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Synthesis *one pot* of Alkyne-2-Chloroquinoline via a Passerini Reaction

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Abstract: A serie of six new alkyne-2-chloroquinoline were synthesized in moderate yields (40-65%) via the Passerini three-component reaction (P-3CR) under mild green conditions. The P-3CR take place when a carboxylic acid, an oxo compound (aldehydes or ketones) and an isocyanide reacted to give α-acyloxy carboxamides. Recently it has been reported that small molecules containing alkynes promote interactions with different proteins in cells facilitating the detection or identification of protein targets.

Keywords: Multicomponent reactions; Passerini reaction; 2-chloroquinolin-3-carboxaldehyde; alkynes.

1. Introduction

Multicomponent reactions (MCRs) are well established as a powerful tool for the rapid construction of novel, complex and structurally diverse compounds from relatively simple or commercially available starting materials [1]. High atom-economy, chemical efficiency, convergence and very high bond-forming-index are typical features of such one-pot process of at least three different starting materials. Especially isocyanide-based multicomponent reactions (IMCR) have been emerging fields of interest in the last decade and recently focus toward the construction of heterocycles and polyheterocycles via MCRs [2-3]. The Passerini reaction (P-3CR) it's the first I-MCR reporteded in 1921 by Passerini, in which a carboxylic acid, an oxo compound and an isocyanide react efficiently to generate α-acyloxycarboxamides [4]. This IMCR is typically carried out with high concentrations of starting materials in an aprotic solvent

[5]. The stereo-electronic nature of the starting materials has direct influence on the reaction times and commonly few hours to several days are required.

The P-3CR reaction is the best method to the synthesis of α-acyloxycarboxamides, which are analogues of depsipeptides. Despsipeptides are analogues of peptides that incorporating an ester functionality, and they can show promising biological activities (Figure 1) [6]..

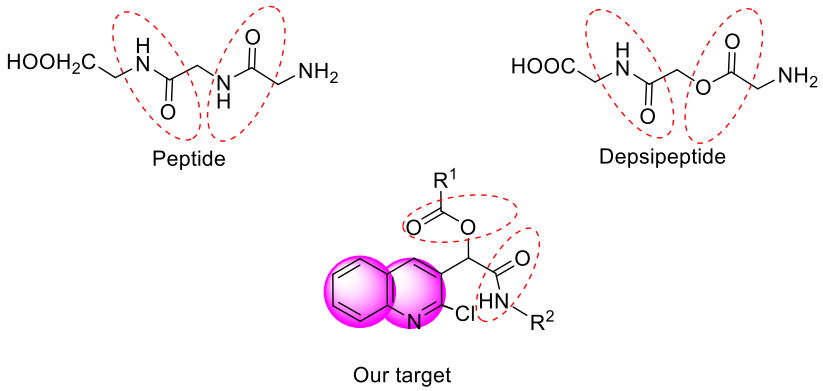


Figure 3. The structures of peptide, depsipeptide and our target.

Nowadays, the design and development of green methodologies and/or strategies are attracting considerable attention. Therefore, more efficient and environmentally friendly methodologies or the Passerini reaction are highly desirable, in this way several variants at conventional protocol have been achieved to improve the yield, decrease the environmental impact, and the reaction times. In this context recently this reaction has been reported in aqueous solution [7], ionic liquid [8,9], eutectic solvents [10] and under solvent free conditions [11]. It is highlight that alternative energy sources as mechanochemistry [12], microwave [13] and ultrasound [14] have been little explored in the P-3CR.

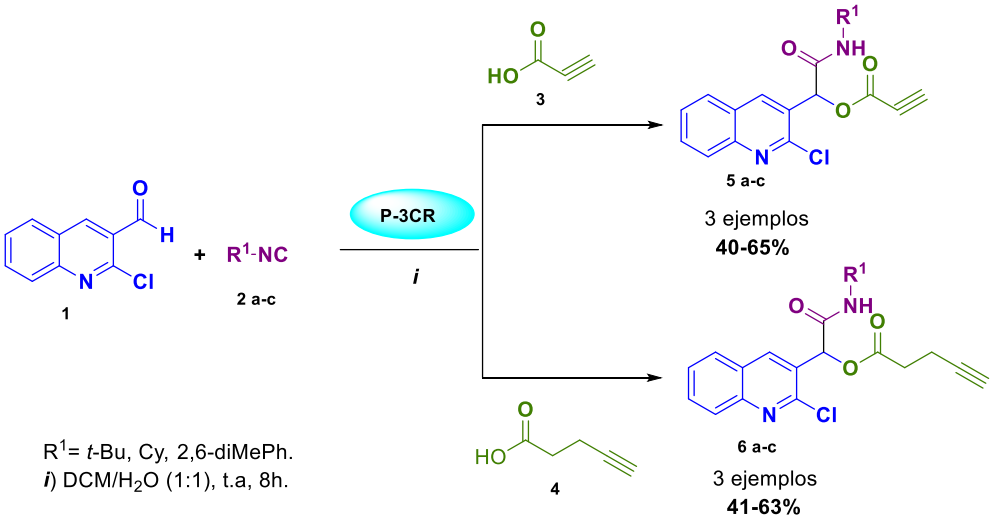
Given our ongoing interest in MCRs and considering the high potential of the Passerini reaction in the synthesis of bioactive molecules, herein we report a new protocol to perform an efficient functionalization of 2-chloroquinolin-3-carbaldehyde using propynoic and 4-pentynoic acid as orthogonal bifunctional reagents resulted in a highly functionalized Passerini-adduct that enabled the subsequent post-transformations. In this respect, the alkyne group has been proved ideal for post-transformation taking place after the multicomponent step.

In this context the use of carboxylic acids that contain an alkyne group in its structure has been little explored in the P-3CR [15,16]. Herein we reported a contribution in this area, with the complex terminal alkyne generated via P-3CR.

2. Results and Discussion

Following our research program toward the efficient synthesis of highly functionalized heterocycles, like alkyne-2-chloroquinoline which were synthesized in moderate yields (40-65%) via the Passerini three-component reaction (P-3CR) under mild green conditions.

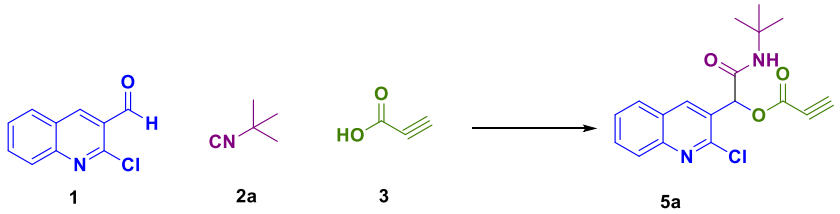
The IMCR synthetic methodology involved a sequential combination of 2-chloroquinoline-3-carboxaldehyde (**1**), 1 equivalent of propynoic acid (**3**) or pentynoic acid (**4**) and 1 equivalent of isocyanide (**2a-c**) in a DCM/H_2O (1:1) mixture. It is well documented that the use of binary systems mixture that involve volatile and green organic solvents can be used to improving yields and decreasing reaction times [17] (**Scheme 1**).



Scheme 1. Strategy for the synthesis of alkyne-2-chloroquinoline

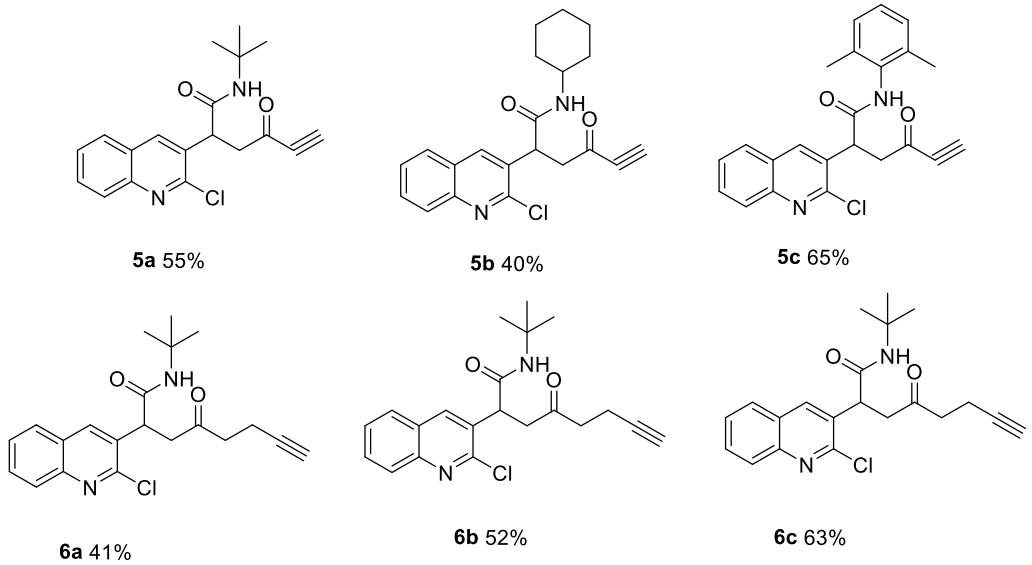
We began our investigation by optimizing the Passerini reaction selecting 2-(tert-butylamino)-1-(2-chloroquinolin-3-yl)-2-oxoethyl propiolate (**5a**) as our model target to optimize the one-pot process. Firstly, the formation of P-3CR product was attempted by the simple mixing of 2-chloroquinoline-3-carbaldehyde (**1**), propynoic acid (**3**) and terbutyl isocyanide (**2a**). The reactions using solvent mixture as MeOH/H_2O (1:1) and surfactant (entry 1 and 7, Table 1) results in low yields, while the same reaction with DCM/H_2O (1:1) mixture at room temperature for 8h was more fruitful (entry 8, Table 1). The reactions were monitored by TLC and the isolated product was confirmed by ^{1}H y ^{13}C NMR.

Table 1. Reaction optimizing conditions **5a.**



Entry	Solvent	T (°C)	Time(h)	Yield (%)
1	MeOH/H_2O (1:1)	r.t	8	17
2	MeOH/H_2O (1:1)	r.t USI	3	21
3	H_2O	r.t	24	n.r
4	H_2O	r.t USI	3	n.r
5	Solvent Free	r.t USI	3	n.r
6	Solvent Free	60 USI	3	n.r
7	Surfactant (1M)	r.t USI	3	12
8	**DCM/H_2O (1:1)**	**r.t**	**8**	**55**

Using optimized conditions, the serie of six new alkyne-2-chloroquinoline were synthesized (shown in scheme 2). The versatility of the developed methodology was examined using different isocyanides moieties as aryl and alkyl **(2a-c)** and two acids (propynoic and pentynoic). The respective products **5a–c** and **6 a-c** were obtained in moderate to good yields (40-65%).



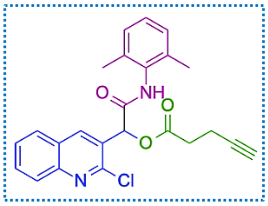
Scheme 2. Substrate scope

3. Experimental Section

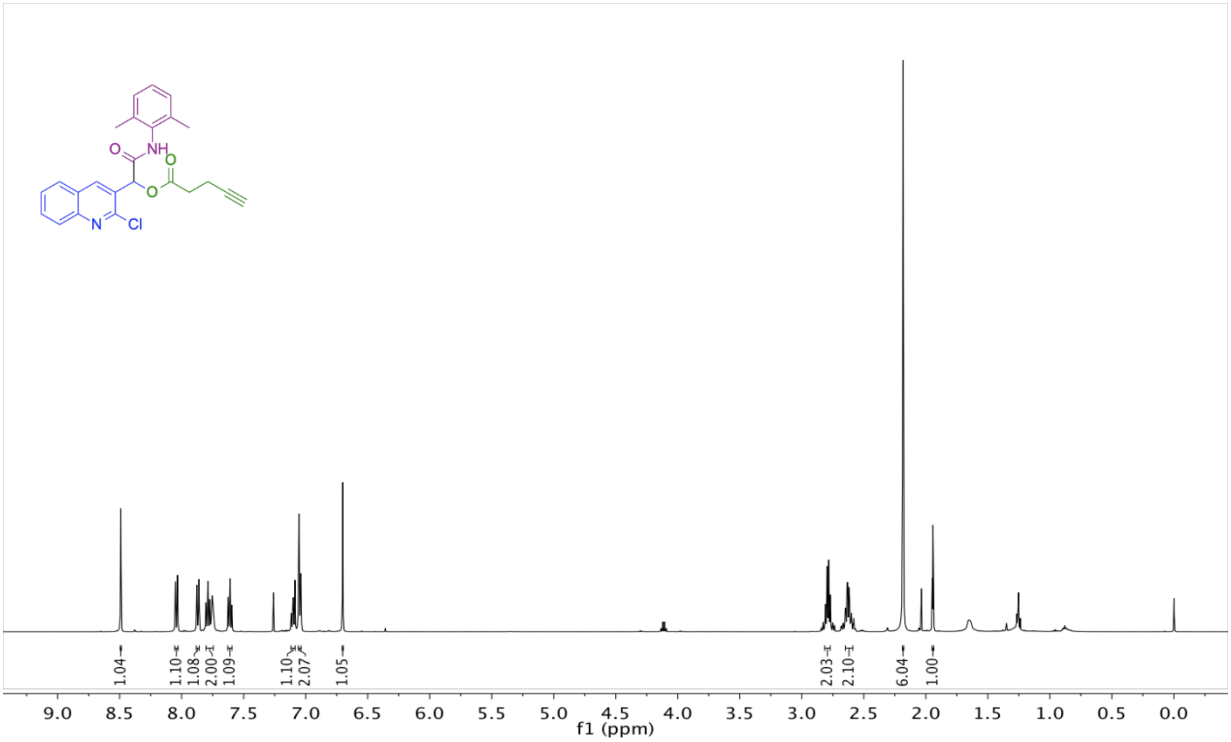
General Information. ^{1}H and ^{13}C NMR spectra were acquired on a 500 MHz spectrometer. The solvent for NMR samples was CDCl3. Chemical shifts are reported in parts per million (δ/ppm). Internal reference for NMR spectra is tetramethylsilane at 0.00 ppm. Coupling constants are reported in Hertz (J/Hz). Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). NMR spectra were analyzed using the MestreNova software version 10.0.1-14719. The reaction progress was monitored by TLC and the spots were visualized under UV light (254 or 365 nm). Flash column chromatography was performed using silica gel (230-400 mesh) and mixtures in different proportions of hexanes with ethyl acetate as mobile phase. Chemical names and drawings were obtained using the ChemBioDraw Ultra 13.0.2.3020 software package.

General method: 2-Chloroquinoline-3-carboxaldehyde **1** (0.365 mmol, 1.0 equiv), carboxylic acid **3** o **4** (0.365 mmol, 1.0 equiv.) and isocyanide **2 a-c** (0.365 mmol, 1.0 equiv.) were dissolved in DCM/H_2O (1:1) mixture were placed in a 10 mL sealed vial. The mixture was stirred at room time for 8 h. Then, the solvent was removed to dryness and the crude was purified by silica-gel column chromatography to afford the products 5a-c and 6a-c.

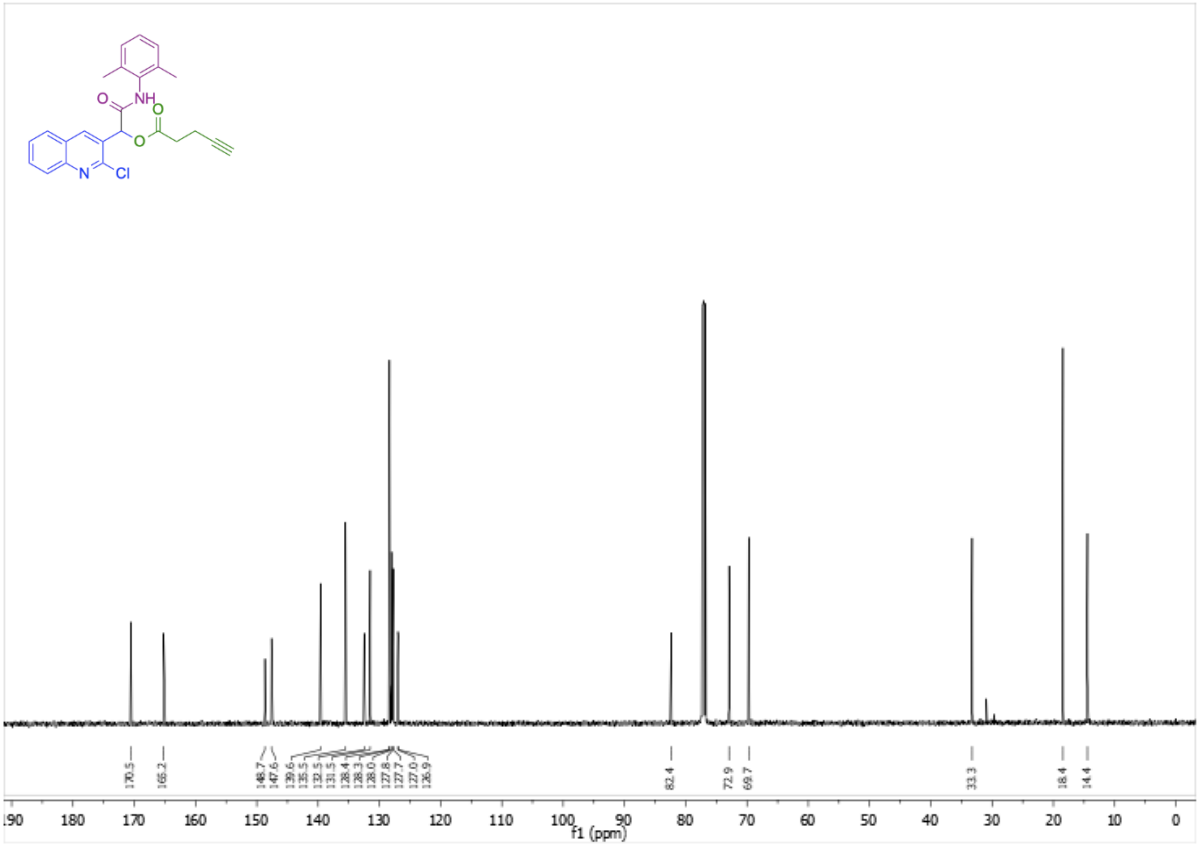
Spectral data



1-(2-chloroquinolin-3-yl)-2-((2,6-dimethylphenyl)amino)-2-oxoethyl propiolate (5c)
White solid (111.0 mg, 65%); Rf = 0.32 (Hexanes-EtOAc = 7/3 v/v); ^{1}H NMR (500 MHz, CDCl3) δ 8.49 (s, 1H), 8.06–8.03 (d, J = 8.4 Hz, 1H), 7.89–7.85 (m, 1H), 7.81–7.73 (m, 2H), 7.63–7.59 (m, 1H), 7.12–7.08 (m, 1H), 7.06–7.03 (m, 2H), 6.7 (s, 1H), 2.83–2.76 (m, 2H), 2.66–2.58 (m, 2H), 2.18 (s, 6H), 1.94 (t, , J = 2.6 Hz 1H); ^{13}C NMR (126 MHz, CDCl3) δ 170.5, 165.2, 148.7, 147.6, 139.6, 135.5, 132.5, 131.5, 128.4, 128.3, 128.0,127.8, 127.7, 127.0, 126.9, 82.4, 73.0, 69.7, 33.3, 18.4, 14.4.



^{1}H NMR spectrum of compound **5c.**



^{13}C NMR spectrum of compound **5c.**

4. Conclusions

A series of six new alkyne-2-chloroquinoline were synthesized in moderate to good yields (40-65%) via the Passerini three-component reaction (P-3CR) under mild green conditions.

Author Contributions: All authors contributed equally to this work.

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Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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