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# A One-pot process for the synthesis of Alkyne-3-tretrazolyl-tetrazolo [1,5-*a*] quinolines

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**Abstract:** An efficient synthesis of alkyne-3-tetrazolyl-tetrazolo[1,5-*a*] quinolones via a one-pot isocyanide-based multicomponent reaction (IMCR) process: I-MCR Ugi-azide /SNAr/ ring-chain azido tautomerization under eco-friendly conditions. We report the one-pot synthesis of tris-heterocycles containing a tetrazolo[1,5-*a*] quinoline connected to a 1,5-disubstituted-tetrazole (1,5-DS-T). The synthesis of these compounds is of great interest in synthetic and medicinal chemistry because these heterocycles are considered privileged scaffolds and their preparation and evaluation may lead to the discovery of novel bioactive molecules.

**Keywords:** isocyanide based multicomponent reaction, Ugi-azide, tetrazolo [1,5-*a*] quinolones, ring-chain azido tautomerization, one-pot process, alkyne moiety

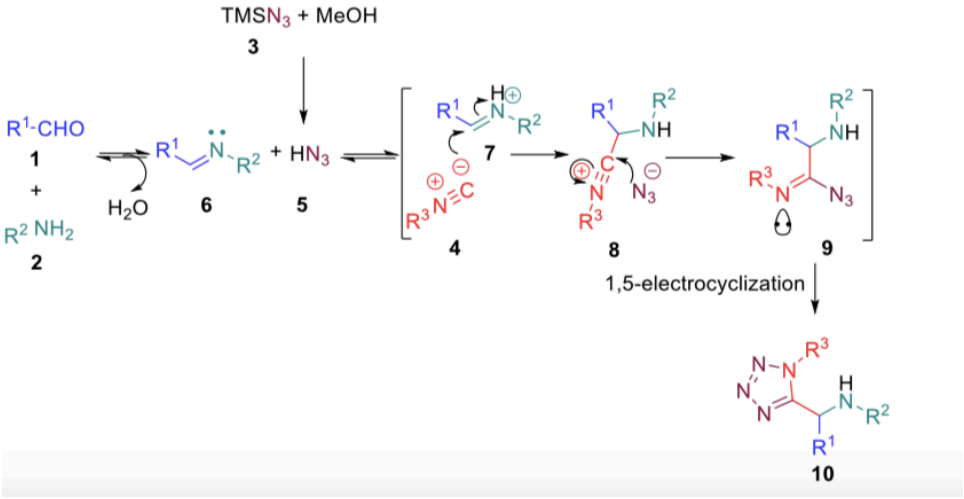
## 1. Introduction

Bis-heterocycles are molecules that can be formed by connecting two heterocyclic scaffolds by fusion, by a directed bound, or via a multi-bond linked, bound, spacer [1]. The purpose behind the combination of two heterocycles is to improve their potential applications in different areas such as chelating agents and metal ligands, and particulary in the development of bioactive molecules and drugs [2]. Many bis-heterocycles can be synthesized by multicomponent reactions (MCRs). A multicomponent reaction is a domino process in which three or more compounds react with each other in one-pot to produce the products in such a way that the majority of the atoms of the reactants are incorporated into the final products. MCRs therefore offer great possibilities for molecular diversity per step reducing time and effort.

There are a number of advantages that make one-pot transformations popular for organic chemists; the procedures are generally simple, saving time and resulting in high atom economies. The one-pot process can be carried out through multi-step sequential processes where the consecutive steps take place under the same reactions conditions [3].The 1,5- disubstituted tetrazoles (1,5-DS-T`s) are bioisosteres of the *cis*-amide bond in peptides as a result of the similarities in their physicochemical propierties [4]. They are an important class of heterocycles with a wide range of applications in coordination chemistry, agriculture, photoimaging agents, and medicinal chemistry [5].

The main routes for the synthesis of 1,5-DS-T`s are [3 + 2] intermolecular cycloadditions[6] between azides and nitriles and Ugi-azide reactions (UA).[7] The UA was reported first by Ugi in 1961. The carboxylic acid used in the classical Ugi reaction is replaced by hydrazoic acid (generated *in situ* from

$NaN_3$ or $TMSN_3$). The proposed mechanism of this one-pot four-component reaction (Scheme 1) involves a condensation between an amine and an aldehyde to give Schiff base **6**, which after protonation by $HN_3$ and nucleophilic attack with isocyanide **4** affords intermediate **8**. Subsequent nucleophilic attack with $N_3^-$ gives intermediate **9**. Finally, an intramolecular electrocyclization occurs to afford 1,5-DS-T`s **10** [8].




**Scheme 1.** Ugi-azide reaction mechanism.

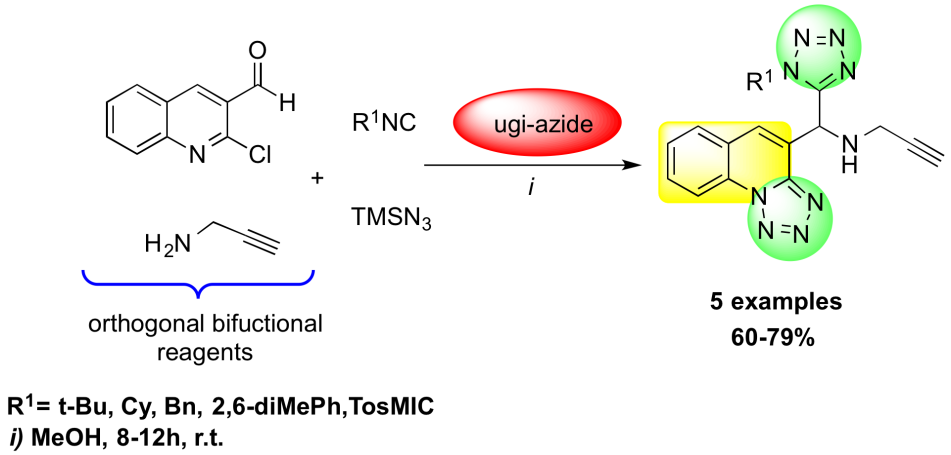
Tetrazolo [1,5-*a*] quinoline is the core moiety of various compounds with interesting pharmacological properties, anticancer [8], antifungal [9], antibacterial [10], and anti-inflammatory properties [11]. Due to the above mentioned medicinal importance of tetrazolo [1,5-*a*] quinoline and 1,5-DS-T moieties individually, there has been an increased interest in the synthesis of *bis*-heterocycles containing the 1,5-DS-T moiety over the past decade.

Herein we report the synthesis of fused *bis*-heterocycles type linked containing tetrazolo [1,5-*a*] quinoline linked to 1,5-DS-T moieties. It is noteworthy that the one-pot synthesis of 1,5-DS-T with linked heterocycle has been little-explored, for example, 1,5-DS-T bound to tiadiazoles [12], chromone [13],quinoline [14] have been prepared previously.

## 2. Results and Discussion

In this work, we described the synthesis of five alkyne-3-tetrazolyl-Tetrazolo[1,5-a] quinolone via a one-pot I-MCR process: Ugi-azide /SNAr/ ring-chain azido tautomerization under eco-friendly conditions in good yields (60-79%).

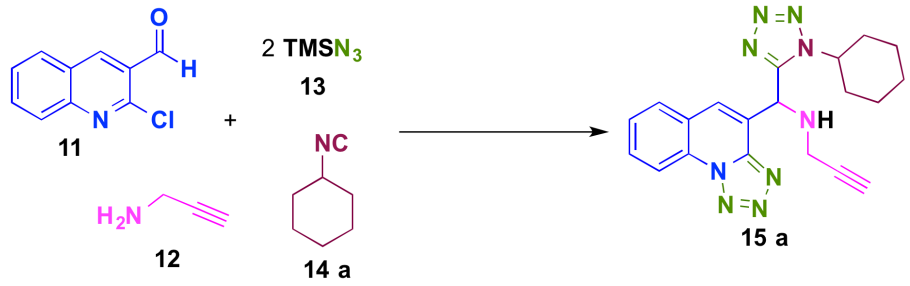
The synthetic methodology involved a sequential combination of 2-chloroquinoline-3-carboxaldehyde (**11**) with 1 equivalent of propargyl amine (**12**), two equivalents of azidotrimethylsilane (**13**), and 1 equiv of isocyanide (**14**) in MeOH at room temperature (**Scheme 2**).




**Scheme 2.** Strategy for the synthesis of alkyne-3-tetrazolyl-tetrazolo[1,5-a] quinolines.

We select The N-((1-Cyclohexyl-1H-tetrazol-5-yl)(tetrazolo[1,5-a]quinolin-4-yl)methyl)prop-2-yn-1-amine (5a) as our model target to optimize the one-pot process Ugi-azide/SNAr/ring-chain azido tautomerization. Thus 2-chloroquinoline-3-carbaldehyde (**11**) was combinated sequentially with one equivalent of propargyl amine (**12**), cyclohexyl isocyanide (**14a**), and two equivalents of azidotrimethylsilane (**13**) using the Ugi-azide standard conditions (MeOH, rt) as starting point. The product **15a** was insolated in 70% after 6h (Entry 1, Table 1). Then we decided to study the effect of temperature. Thus the reaction was performed in methanol at reflux at 70°C after 6h (Entry 2, Table 1), the product **15a** was synthesized in 20%. In this context, we used microwaves (Entry 3, Table 1) and ultrasound (US) (Entry 4, Table 1) as irradiation methods in order to reduce the reaction time and eventually to increase the yields but the experiment was not successful with respect to the experiment at room temperature the reaction time decreases but the yield is lower 54 or 40% respectively.

**Table 1**. Screening Conditions



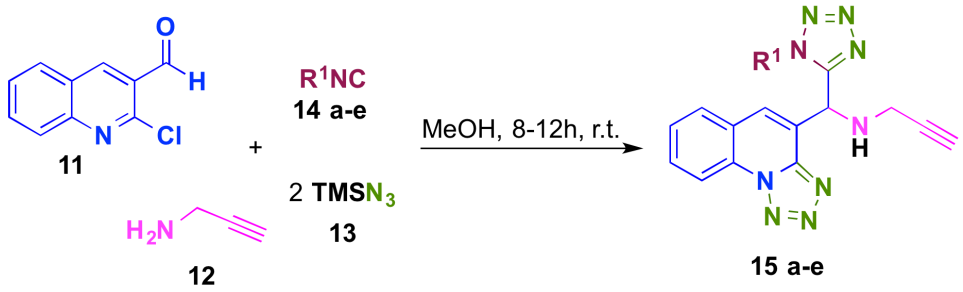

| *entry* | *solvent* | t *(h)* | *T* °C | *yield (%)* |
|---|---|---|---|---|
| ***1*** | **MeOH** | **6** | **r.t** | **70** |
| *2* | MeOH | 6 | 70 | 20 |
| *3* | MeOH | 1 | 85[a] | 54% |
| *4* | MeOH | 1.5 | 60[b] | 40% |

[a] MW (100 W) [b] US (42 kHz).

After an exploration of the reaction conditions varying the temperature and irradiation methods, optimal conditions to prepare alkyne-3-tetrazolyl-tetrazolo[1,5-a] quinolines **15a-e** were found. Using the optimal

conditions (MeOH, r.t, 8-12 h), we synthesized the compounds in good yields (60-79%) (Table 2). As seen in the Scheme 2 good reaction scope was found. The stereoelectronic nature of substituents in the isocyanide moiety varies from alkyl to aryl and benzyl substituents. Steric and electronic effects from the isocyanide impacted the yields of the corresponding compounds. When the poorly nucleophilic 2,6-dimethylphenyl isocyanide was used, the yield was slightly lower in comparison with cyclohexyl and *t*-butyl isocyanides analogs.

**Table 1**. Substrate scope.




| *15* | *R¹* | *Yield (%)* |
|---|---|---|
| ***15a*** | Cy | 79 |
| ***15b*** | *t*-Bu | 74 |
| ***15c*** | 2,6-diMePh | 68 |
| ***15d*** | Bn | 64 |
| ***15e*** | TosMIC | 60 |

With respect to screening conditions, higher yields were observed at room temperature. When we used microwave or ultrasound irradiation, the time of reaction was shorter (1 and 2 hours respectively) but the yields were lower in comparison with the room temperature reaction.

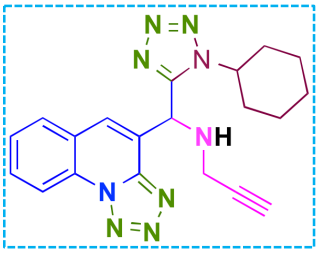
## 3. Experimental Section

***General Information***. $^{1}H$ and $^{13}C$ NMR spectra were acquired on a 500 MHz spectrometer. The solvent for NMR samples was $CDCl_3$. Chemical shifts are reported in parts per million ($\delta$/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). IR spectra were recorded with an ATR accessory using neat compounds. The wavelengths are reported in reciprocal centimeters **($\nu_{max}$/cm$^{-1}$).** HRMS spectra were acquired via electrospray ionization (ESI) in positive ion mode and recorded via the time-of-light (TOF) method. Reactions at reflux were performed in round-bottomed flasks using a recirculation system mounted on a sand bath with electronic temperature control. Microwave assisted reactions were

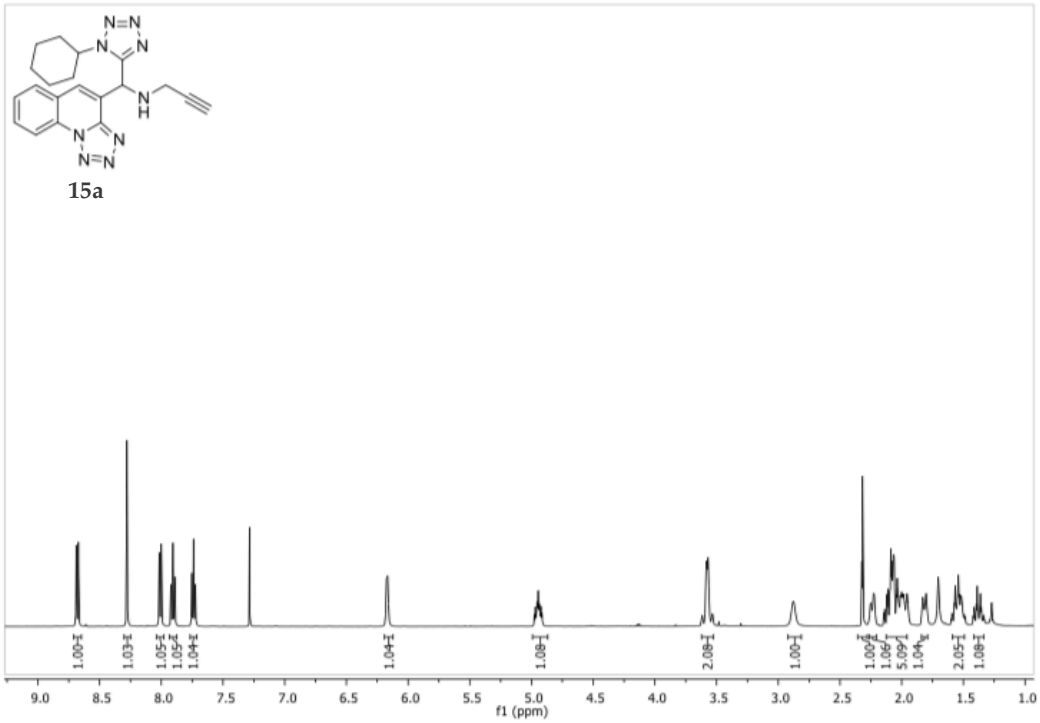
performed in vials on closed vessel mode using a CEM Discover monomodal MW reactor without pressure sensor. Ultrasound irradiated reactions were performed in vials placed into a water bath of a Branson 1510 sonicator cleaner working at 42 kHz ± 6% frequencies. The reaction progress was monitored by TLC 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. Melting points were determined on a Fisher-Johns apparatus and were uncorrected.

***General method:*** 2-Chloroquinoline-3-carboxaldehyde **11** (0.52 mmol, 1.0 equiv), propargyl amine **12** (0.52 mmol, 1.0 equiv.), azidotrimethylsilane **13** (1.12 mmol, 2.0 equiv.) and isocyanide **14** (0.052 mmol, 1.0 equiv.) were dissolved in MeOH in a round-bottom flask equipped with a magnetic stirrer bar. The resulting mixture was stirred for 8-12h at room temperature. The solvent was evaporated under reduced pressure until dryness, the organic layer was purified by flash chromatography eluting with hexanes-EtOAc (7/3 v/v) as eluent to afford compounds **15a-e**.

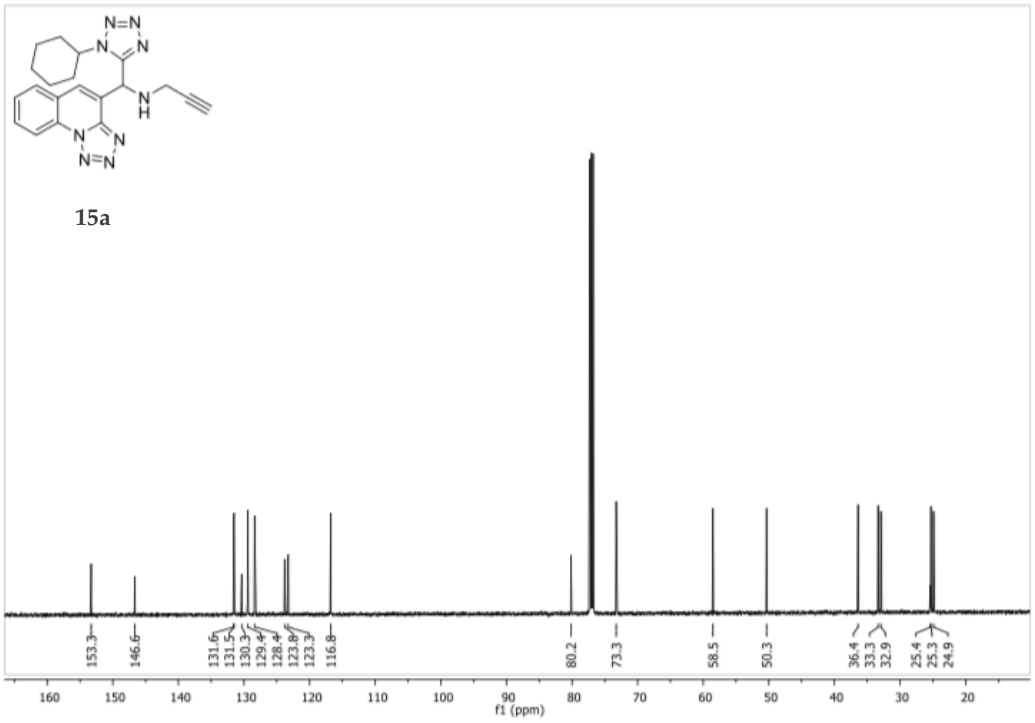
**Spectral data**




**N-((1-Cyclohexyl-1H-tetrazol-5-yl)(tetrazolo[1,5-a]quinolin-4-yl)methyl)prop-2-yn-1-amine** (**15a**). Pale yellow solid (112.0 mg, 79%); mp = 173–174 °C; Rf = 0.29 (Hexanes-EtOAc = 1/1 v/v); $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 8.4 Hz, 1H), 8.28 (s, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.93–7.88 (m, 1H), 7.76–7.72 (m, 1H), 6.17 (s, 1H), 4.99–4.90 (m, 1H), 3.63–3.52 (m, 1H), 2.88 (s, 1H), 2.32 (t, J = 2.4 Hz, 1H), 2.26–2.21 (m, 1H), 7.93–7.88 (m, 1H), 2.15–1.94 (m, 5H), 1.84–1.79 (m, 1H), 1.60– 1.48 (m, 2H), 1.42–1.32 (m, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 153.3, 146.6, 131.6, 131.5, 130.3, 129.4, 128.4, 123.8, 123.3, 116.8, 80.2, 73.3, 58.5, 50.3, 36.4, 33.3, 32.9, 25.4, 25.3, 24.9; FT-IR (ATR)νmax/cm−1 3340 (N−H), 1616 (N=H), 1279 (N−N=N); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{20}H_{22}N_9$ 388.1992, found 388.1985.




$^{1}$H NMR spectrum of compound **15a**




$^{13}$C NMR spectrum of compound **15a**

## 4. Conclusions

A series of five alkyne-3-tetrazolyl-tetrazolo[1,5-***a***]quinolines was synthesized in good yields (60-79%) in one pot under eco-friendly conditions at room temperature. This work represents a contribution in the synthesis of fused bis-heterocycles (15a-e) containing 1,5-DS-T and tetrazolo[1,5-***a***]quinoline. The use of the bifunctional groups allows us to obtain highly functionalized molecules with enormous potential in post-transformations for the generation of more complex molecules.

**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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