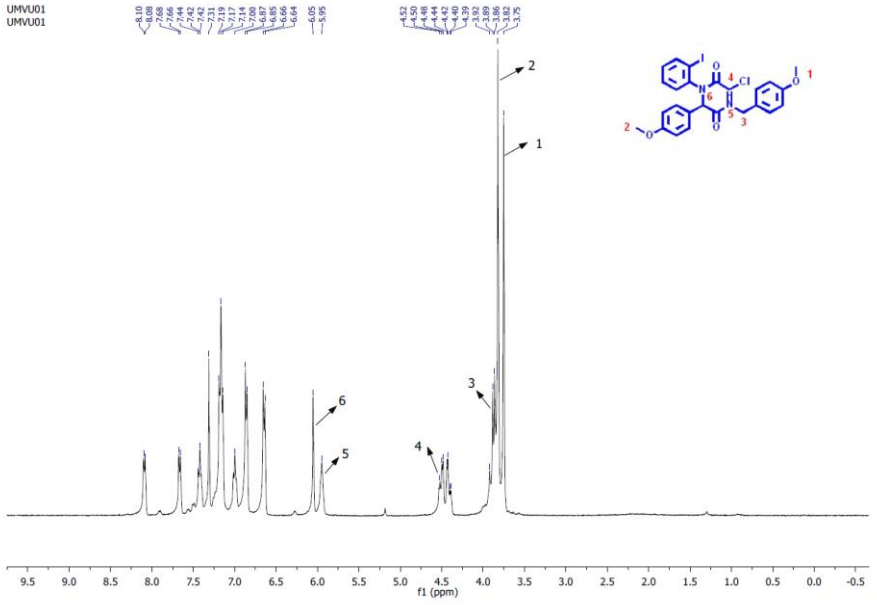


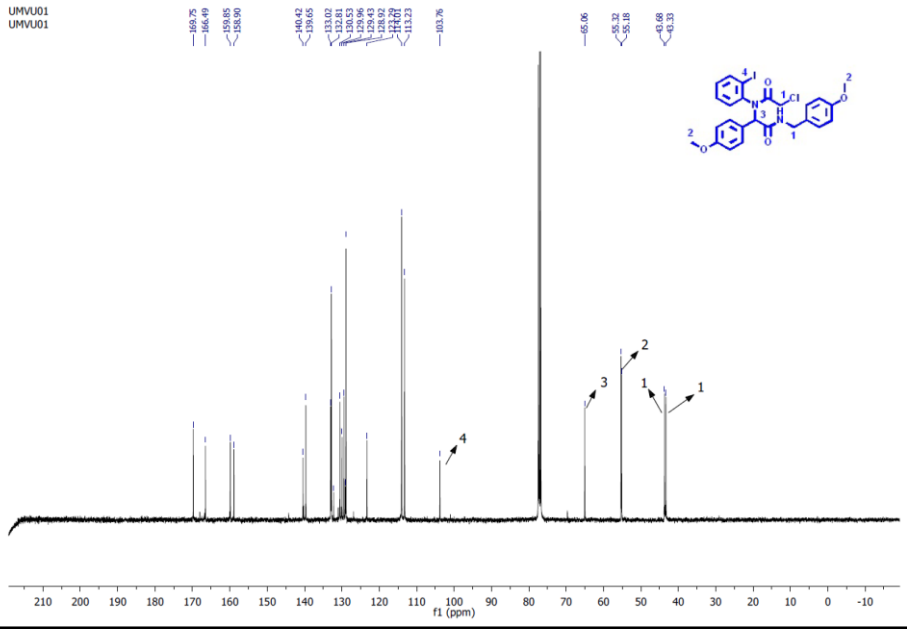

**Figure 3.** Obtained derivatives.

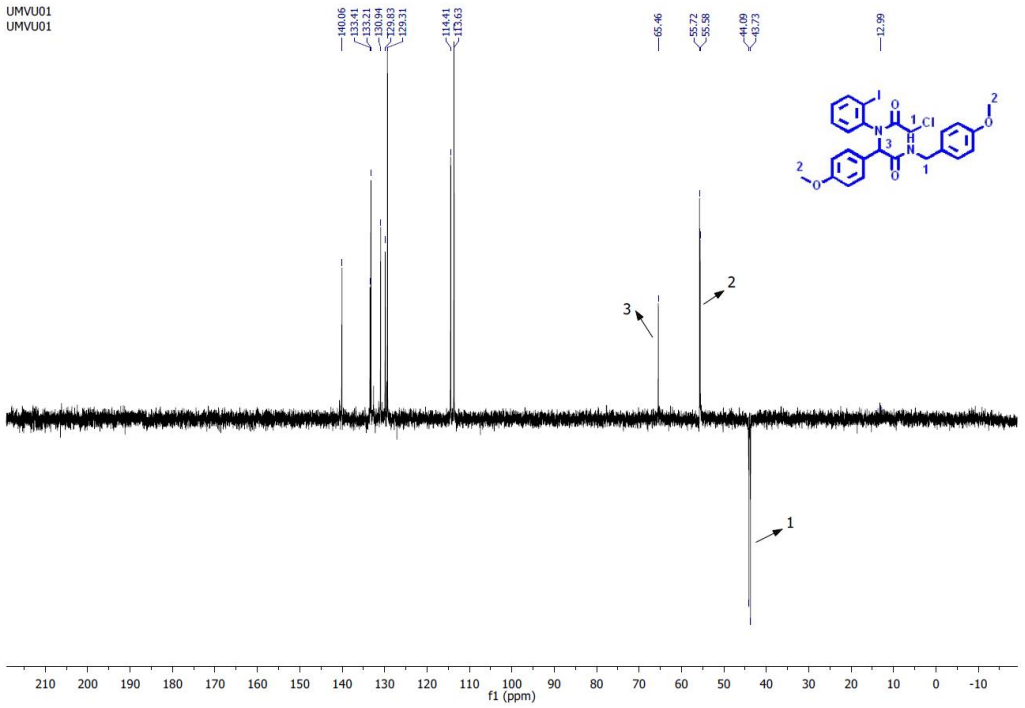
The obtained compounds including intermediates characterized by $^{1}$H-NMR, $^{13}$C-NMR, and final product 155a is confirmed and described by HRMS where we found mass is 373. The observations based the $^{1}$H -NMR and $^{13}$C-NMR where characteristic signals of Ugi adduct 154a 3.75 ppm, 3.82 ppm that represents methoxy groups substituted on phenyl rings, 3.82–3.92 ppm represents multiplet methylene group of benzyl of isocyanide and 4.39–4.52 ppm represents methylene protons of acid component in the adduct. 5.95 ppm singlet is the amide proton, and 6.05 is singlet represents the quaternary proton. These are the characteristic signals that confirm the formation of Ugi adduct 154a, as well as the product, is $^{13}$C-NMR the particular signs of adduct are aliphatic carbons which corresponds to methylene carbons at 43.33 ppm and 43.68 ppm and methoxymethyl carbons at 55.18 ppm and 55.32 ppm and quaternary carbon at 65.06 ppm and aromatic halogenated carbon at 103.76 ppm, by these if we observe in the final product the main observation is absence of the methylene carbon at 45.5 ppm and absence of Quaternary proton which changes the chemical shift of the carbon at 169.9 ppm palladium mediated cyclisation confirmed by the absence of the aromatic carbon at 103.76 ppm, these all observations as well as the HRMS analysis gives the brief confirmation of the final product is substituted quinoxalin-2(1H)-ones.

## Spectral Analysis

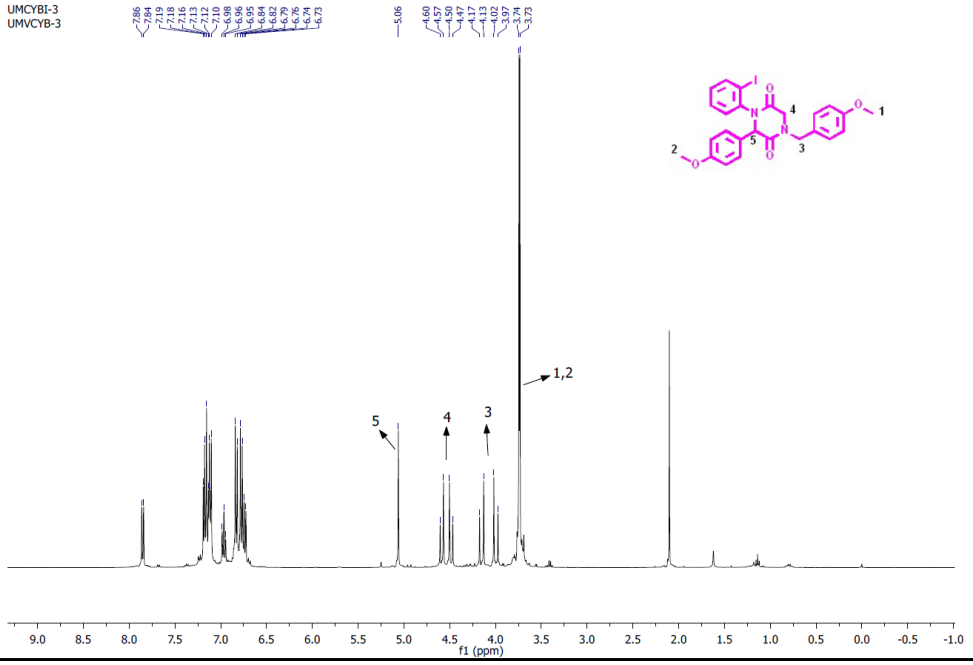
**$^{1}$H, $^{13}$C, DEPT NMR of 2-chloro-N-(2-iodophenyl)-N-(2-((4-methoxybenzyl) amino)-1-(4-methoxyphenyl)-2-oxoethyl) acetamide 5a**

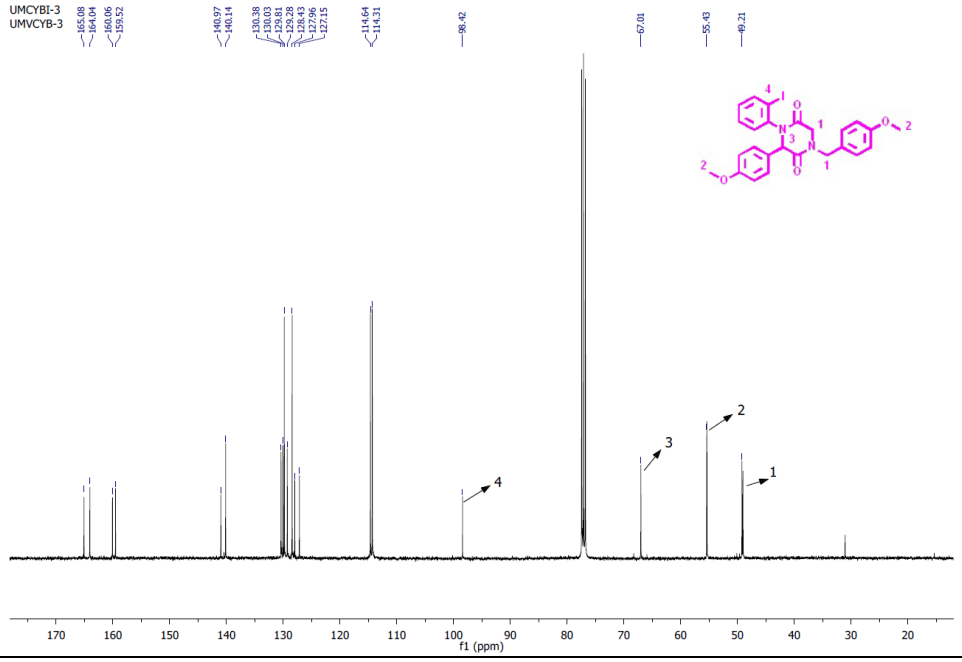


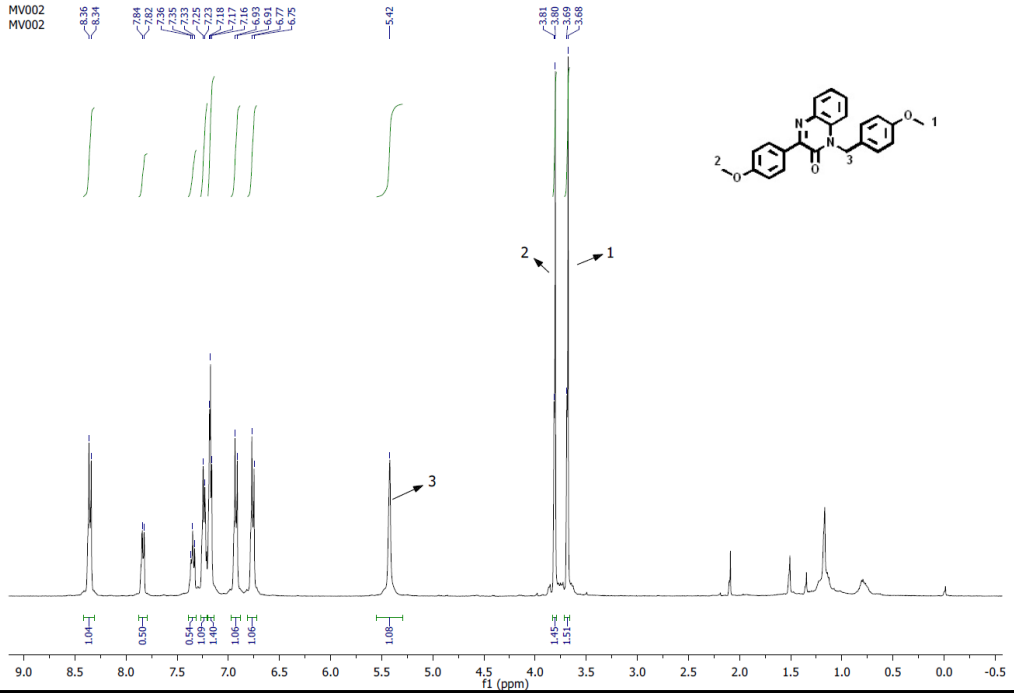


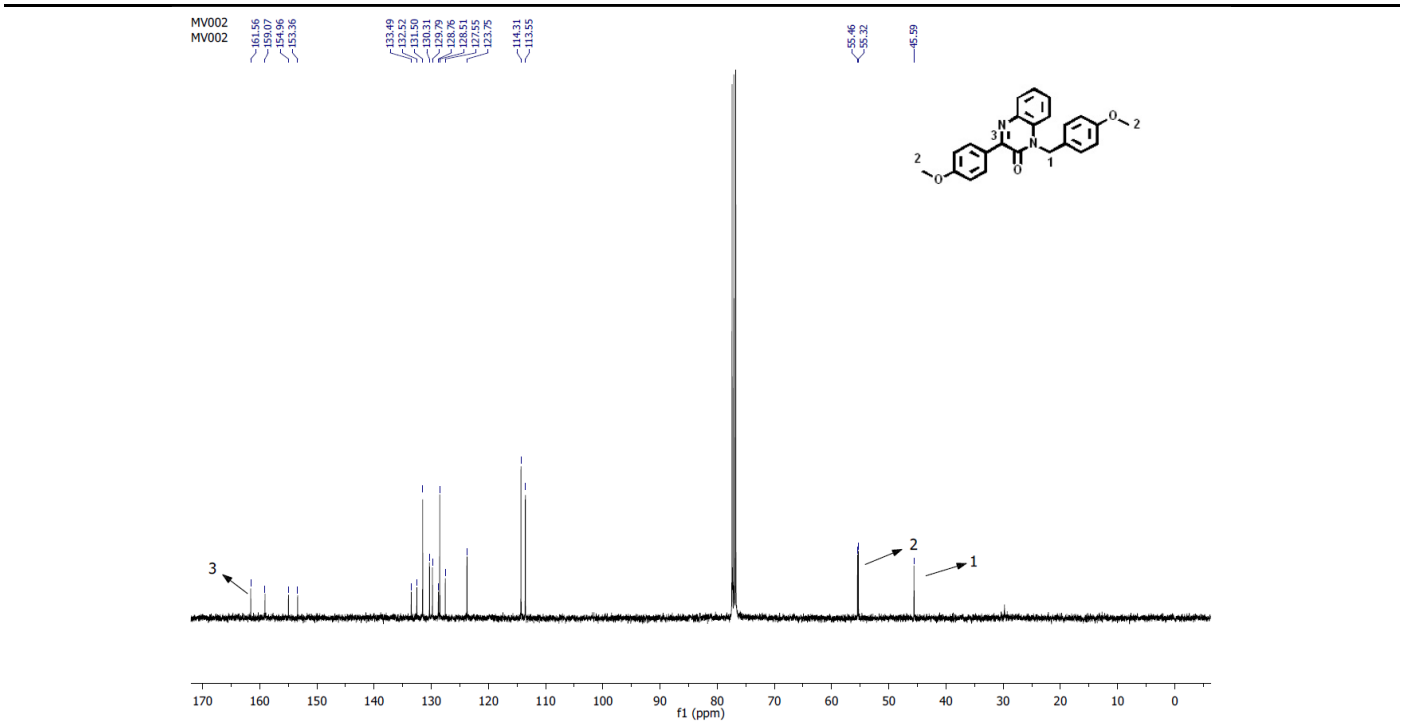

**$^{1}$H, $^{13}$C, DEPT of 4-(2-iodophenyl)-1-(4-methoxybenzyl)-3-(4-methoxyphenyl) piperazine-2, 5-dione 5a'**

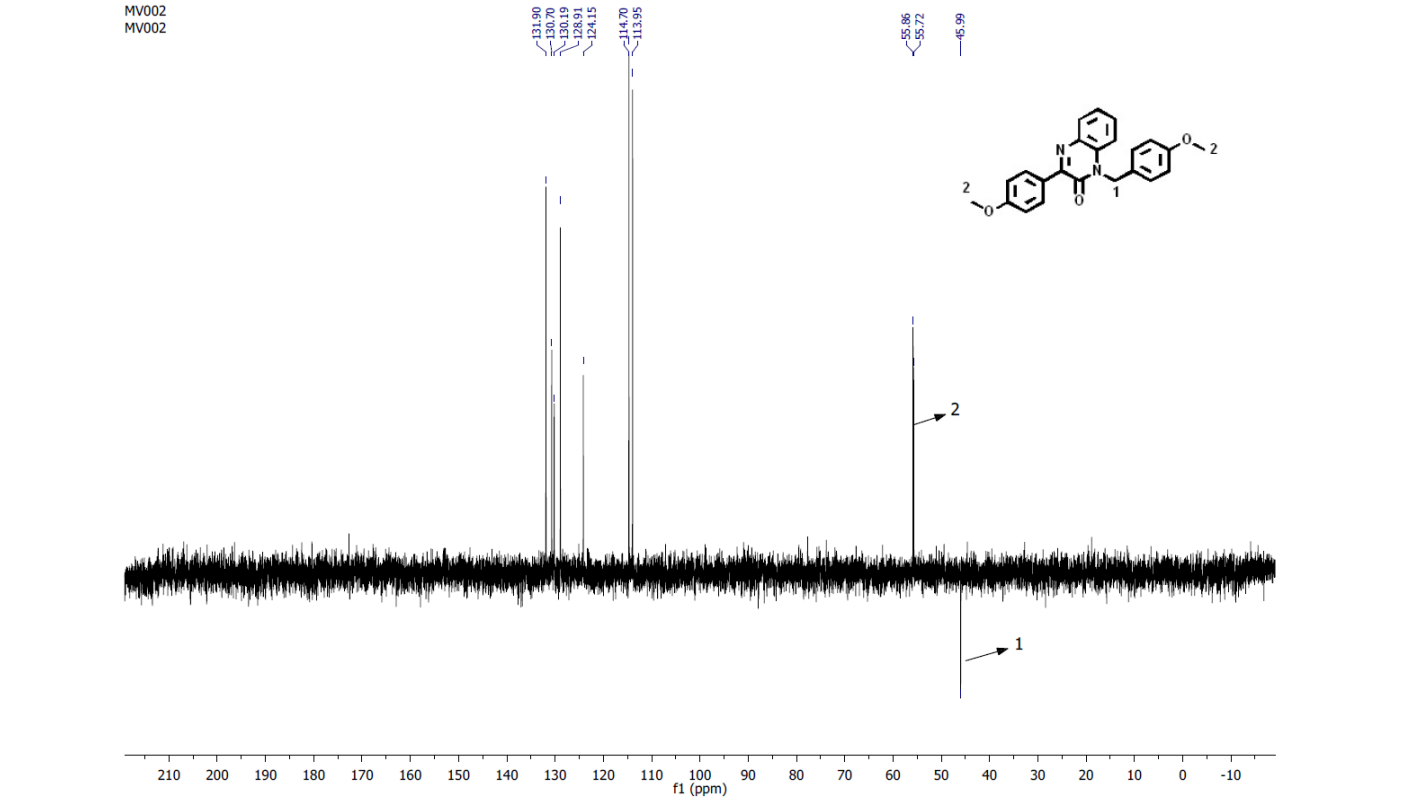





**$^{1}$H, $^{13}$C, DEPT, HRMS of 1-(4-methoxybenzyl)-3-(4-methoxyphenyl) quinoxalin-2(1H)-one 6a**






## 2. Conclusions

In summary, we have developed an alternative synthetic route for quinoxalin-2(1H)-one derivatives in two steps of the reaction, using Ugi 4CR followed by palladium mediated cyclization as post condensation process in moderate yields. We have studied the tuning of the points of diversity in Ugi adduct. The quinoxalin-2(1H)-one derivatives are well characterized by NMR.

**Author Contributions:**

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**Data Availability Statement:**

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**Conflicts of Interest:** The authors declare no conflict of interest.

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