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MASTER THESIS

Synthesis of morpholines through the PPh_3-catalyzed post-Ugi intramolecular umpolung oxa-Michael addition

by

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List of abbreviations

Alk	**Alkyl**
Ar	**Aryl**
Bn	**Benzyl**
tBu	**Tertiary butyl**
$CDCl_3$	**Deuterated chloroform**
DCM	**Dichloromethane**
DKP	**Diketopiperazine**
DMF	**Dimethylformide**
Et	**Ethyl**
EtOAc	**Ethyl acetate**
EtOH	**Ethyl alcohol**
Hex	**Hexane**
i-PrOH	**Isopropyl alcohol**
MCR	**Multicomponent reaction**
Me	**Methyl**
MeCN	**Acetonitrile**
MeOH	**Methyl alcohol**
MW	**Molecular weight**
NMR	**Nucleic magnetic resonance**
Ph	**Phenyl**
PPh_3	**Triphenylphosphine**
Rt	**Room temperature**

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Table of Schemes

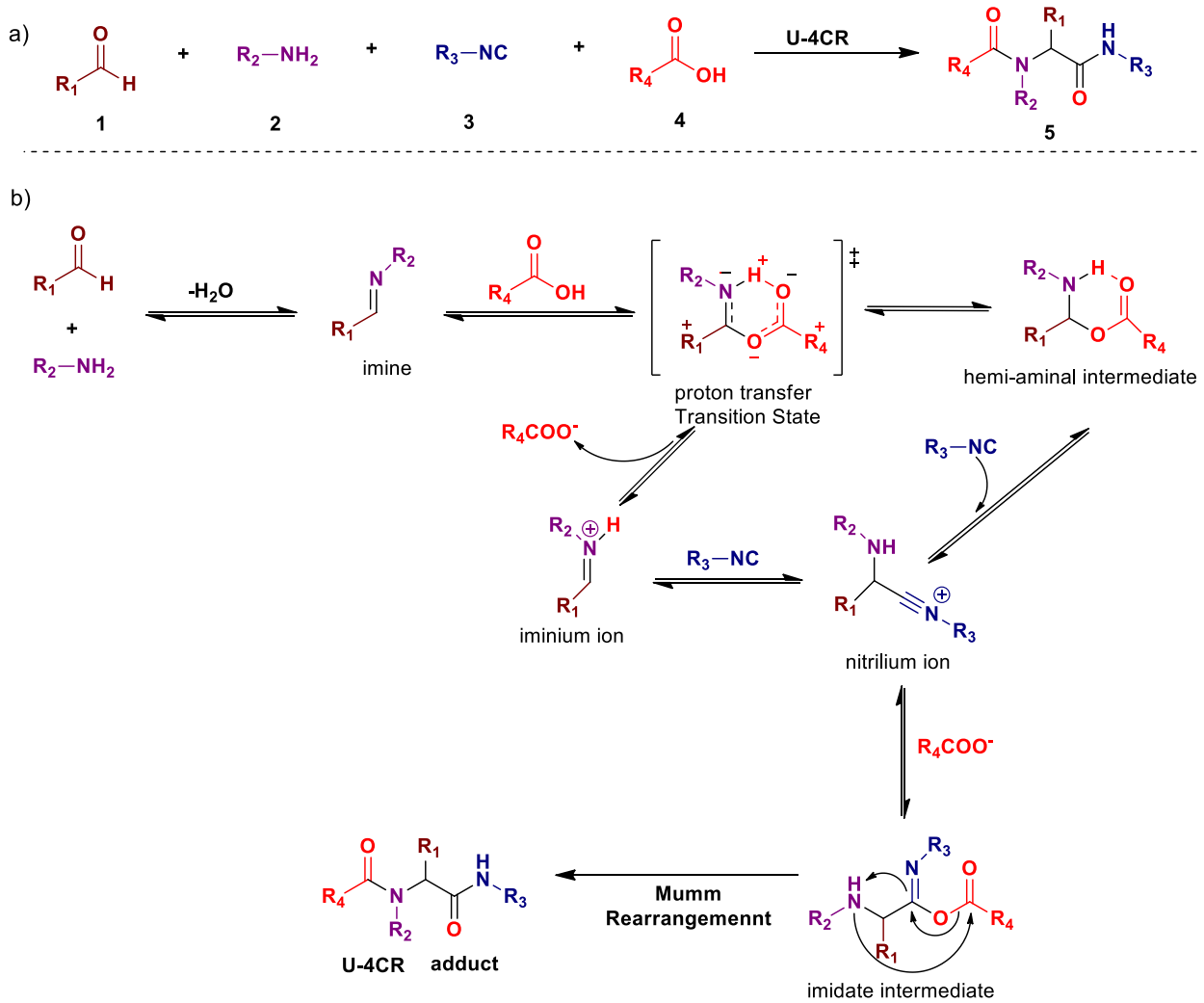
Chapter 1

1.1 Introduction

One of the main directions in the development of modern organic chemistry is to increase the efficiency of the synthesis of complex structures. The goal of organic synthesis is not only to obtain target compounds, but also to develop methodologies with the lowest cost and minimum harm to the environment. At the present time, multicomponent reactions that are based on the idea of mixing of more than two starting reagents are of particular interest. Their main advantage is that they provide the ability to create fully convergent synthetic strategies with a minimum number of steps. Moreover, this leads to a decrease in the number of operations and the purification of synthesized compounds that makes it possible to automate such processes. These approaches reduce amounts of waste and by-products, as well as the consumption of organic solvents which opens up new opportunities for the development of green chemistry. Another attractive feature of multicomponent reactions is their diversification potential that comes from the fact that they utilize three or more variable starting materials, and the final structure typically incorporates the structural fragments deriving from each of the starting compounds. This can also be coupled with the incorporation of additional functional groups that could be further deployed in a variety of post-transformations.

The concept of Multicomponent Reactions (MCR) has been advanced in works of Ivar Karl Ugi through the discovery of a novel isocyanide-based four-component reaction in 1959 [1]. He has also divided several known MCRs into three main types according to their mechanistic paths that composed of elementary MCR stages. MCRs can be used to reduce the number of steps required for the synthesis of a complex organic compound from 5-8 to 1 [2]. In the reaction polar aprotic such as dimethylformide (DMF) and polar protic solvents such as methanol (MeOH) are used as solvent. Due to the high concentration of reagents and only one equivalent of water molecule is lost during the reaction, the chemical yield is

quite high. In particular, the four-component Ugi reaction is considered exothermic and the reaction is complete after the addition of the isocyanide. As a rule the Ugi reaction is a combination of an aldehyde or ketone **1** with a primary amine **2**, an isocyanide **3**, and a carboxylic acid **4** with the formation of linear Ugi adduct **5** (Scheme 1) [2]. Linear Ugi adducts with reactive functional groups undergoes secondary reactions to form a ring and useful in the synthesis of peptides and peptidomimetics [3].



Scheme 1 a) General Ugi four component reaction; **b)** Mechanism of general Ugi four component reaction

The aldehyde or ketone **1** reacts with the amine **2** and converts to the imine with the loss of water molecule [4]. Then protonation by carboxylic acid **4** occurs, which activates the resulting iminium ion for the nucleophilic addition from the

isocyanide **3** with terminal carbon. The resulting intermediate nitrilium ion product undergoes a second nucleophilic attack from the carboxylic acid anion. Then the imidate intermediate goes through a Mumm rearrangement, and the acyl group is transferred to nitrogen from oxygen [2]. All the reactions are reversible, except for the Mumm rearrangement [5].

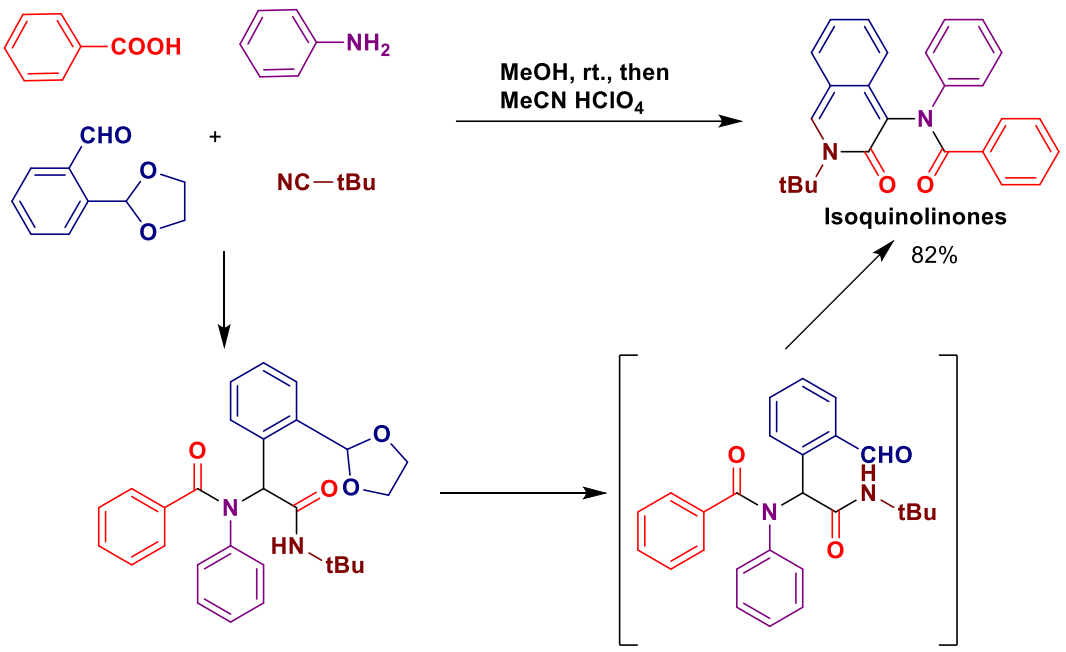
1.2 Literature review

Multicomponent reactions serve as a powerful tool for quick and low-cost assembly of complex structures from conventional raw materials and with a very low production of waste.

Since in multi-component reactions, it is possible to use reagents with additional functional groups, so that the Ugi-4CR product might cyclize to form a new heterocycle which is called post-Ugi transformation. Post-Ugi transformation is a promising trend in modern organic chemistry which offers great opportunities to obtain unknown diverse heterocyclic systems. In other words, this strategy is available due to the general nature of the Ugi reaction and the compatibility of this reaction with a whole range of orthogonal functional groups.

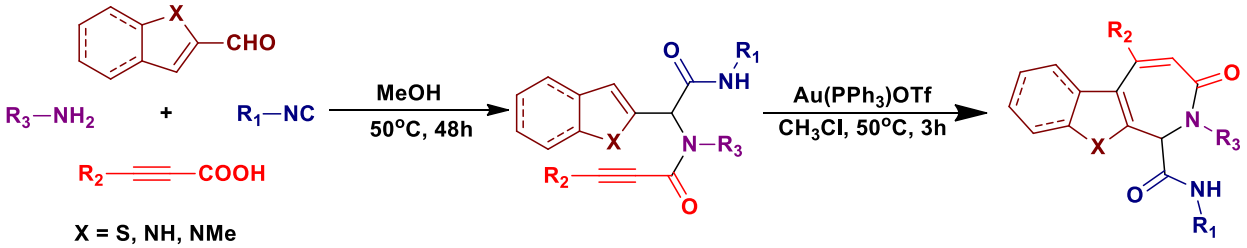
In 2013, Yang and coworkers utilized a mono-protected bis-aldehyde to produce a variety isoquinones via post-Ugi cyclizations (Scheme 2) [6]. The optimal assumption was that isoquinolines are formed via intramolecular condensations of isocyanide-originated amide group with the second deprotected aldehyde group. This strategy could provide access to a variety of isoquinones from conventional launch materials. In order to assess the magnitude and potential of these reactions, scientists have conducted research on a number of available carbonic substances.

The work of Fedoseev and co-workers' provided effective procedure for obtaining of tetrazole-isoquinoline/pyridone hybrids via rhodium (III)-catalyzed intermolecular annulations and Ugi-azide reaction. The modified procedure is straightforward, and the scope of syntheses quite comprehensive [7].



Scheme 2 One-pot synthesis of Isoquinolinones

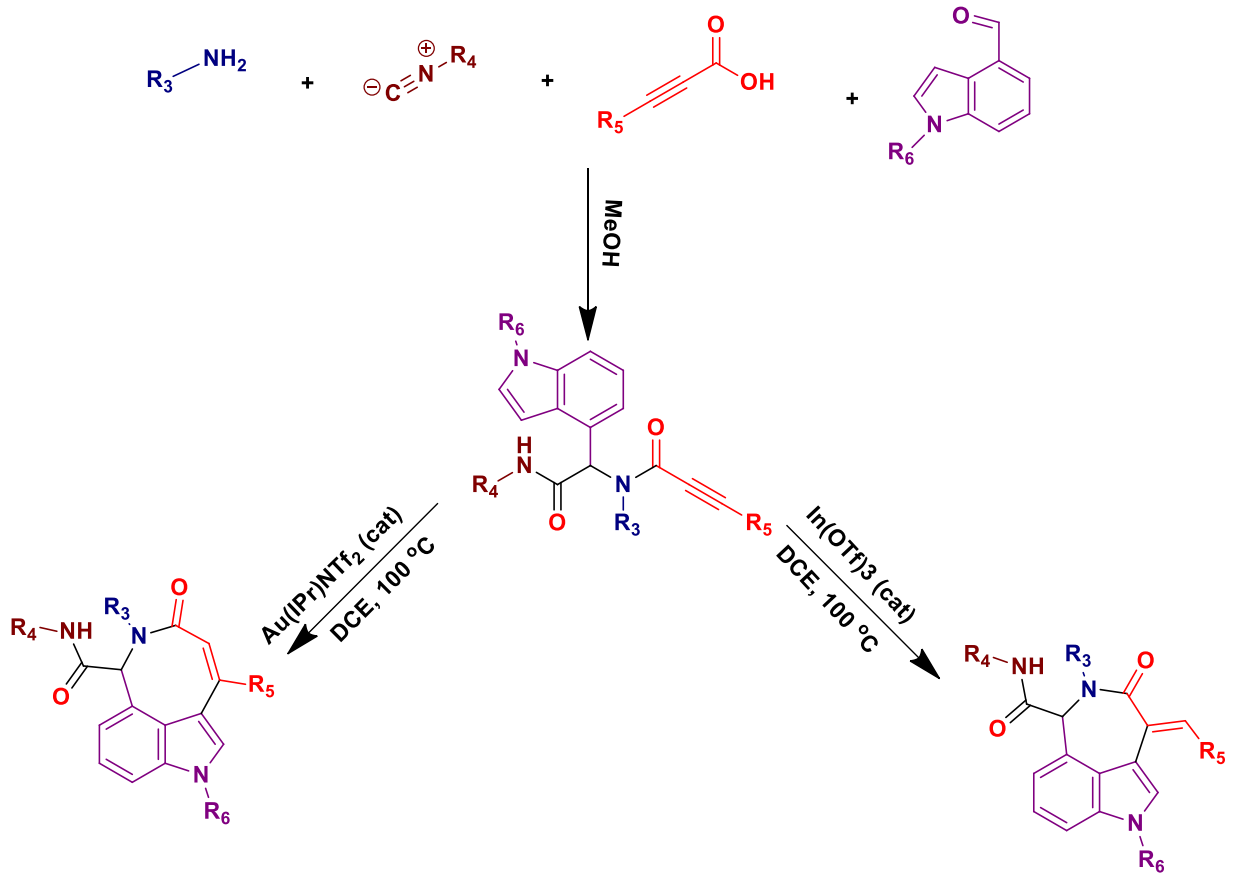
In following research, the authors disclosed an approach towards compounds bearing pyrrole, indole, furan, and other electron-rich arene fragments through the in two step sequence involving Ugi reaction and subsequent gold-catalyzed dearomative spirocyclization/1,6-addition cascade [8]. If the carbonyl group is transferred to the second position of indole, it is possible to obtain other types of reaction of Ugi adducts, which are subject to active catalyzed substances, as a result, azepinoindoles can be obtained (Scheme 3) [9].



Scheme 3 Synthesis of azepinbenzothiophene

In scheme 4, when the carbonyl group is transferred to the 4-position of indole and with the help of a solvent, as a result of which a new type of adducts have been attained. Furthermore, the selectivity of these oxo-cyclizations might be controlled and modified by the choice of the appropriate catalytic system. The cations of

these catalysts close the cycle, which leads to the formation of products such as azepino indole and azocino indole [10].

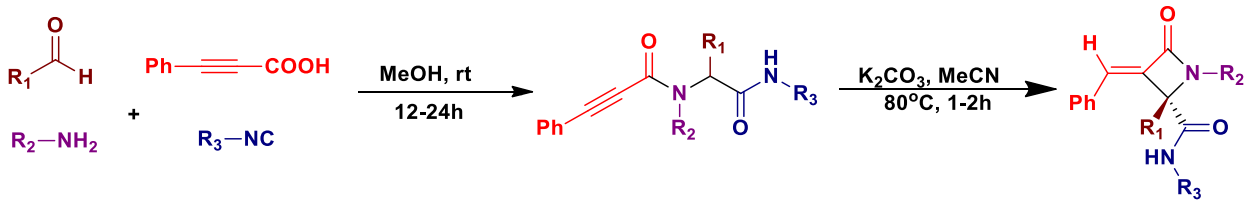


Scheme 4 Formation of azepino indole and azocino indole products

The nucleophilic characteristics of indole determine the substrates bearing the transition metal carbocyclization catalyst. The derivative of pyrrole-2-carbaldehyde has been effectively utilized for the regioselective formation of pyrrolo[2,3-c]azepines and pyrrolo[2,3-c]pyridines through the Pt(II)- /cationic Au(I)-catalysis [11]. Taking into account the main role of catalysts, such as gold and silver, in achieving high yields of target imidazole-containing products, researchers conclude that the yield of the target product increases when passing from methanol to imidazole-diazepines. During the research, the optimal ratio of catalysts was determined and the most suitable solvent was selected. In general, a characteristic feature of the structure under consideration is the hydrogen bond between the imino and amino groups which stabilize this molecule. Briefly, the composition of the products is directly affected by the conditions of synthesis and

the nature of the solvent. We assume that the correct choice of the solvent allows controlling the ratio of products. Initially, the reaction was carried out in methanol as a standard solvent and the target Ugi adducts were isolated at room temperature. The use of catalysis is one of the main pathways for the development of organic synthesis: an increasing number of chemical transformations, including multicomponent reactions, are currently carried out with the help of a catalyst. However, the use of catalysis in a multicomponent reaction often leads to a set of products of a mono- or bi-molecular reaction [12].

In addition, Ugi-4CRs have found widespread applications in drug discovery and natural product synthesis [13]. For instance, β-lactams are a four-membered cycle that contains a nitrogen atom. They are a major part of the structure of antibiotics such as penicillin and monobactams. Due to their low toxicity and high efficiency, β-lactams are used in chemotherapy. In 2014 Balalaie and co-workers provided a constructive synthesis of β-lactams through four-component Ugi reaction (Scheme 5).

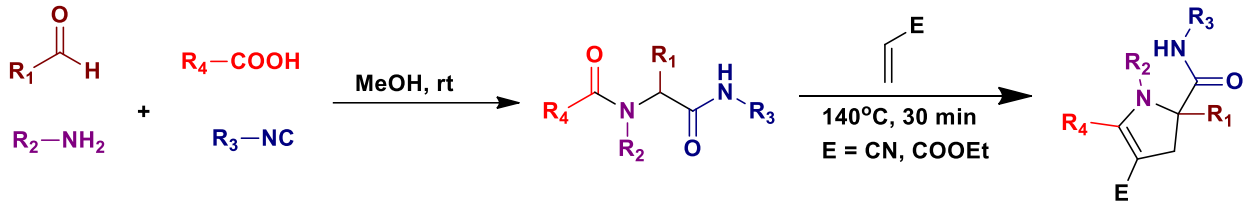


Scheme 5 Synthesis of β-lactams

At the beginning of synthesis, the interaction of starting materials, such as phenyl propiolic acid, anilines, benzaldehydes, and isocyanides was performed to allow Ugi adducts. After that, the addition of K_2CO_3 as a base to the Ugi adducts lead to the formation of β-lactams at 80°C for 2 hours. An important aspect in this synthesis is the establishment of Trans (E) - isomer structure due to π–π stacking interaction [14].

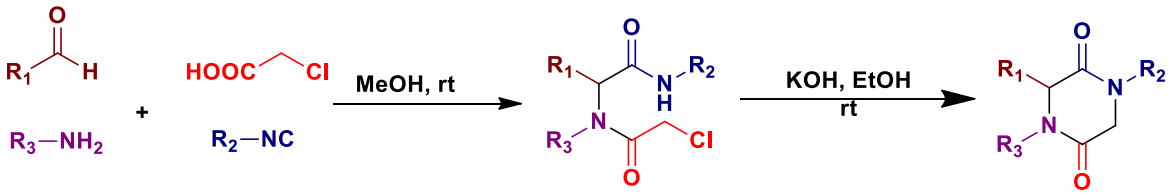
The next important components in pharmacology are dihydropyrroles, often called pyrrolines. Pyrrolines are five-membered heterocycle that contains one double bond (differing in position) and a nitrogen atom. In the same year, El Kaïm

and his co-workers have published a quick and effortless synthesis of pyrrolines (Scheme 6). This reaction was subjected to microwave irradiation in the presence of DIPEA where acrylonitrile was added to the Ugi adduct as a Michael acceptor [14, 15].



Scheme 6 Synthesis of pyrroline

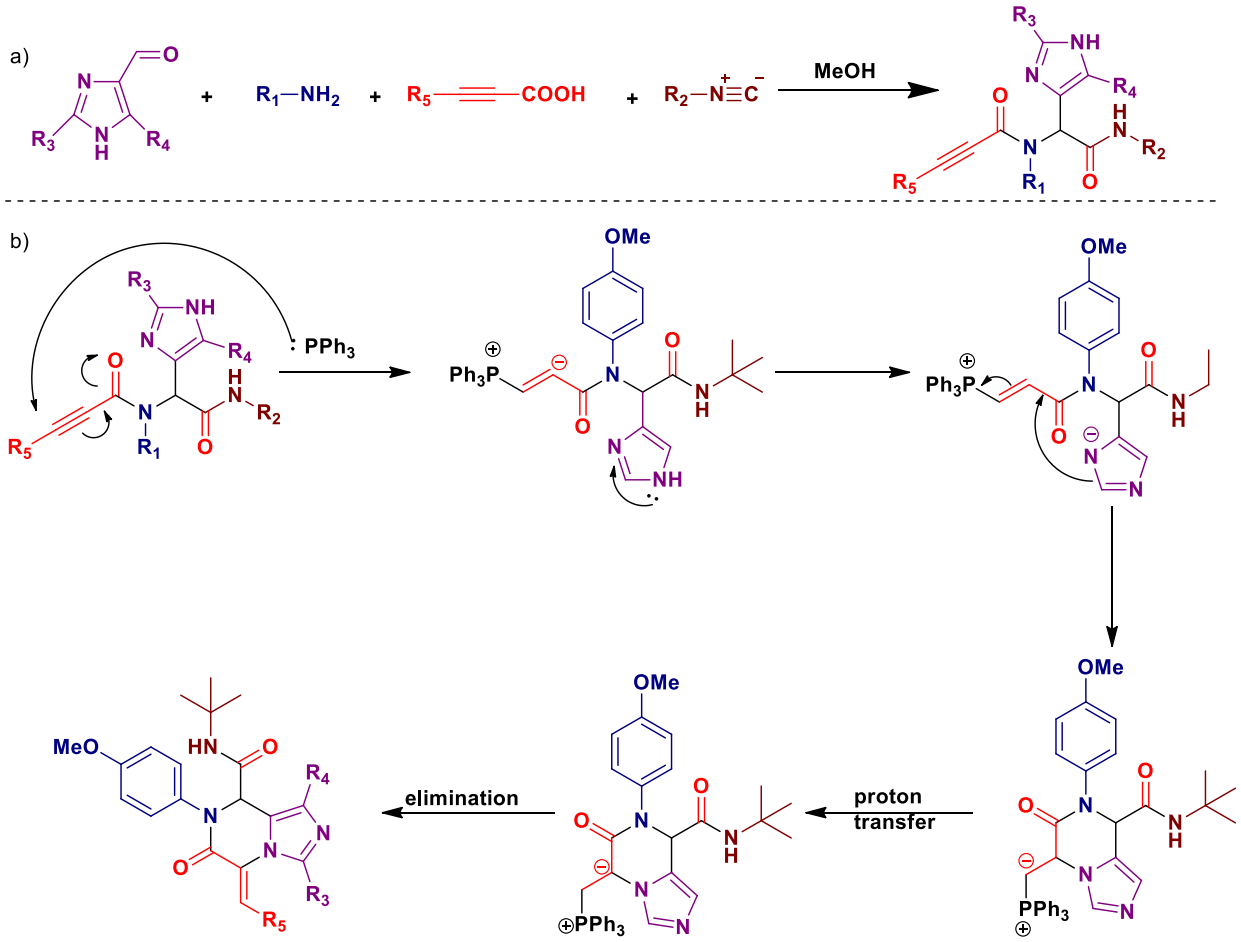
Another series of syntheses using the four-component Ugi reaction was described in 2001. 2, 5-Diketopiperazine is a six-membered cyclic dipeptide that contains two nitrogen atoms and two carbonyl groups. In Scheme 7, the obtained Ugi adduct was subjected to ultrasonic irradiation with ethanol KOH at room temperature [16].



Scheme 7 Synthesis of 2,5-DKPs

Multicomponent Ugi reactions open up access to a huge variety of structures including those of natural origin, which can exhibit a wide spectrum of biological activity, and the range of available compounds is constantly increasing. The method of increasing the selectivity of four-component Ugi reactions is directly related to the use of catalysts as a result of which the yield of the target products increases as well as carrying out syntheses under milder conditions [17]. Besides, the reaction between dicyanoalkenes with isocyanides and O-nucleophilic radical makes it possible to obtain a wide range of substituted with imidazopyrazinone and imidazodiazepinone under certain conditions (Scheme 8). This allows the formation of new zwitterionic heterocyclic systems including the imidazole ring.

After that, the reaction of heteroannulations of Larock with propargyl amine is carried out which is possible to regulate the reaction paths (endo-selective and exo-selective) with the addition of various catalysts [18].



Scheme 8 General mechanism for the synthesis of imidazopyrazinone

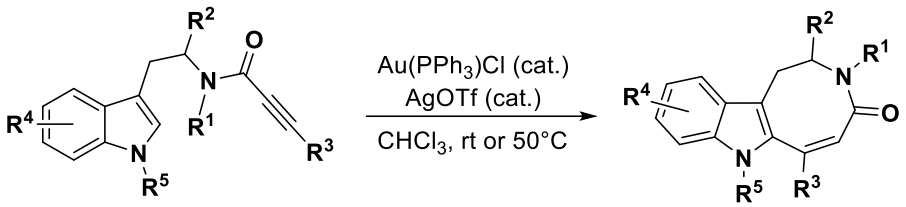
Scheme 11 illustrates the production of struc turally diverse bicyclic imidazo[1,5-a]pyrazine and imidazo[1,5-a][1,4]-diazepine scaffolds through the combination of an Ugi-4CR reaction of easily available building blocks that the amine component is activated by a hydroxyl group [18]. In the beginning, the lone pair of triphenylphosphine is attached to propargylamide which leads to a nucleophilic attack. Then, an intermediate product is carried out with phosphine as the Bronsted base. The next step is umpolung aza-Michael addition to the α-position of imidazole moiety and provided the exo-selective product by proton transfer [19].

1.3 Objectives of the current work

The main purpose of this work is a directed search for new post-Ugi transformation relying on the reactivity of a triple bond, as well as the optimization of the conditions for carrying out Ugi reactions and their use in organic synthesis. Specifically, we wanted to alter the regioselectivity of one of the known post-Ugi transformations utilizing hydroxypropargylamides Ugi adducts. The effect of presence of nucleophilic functional groups such as alcohols on the outcome of Ugi reaction has also been investigated.

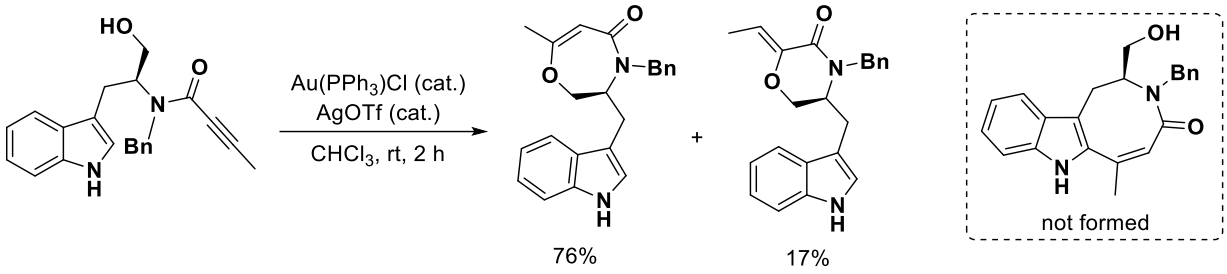
Our group has a long-standing interest in utilizing the triple bond reactivity in organic synthesis. We are particularly interested in obtaining diverse carbo-, hetero- and oxo-cyclizations by activating the triple bond in propiolic acid, where the intramolecular nucleophilic attack occurs. The main criteria for choosing nucleophiles for theses process include their tolerance towards the Ugi reaction conditions leading to the formation of intermediate Ugi adducts as well as their ability to react with activated triple bond. The choice of a solvent plays a huge role in reactions of this type, which often determines their direction [20].

In 2012, Van der Eycken and coworkers developed a cationic gold-catalyzed intramolecular alkyne hydroarylation reaction for the synthesis of variously substituted azocino[4,5-b]indoles from tryptamine-derived propargylamides (Scheme 9) [21].



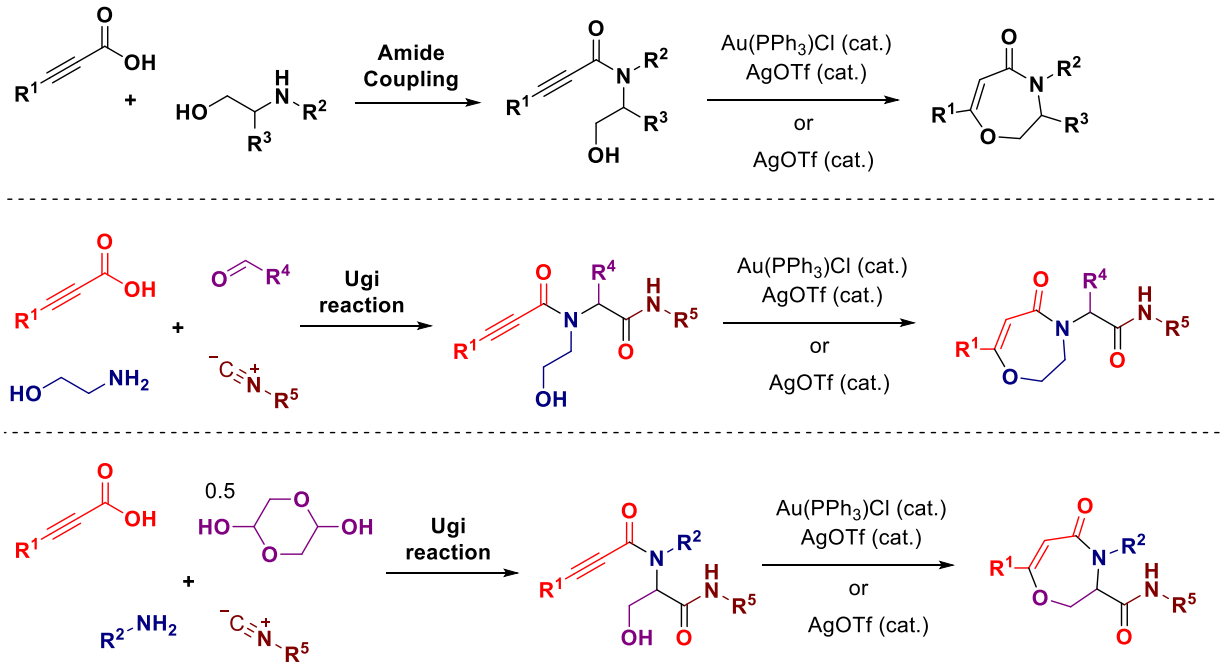
Scheme 9 Synthesis of azocino[4,5-b]indoles via cationic Au(I)-catalyzed intramolecular alkyne hydroarylation

In the course of the above research another potentially useful transformation was accidentally discovered. While the common pathway involved the carbocyclization of propargylamides into azocino[4,5-b]indoles, one substrate bearing an alcohol functional group yielded oxazepine as the major product, along with minor amounts of morpholine (Scheme 10) [21].



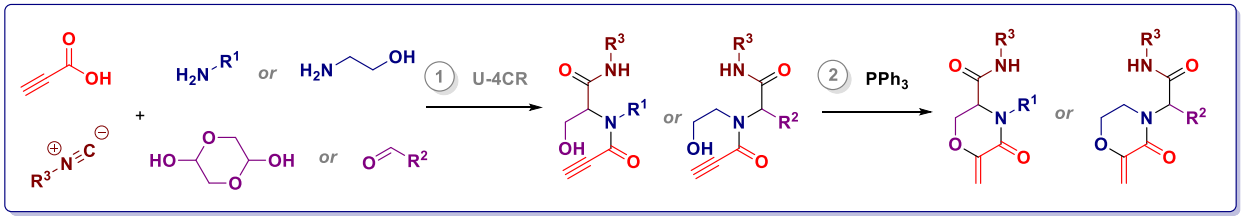
Scheme 10 Unexpected formation of oxazepine

In 2015, the group of Van der Eycken extended the scope of this approach, in order to establish a general and selective entry towards the oxazepine scaffold applying cationic gold or silver catalysis and utilizing three different types of hydroxypropargylamide substrates derived from either amide coupling or four-component Ugi reactions (Scheme 11) [22].



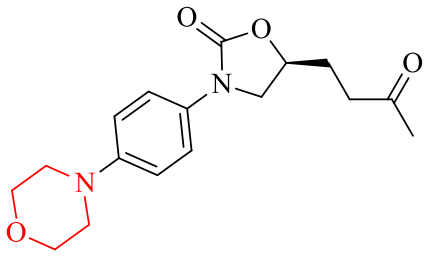
Scheme 11 General strategy for the generation of oxazepines

The major goal of the present study is to alter the regioselectivity of the cycloisomerization of Ugi hydroxypropargylamide adducts from 7-endo-dig to the 6-exo-dig mode. Towards this goal, we have attempted to switch from the Lewis acid catalysis to the catalysis by the triphenyl phosphine hoping that the letter can direct the reaction through the umpolung aza-Michael addition similar to that is described at the end of literature review section. Therefore, our subsequent research efforts have been focusing on two major stages that included the preparation of Ugi adducts and PPh_3-catalyzed post-Ugi cyclizations (Scheme 12). During this research, we were able to produce two distinct types of morpholine containing heterocyclic scaffolds.

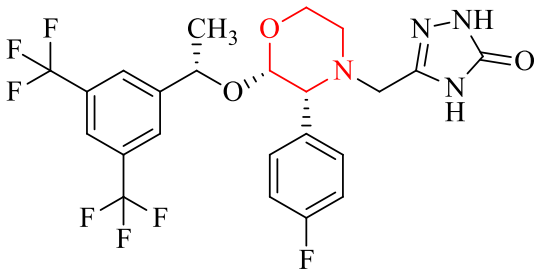


Scheme 12 Synthesis of morpholines through Ugi reaction

It is important to stress that this research towards morpholine heterocycles was particularly inspired by the wide occurrence of this privileged motif in pharmaceuticals. Morpholine is a core part of a number of commercial drugs, such as Linezolid for the treatment of infectious and inflammatory diseases; Aprepitant to prevent chemotherapy-induced nausea (Figure 1) [23, 24].



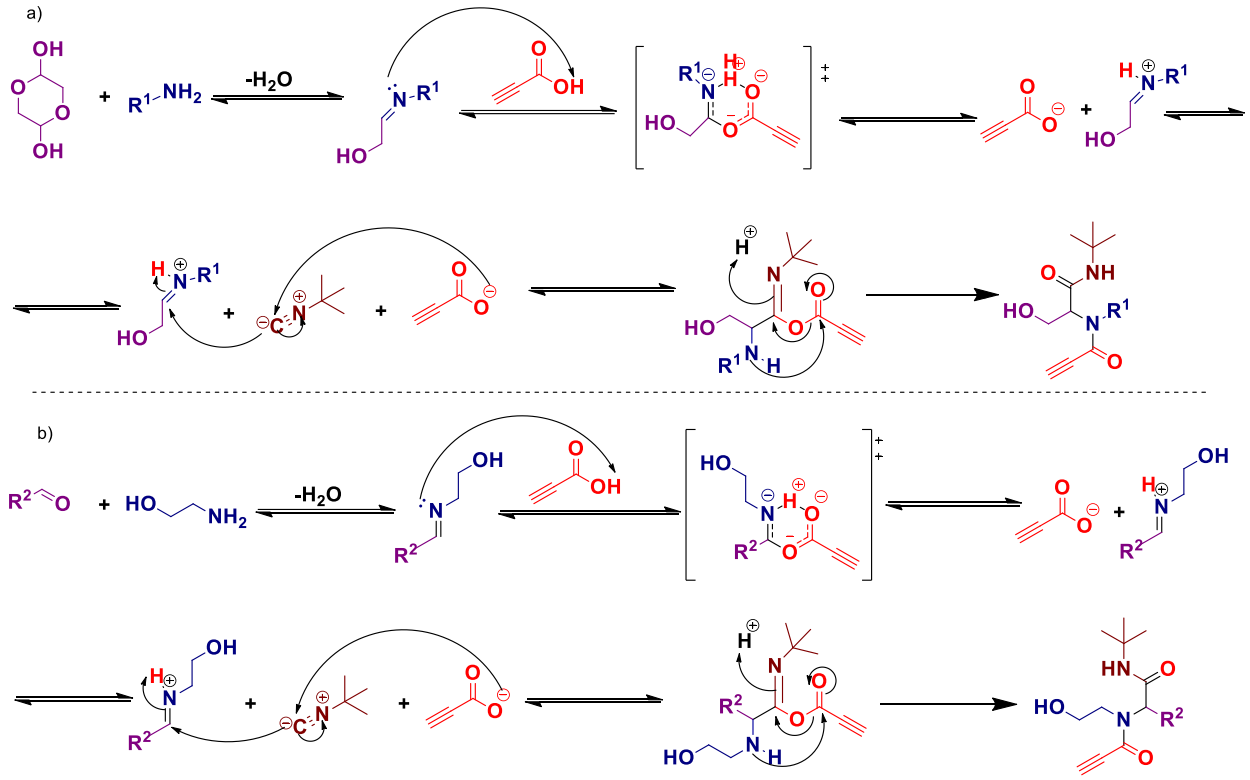
Linezolid



Aprepitant

Figure 1 Chemical structures of the commercial morpholine containing drugs

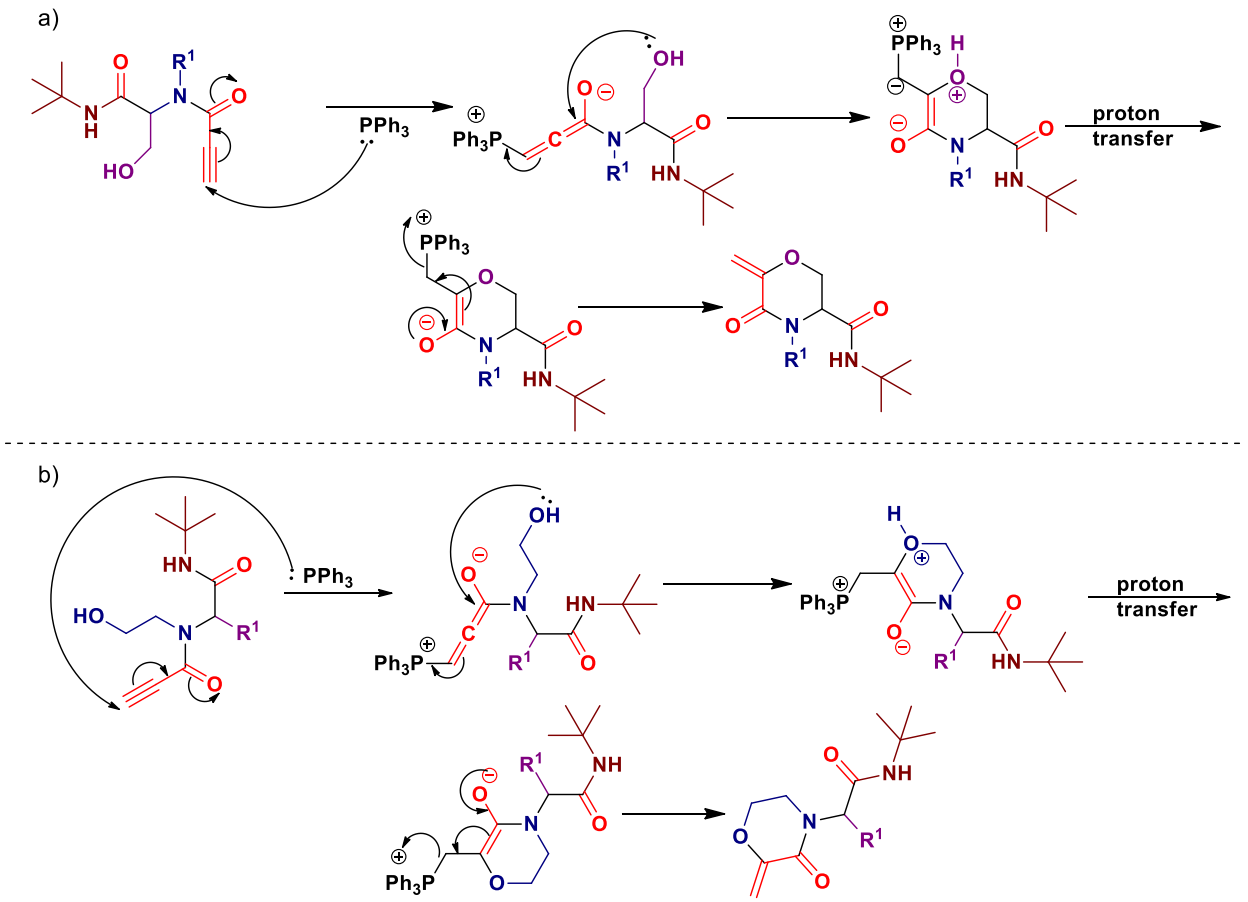
Our research group is interested in the synthesis of morpholines, which is achieved through the four component Ugi reaction (Scheme 13). This synthesis consists of two main stages: obtaining the Ugi substrate and obtaining oxo-cyclization using triphenylphosphine as a catalyst. It should be noted that the first stage takes place under mild conditions representing an interesting substrate with a high yield of the target product. The second stage is called post-Ugi transformation. The resulting adduct will react with a catalyst and in our case triphenylphosphine. Further, an intramolecular polarity inversion is afforded which is called the umpolung oxa-Michael addition [25, 26].



Scheme 13 Mechanism for the synthesis of two types of hydroxypropargylamides *via* the Ugi reaction: a) for Ugi adduct 7; b) for Ugi adduct 10

The plausible mechanism for the synthesis of morpholine through the post-Ugi transformation reaction (Scheme 14) is similar to that of imidazopyrazinone production. Triphenylphosphine will attack the triple bond resulting in nucleophilic attachment to the activated alkynes. Then, intramolecular nucleophilic addition of

oxygen to active carbon occurs transferring a proton from oxygen to the C=C bond. At the end of cyclizations, triphenylphosphine is eliminated from the heterocycle [18, 27].



Scheme 14 Mechanism for the synthesis of morpholines *via* post-Ugi intramolecular transformation: a) for morpholines of type 11; b) for morpholines type 12

The Ugi-4CR is one of the remarkable reactions that can be used for chemical library expansion. This chemical library represents the scope of chemical products that might utilize in various directions. Further, these libraries can be treated with living organisms and enzymes in order to find new active pharmaceuticals.

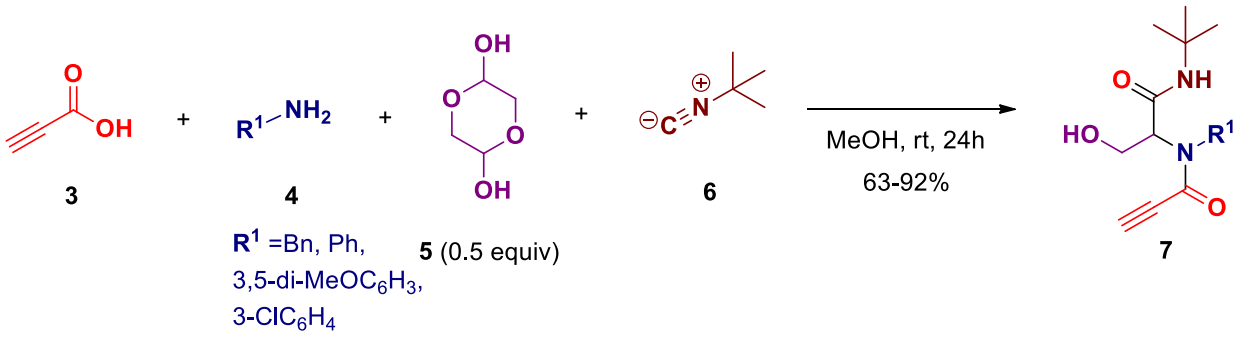
Chapter 2

2. Results and Discussion

2.1. Assembly of hydroxypropargylamides *via* a Cascade Ugi reaction

One of the key advantages of Ugi-4CR is that it allows a facile installment of various functional groups that can be further employed in a large variety of post-transformations [28] leading to the construction of extensive libraries of potentially bioactive heterocycles [29].

Following our goal, we have prepared the required Ugi adducts **7 a-d** (Scheme 15). Reacting propiolic acid (**3**) with amines **4**, glycolaldehyde dimer (**5**), and *tert*-butyl isocyanide (**6**) afforded hydroxypropargylamides of type **7**. These reactions were carried out in methanol at room temperature for 24 hours and capable to obtain desired Ugi adducts in good to high yields of 63-92% (Table 1, entries 1-6).



Scheme 15 Synthesis of hydroxypropargylamides **7** *via* Ugi reaction

Table 1 Scope of Ugi adducts **7**

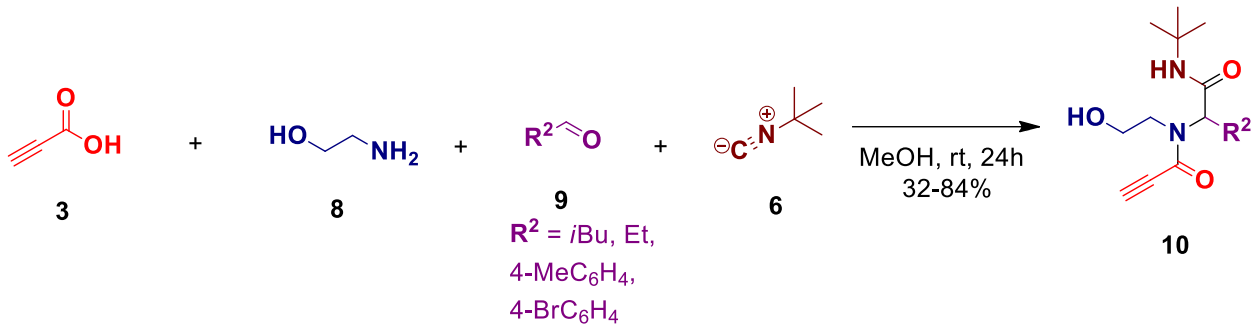
Entry	Scale, mmol	Concentration, M	R^1	Ugi adduct **7**	Yield, %
1	0.3	0.3	Bn	**7a**	80[a]
2	0.3	0.06	Bn	**7a**	92[a]

3	2	0.06	Bn	**7a**	85[b]
4	0.8	0.06	Ph	**7b**	84[b]
5	0.8	0.06	3,5-di-$MeOC_6H_3$	**7c**	63[b]
6	0.8	0.06	3-ClC_6H_4	**7d**	77[b]

[a] Determined by ^1H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. [b] Isolated yield.

With respect to the scope, we have mainly focused on evaluation the amine component **4** using benzyl amine (**4a**) and several aromatic amines bearing different substitution patterns. Optimization has been performed using benzyl amine **4a**. In particular, we have varied the dilution and scale of the reaction (Table 1, entries 1-3). We have optimized reactions for hydroxypropargylamides by changing concentration from 0.3M to 0.06M. According to experimental data, we have noticed that for Ugi adducts of type 7 the low concentration are favorable. The combination of phenylamine **4b** with propiolic acid **3**, glycol dimer aldehyde **5**, and isocyanide **6** demonstrates good yield of 84% (Table 1, entry 4). In order to analyze how steric hindrances affect the structure, we attempted to utilize dimethoxybenzene **4c** that led to a slightly diminished yield of the desired products in comparison with other reactions (Table 1, entry 5 versus entries 1-4). The last amine that we investigated is 3-chloroaniline **4d** that reacted well delivering the desired hydroxypropargylamide 7d in a good yield of 77%.

Next, reacting propiolic acid (**3**) with ethanolamine (**8)**, various aldehydes **9** and *tert*-butyl isocyanide **8** afforded hydroxypropargylamides of type **10** (Scheme 16). In this case the substrate scope study has been focused on the evaluation of the aldehyde component **9**. We were rather pleased to find that our approach has successfully tolerated both aliphatic and aromatic aldehydes **9** delivering hydroxypropargylamides **10** with the yields ranging from 32 to 84% (Table 1, entries 1-7).



Scheme 16 Synthesis of hydroxypropargylamides **10** through Ugi reaction

Table 2 Scope of Ugi adducts **10**

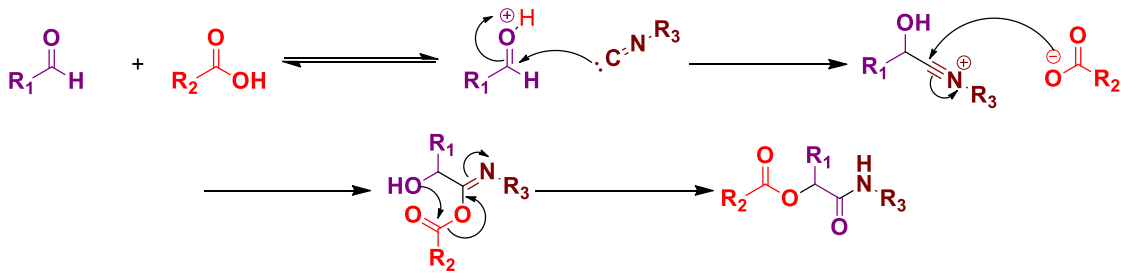
Entry	Scale, mmol	Concentration, M	R^1	Ugi adduct **10**	Yield, %
1	0.3	0.3	*t*Bu	**10a**	84[a]
2	0.3	0.06	*t*Bu	**10a**	70[a]
3	0.8	0.3	*t*Bu	**10a**	76[b]
4	0.8	0.3	Et	**10b**	32[b]
5	1	0.3	4-Me-C_6H_4	**10c**	40[b]
6	0.8	0.3	4-Br-C_6H_4	**10d**	68[b]
7	0.8	0.3	3,4,5-tri-MeO-C_6H_2	**10e**	53[b]

[a] Determined by ^{1}H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. [b] Isolated yield.

As illustrated in Table 2 we have optimized syntheses of hydroxypropargylamides by changing the scale and dilution of the process (Table 2, entries 1-3). The influence of propionaldehyde **9b** on the Ugi synthesis is quite different, and the lowest yield of 32% was observed for this reaction (Table 2, entry 4) (the NMR spectra are attached for details). The interaction of para methyl benzaldehyde **9c** with propiolic acid **3**, tert-butyl isocyanide **6**, and ethanolamine **8** gives a 40%, as a result, led to a low undesirable outcome (Table 2, entry 5) (the NMR spectra are

attached for details). The application of electron-withdrawing para bromobenzaldehyde **9d** instead of the traditional aldehyde demonstrates the obtaining appropriated Ugi adducts which are equal to 68% (Table 2, entry 6). Further, the usage of bulky electron-donating 3,4,5-trimethoxybenzaldehyde **9e** through the Ugi four-component reaction allows adducts to be obtained in moderate to good yields of 53% (Table 2, entry 7). The diminished yield can be explained by losses of product during the isolation by column chromatography.

For all above syntheses were utilized polar protic solvent, namely methanol (MeOH) since for the Ugi four-component reactions that type of solvents operate in a good way. In contrast, for Passerini three-component reactions (P-3CR) apolar-protic solvents are more preferable, along the lines of dichloromethane (DCM) and tetrahydrofuran (THF). The plausible mechanism of P-3CR is considered to include the key intermediate oxo component of the stereogenic step where its carbonyl activity increases which led to the nucleophilic attack of isocyanide, while for U-4CR the major intermediate product is the less reactive Schiff base than the oxo component of P-3CR. U-4CR's intermediate have need of the activation via protonation with Lewis acid, and as a consequence, the isocyanide nucleophilic attack occurs in the stereogenic step (Scheme 17). This actively demonstrates that, methanol as a solvent stabilizes the hydrogen bond between Schiff base and a carboxylic acid, as a result, nucleophilic attack of the isocyanide occurs toward Schiff base [30].

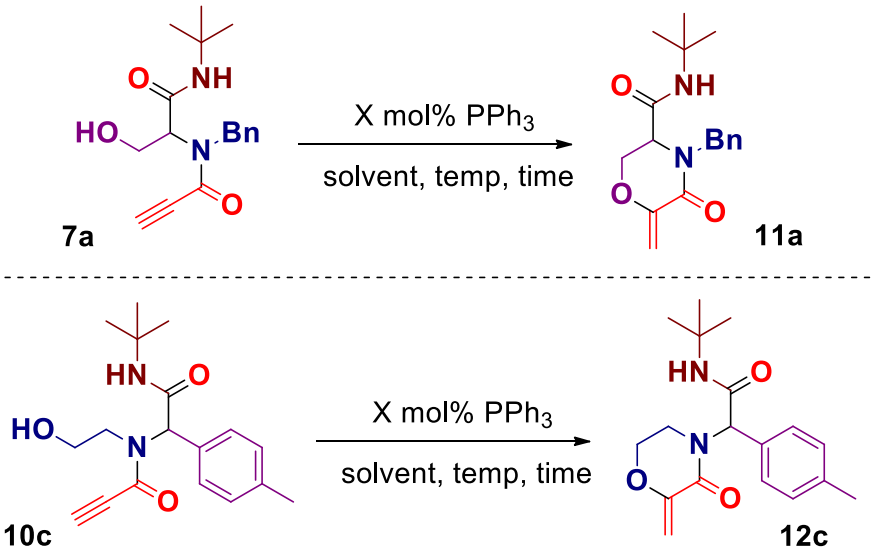


Scheme 17 Mechanism for the for Passerini three-component reactions

2.2. PPh_3 catalyzed hydroxypropargylamide cyclizations for the synthesis of morpholines

Basically, we have effectively demonstrated basic components for the construction of the diverse cascade engaging Ugi-4CR followed by hydroxypropargylamides and umpolung intramolecular oxa-Michael addition leading to morpholine containing heterocycles.

Next, we have decided to choose two Ugi adducts (**7a** and **10c**) for further comprehensive analysis (Scheme 18). We have started the modification of post-Ugi intramolecular transformation syntheses using PPh_3 as a catalyst by varying the temperature, solvent, and time (Table 3 entries 1-14).



Scheme 18 Synthesis of morpholines through post-Ugi reaction

Table 3 Optimization of reaction conditions for the synthesis of morpholines 11a and 12c[a]

Entry	Substrate	X, mol%	Solvent	Temp, °C	Time, h	Conversion of **7a** or **10c**, %[b]	Yield of **11a** or **12c**, %[b]
1	**7a**	20	EtOAc	80	4	95	30

2	**7a**	20	DCM	60	4	100	52
3	**7a**	20	MeCN	80	3	100	34
4	**7a**	20	MeOH	80	3	100	45
5	**7a**	20	EtOH	80	3	100	70
6	**7a**	20	i-PrOH	80	3	100	73 (66)[c]
7	**7a**	10	i-PrOH	80	6	100	66
8	**7a**	30	i-PrOH	80	2	100	62
9	**7a**	10	i-PrOH	rt	120	88	43
10	**10c**	20	EtOH	80	3	100	71
11	**10c**	20	i-PrOH	80	3	100	90 (89)[c]
12	**10c**	10	i-PrOH	80	6	100	81
13	**10c**	30	i-PrOH	80	2	100	78
14	**10c**	30	i-PrOH	rt	24	90	60

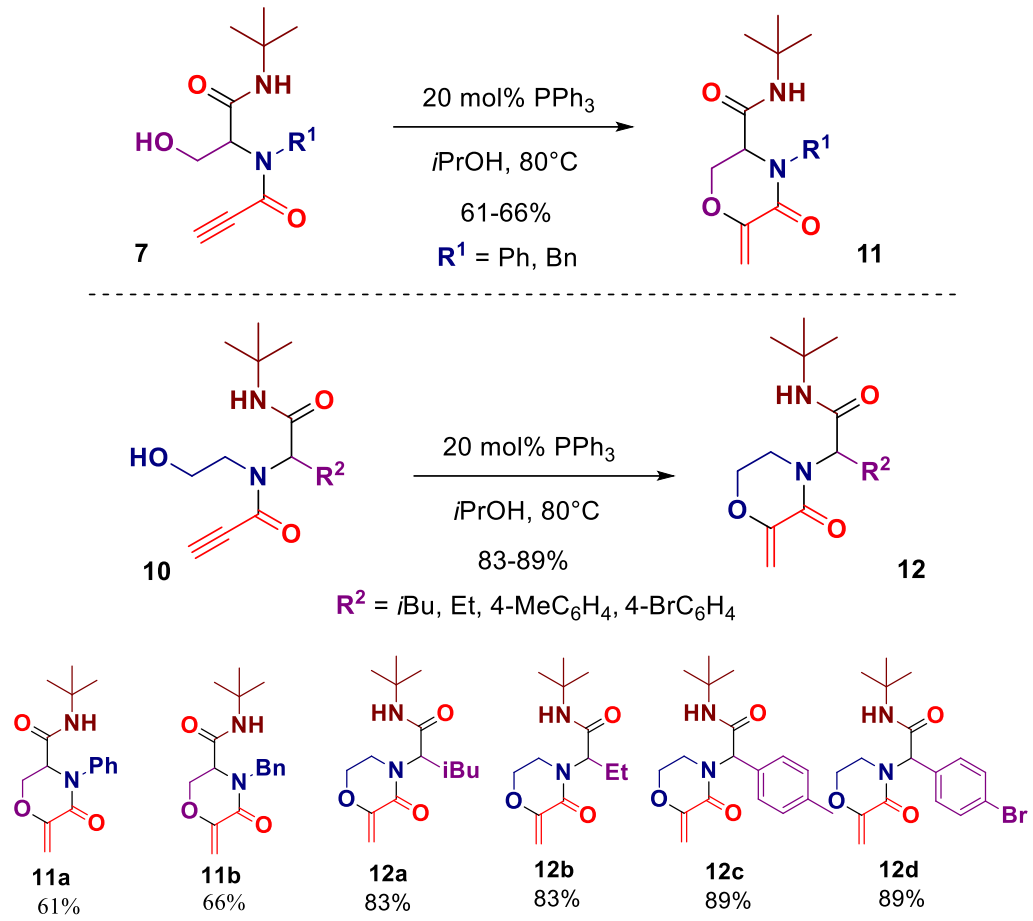
[a] All reactions were run on 0.2 mmol scale in 4 mL of solvent. [b] Determined by ^{1}H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. [c] Isolated yield is given in a parenthesis.

In order to extend the chemical library, we have optimized the syntheses of morpholines with PPh_3-catalyzed post-Ugi intramolecular transformation. First, the straightforward combinations of Ugi adduct **7a** with PPh_3 loading were successfully dissolved in ethyl acetate (EtOAc) at 80^{o}C for 4 hours, and the lowest yield of 30% was obtained (Table 3, entry 1). After that, we have changed the solvent to dichloromethane (DCM) and the temperature was decreased to 60^{o}C. That type of synthesis gave a moderate yield of 52% (Table 3, entry 2). Further, we worked on changing the solvents to methyl cyanide (MeCN) or methanol (MeOH), temperature was increased as well and the reaction proceeded for 3 hours; as a result, the substrate is fully converted, but the yield is lower (Table 3, entries 3, 4). Then when we changed the solvent to ethanol, the product yield increased from

moderate to good, from 45% to 70%, respectively (Table 3, entry 5). As a final point, we switched to the use of isopropyl alcohol (i-PrOH) as a solvent and attempted to modify the catalyst loading and time of the reaction. The optimization of catalyst screening in interaction with hydroxypropargylamide provided the desired products in good to high yields (Table 3, entries 6-9).

Further series of optimization of hydroxypropargylamides of type **10c** for the synthesis of morpholine containing heterocycles was accomplished through the catalyst of triphenylphosphine by the acting of various solvents, such as ethanol, and isopropyl alcohol (Table 3, entries 10-14). Initially, we treated substrate **10c** in the ethanol solvent at 80^{o}C for 3 hours. Complete conversion was observed for type **12c** with the formation of the desired product in 71% yield (Table 3, entry 10). We also carried out hydroxypropargylamide type 10c through PPh3-catalyzed post-Ugi-cyclizations with isopropanol (i-PrOH) at an elevated temperature of 80°C. We have varied the time from 2 to 6 hours and catalyst loading of the reaction (Table 3, entries 11-13). In order to identify how heat condition affects to the product yield, the synthesis was carried out at room temperature for 24 hours. The product yield was moderate, approximately equal to 60% without complete conversion (Table 3, entry 14).

Finally, treating hydroxypropargylamides **7** and **10** with catalytic amounts of triphenylphosphine in isopropanol at 80°C yielded morpholines **11** and **12**, respectively through the intramolecular umpolung oxa-Michael addition (Scheme 19).



Scheme 19 Synthesis of morpholines **11** and **12** through the PPh_3-catalyzed post-Ugi intramolecular transformation

All prepared Ugi adducts **7** and **10**, as well as target morpholines **11** and **12** were characterized by ^{1}H and ^{13}C NMR spectroscopy. In addition, we were able to confirm the identity of products **7**, **11a** and **11b** through the high resolution mass spectrometry (HRMS) method using an Agilent 1100 series HPLC coupled to an Agilent 6220A TOF-MSD, equipped with ESI/APCI ionization source (see experimental section for details).

Overall, we developed a route towards two series of densely functionalized morpholines **11** and **12** through the PPh_3-catalyzed post-Ugi intramolecular umpolung oxa-Michael addition. This process is complementary to our previously developed approach to oxazepines *via* Lewis acid-catalyzed intramolecular oxa-Michael addition.

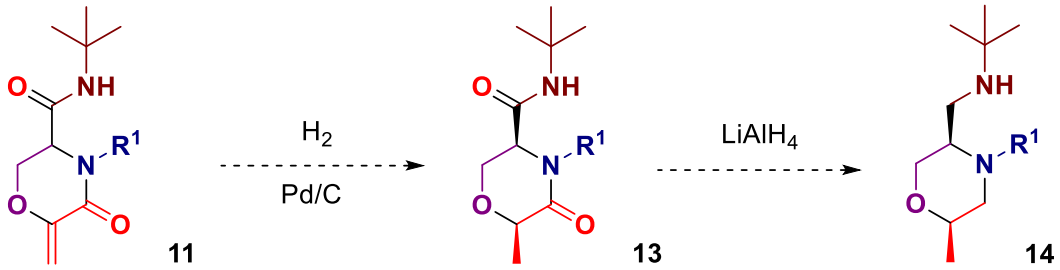
As a rule, carboxylic acid plays a significant role in the Ugi reaction since the essential structure of the product is described by the species of carboxylic acid and its derivatives. The particular reason for this circumstance, that propiolic acid is a suitable item in view of its reactivity, stability and capability to convert into other substrates maintaining selectivity [31-33].

Importantly, under modified conditions, diverse Ugi adducts that consider aldehyde, isocyanide, carboxylic acid, and aniline with electron-donating and electron-withdrawing functional groups are reacted easily and gave products ranging from good to high results. Post-Ugi transformation is carried out by a nucleophilic attack from triphenylphosphine to activated the triple bond and create a zwitterionic structure by the proton transfer. In our optimized synthesis, hydroxypropargylamides straightforward reacted with triphenylphosphine catalyst via intramolecular oxa-Michael addition that considers modification functional groups.

To sum up everything that has been stated so far, methods for reliable control of regioselectivity were proposed and it was also found that carrying out the reaction in the presence of methanol significantly expands the field of application and allows this reagent to be considered a universal activator of its substrates.

Conclusions and future perspectives

We have effectively developed a two-step selective approach for the synthesis of diverse morpholine-containing heterocycles through the post-Ugi cycloisomerization in the presence of PPh_3 catalyst. All the cyclized products were attained in high yields with superior regioselectivity. The scope of the approach has been investigated in depth with different kinds of substrates that properly extended the chemical library towards desired products. The resulting heterocycles could be explored in subsequent chemical transformations such as catalytic hydrogenation of exocyclic double bond as well as amide group reduction (Scheme 20). Furthermore, acquired morpholine-containing products will be investigated for their biological activity.



Scheme 20 Proposed modifications of morpholines **11**.

Chapter 3

3. Experimental part

General information

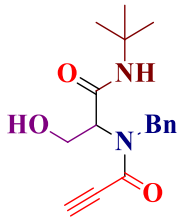
In order to determine the chemical structure of substances ^{1}H and ^{13}C FT NMR spectra (JNM-ECA 500) were used with 500 and 126 MHz. All chemical shifts were recorded in parts per million. As residual solvent deuterated chloroform ($CDCl_3$) were used.

Mass spectra were recorded with a Bruker Maxis HRMS-ESI-qTOF spectrometer (electrospray ionization mode).

All starting materials and solvents were used without further purification and purchased from commercial sources.

3.1. General procedure for the synthesis of Ugi adduct 7

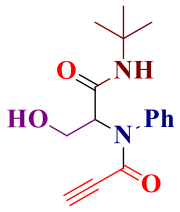
Propiolic acid **3** (0.8 mmol) was dissolved in methanol (13.33 ml), and the adequate amine **4** (0.8 mmol), glycolaldehyde dimer **5** (0.4 mmol), and isocyanide **6** (0.8 mmol) were added successively. The reaction proceeded in a sealed screw-cap vial equipped with a magnetic stirrer at room temperature for 24 hours. At the end of this time, the reaction was transferred to a round bottom flask and evaporated with silica gel. The reaction was separated into fractions on a chromatographic column with EtOAc/Hex system (50% / 50%), as a result of which the desired Ugi adducts **7 a-d** were obtained. This adduct consists of a mixture of two rotamers; therefore, the NMR spectra for ^{1}H and ^{13}C do not particularly coincide.



7a

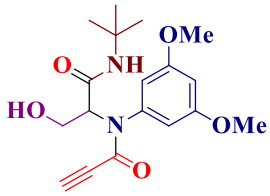
N-benzyl-N-(1-(tert-butylamino)-3-hydroxy-1-oxopropan-2-yl) propiolamide:

3:1 mixture of rotamers, white solid, 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 6.00 (bs, 0.75H), 5.43 (bs, 0.25H), 5.12 – 5.03 (m, 1H), 4.83 (d, J = 16.0 Hz, 0.75H), 4.67 – 4.57 (m, 0.25H), 4.42 (dd, J = 6.2, 5.4 Hz, 0.75H), 4.25 (d, J = 14.7 Hz, 0.25H), 4.18 (dd, J = 11.1, 8.0 Hz, 0.25H), 3.97 (dd, J = 11.8, 6.4 Hz, 0.75H), 3.72 (dd, J = 11.4, 5.4 Hz, 0.25H), 3.72 (dd, J = 11.8, 5.2 Hz, 0.75H), 3.24 (s, 0.75H), 3.24 (s, 0.25H), 3.20 (bs, 1H), 1.18 (s, 6.75H), 1.14 (s, 2.25H); $^{13}C\{1H\}$ NMR (126MHz, CDCl3) δ 171.2, 168.1, 154.8, 154.5, 137.2, 136.4, 129.0, 128.3, 128.2, 128.0, 127.7, 81.3, 80.9, 75.7, 75.5, 63.5, 61.5, 60.6, 60.4, 59.8, 52.6, 51.7, 51.4, 28.4, 28.3. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{17}H_{22}N_2O_3Na^+$ 325.1523; Found 325.1525.



7b

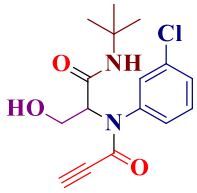
N-(1-(tert-butylamino)-3-hydroxy-1-oxopropan-2-yl)-N-phenylpropiolamide: white solid, 84% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 - 7.36 (m, 3H), 7.30 (dd, J = 6.4, 3.0 Hz, 2H), 6.54 (bs, 1H), 5.00 (t, 1H), 3.85 (dd, J = 11.6, 7.2 Hz, 1H), 3.64 (dd, J = 11.6, 6.1 Hz, 1H), 2.91 (s, 1H), 2.30 (bs, 1H), 1.38 (s, 9H); ^{13}C{1H} NMR (126 MHz,) δ 169.40, 155.62, 139.18, 130.27, 130.21, 82.81, 76.56, 61.31, 61.12, 52.63, 30.68, 29.61. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{20}N_2O_3Na^+$ 311.1366; Found 311.1368.



7c

N-(1-(tert-butylamino)-3-hydroxy-1-oxopropan-2-yl)-N (3,5dimethoxyphenyl)propiolamide:

white solid, 63% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (bs, 1H), 6.48 (t, *J* = 2.2 Hz, 1H), 6.44 (d, *J* = 2.2 Hz, 2H), 4.96 (t, 1H), 4.10 (q, *J* = 7.1 Hz, 1H), 3.91 – 3.83 (m, 1H), 3.76 (s, 6H), 3.66 (d, *J* = 5.6 Hz, 1H), 2.95 (s, 1H), 2.81 (bs, 1H), 1.36 (s, 9H); ^{13}C{1H} NMR (126 MHz,) δ 168.59, 161.00, 154.58, 139.70, 107.50, 101.36, 81.70, 75.67, 60.55, 60.34, 60.12, 55.64, 51.71, 51.70, 29.81, 28.71, 21.19, 14.31. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{18}H_{24}N_2O_5Na^+$ 371.1577; Found 371.1579.



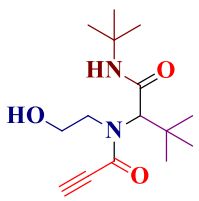
7d

N-(1-(tert-butylamino)-3-hydroxy-1-oxopropan-2-yl)-N-(3-chlorophenyl)propiolamide:

white solid, 77% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, 2H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.25 (bs, 0.30H), 6.60 (bs, 0.80H), 4.96 (t, *J* = 5.9 Hz, 1H), 3.87 (dd, *J* = 11.3, 6.5 Hz, 1H), 3.68 (dd, *J* = 11.3, 5.9 Hz, 1H), 2.96 (s, 1H), 1.34 (s, 9H); ^{13}C{1H} NMR (126 MHz,) δ 167.93, 154.44, 139.47, 134.68, 130.28, 129.98, 129.72, 127.99, 82.42, 75.51, 60.45, 60.37, 51.86, 28.69. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{19}ClN_2O_3Na^+$ 345.0976; Found 345.0979.

3.2. General procedure for the synthesis of Ugi adduct 10

Propiolic acid **3** (1.0 mmol) was dissolved in methanol (3.25 ml), and corresponding various aldehyde **9** (1.0 mmol), ethanolamine **8** (1.0 mmol), and isocyanide **6** (1.0 mmol) were added, respectively. The reaction proceeded in a sealed screw-cap vial equipped with a magnetic stirrer at room temperature for 24 hours. At the end of this time, the reaction was transferred to a round bottom flask and evaporated with silica gel. The reaction was separated into fractions on a chromatographic column with EtOAc/Hex system (50% / 50%), as a result of which the desired Ugi adducts **10 a-e** were obtained. This adduct consists of a mixture of two rotamers; therefore, the NMR spectra for ^{1}H and ^{13}C do not particularly coincide.

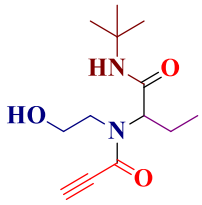


10a

N-(tert-butyl)-2-(N-(2-hydroxyethyl)propiolamido)-3,3-dimethylbutanamide:

3:1 mixture of rotamers, white solid, 84% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (s, 0.78H), 6.05 (s, 0.22H), 4.65 – 4.60 (m, 1H), 4.49 (t, *J* = 7.7 Hz, 1H), 3.96

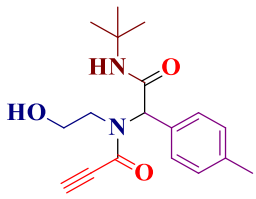
(dd, *J* = 15.0, 2.4 Hz, 1H), 3.78 (ddd, *J* = 12.6, 9.7, 5.4 Hz, 2H), 3.65 (dd, *J* = 15.0, 3.0 Hz, 1H), 3.27 (s, 0.25H), 3.19 (s, 0.75H), 1.35 (s, 2H), 1.33 (s, 7H), 1.25 (s, 2.4H), 0.95 (dd, *J* = 9.8, 6.6 Hz, 6.6H). Chemical Formula: $C_{15}H_{26}N_2O_3$.



10b

N-(tert-butyl)-2-(N-(2-hydroxyethyl)propiolamido) butanamide:

1:3 mixture of rotamers, white solid, 32% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (s, 0.25H), 6.31 (s, 0.75H), 4.97 (bs, 0.70H), 4.45 (t, 0.24H), 4.23 (t, *J* = 7.8 Hz, 0.76H), 3.90 (d, *J* = 15.4 Hz, 1H), 3.78 – 3.73 (m, 2H), 3.66 (dd, *J* = 16.0, 5.3 Hz, 1H), 3.53 (bs, 0.30H), 3.27 (s, 0.28H), 3.21 (s, 0.72H), 1.94 (dd, *J* = 14.1, 6.9 Hz, 1H), 1.82 (dd, *J* = 14.3, 6.8 Hz, 1H), 1.31 (s, 2.24H), 1.30 (s, 6.76H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C{1H} NMR (126 MHz,) δ 171.02, 169.47, 155.40, 154.88, 81.01, 80.33, 75.80, 65.00, 62.12, 61.33, 60.76, 51.88, 50.20, 29.75, 28.55, 28.50, 22.85, 21.59, 10.86. Chemical Formula: $C_{13}H_{22}N_2O_3$.

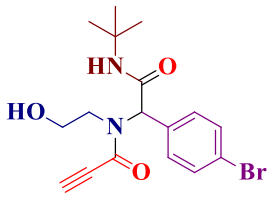


10c

N-(2-(tert-butylamino)-2-oxo-1-(p-tolyl)ethyl)-N-(2-hydroxyethyl) propiolamide:

3:1 mixture of rotamers, white solid, 84% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (s, 4H), 6.06 (bs, 0.15H), 5.95 (s, 0.15H), 5.61 (bs, 0.85H), 5.58 (s, 0.85H), 4.30-4.10 (m, 0.85H), 3.81 (ddd, *J* = 15.0, 7.5, 3.3 Hz, 0.85H), 3.78 – 3.74 (m, 0.15H), 3.74 – 3.67 (m, 0.85H), 3.65 (dd, *J* = 5.5, 2.9 Hz, 0.15H), 3.63 – 3.56 (m, 0.85H), 3.48 – 3.40 (m, 0.15H), 3.27 (s, 0.15H), 3.16 (s, 0.85H), 3.12(bs, 1H), 2.93

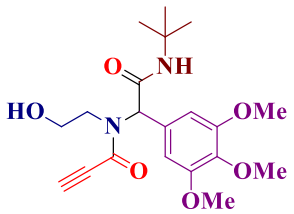
(ddd, *J* = 14.7, 7.7, 3.0 Hz, 0.15H), 2.37 (s, 3H), 1.37 (s, 1.35H), 1.33 (s, 7.65H); ^{13}C {1H} NMR (126 MHz, CDCl3) δ 170.00, 169.43, 155.19, 154.90, 139.40, 139.32, 130.31, 130.09, 130.04, 129.89, 129.68, 80.66, 79.87, 75.98, 75.84, 66.56, 63.86, 61.12, 60.81, 52.45, 52.36, 49.86, 46.71, 28.66, 28.54, 21.28. Calculated for $C_{18}H_{24}N_2O_3$.



10d

N-(1-(4-bromophenyl)-2-(tert-butylamino)-2-oxoethyl)-N-(2-hydroxyethyl) propiolamide:

1:3 mixture of rotamers, white solid, 68% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.37 (s, 0.12H), 5.93 (s, 0.15H), 5.73 (s, 0.78H), 5.53 (s, 0.82H), 4.10 (q, *J* = 7.1 Hz, 1H), 3.82 – 3.70 (m, 2H), 3.63 – 3.57 (m, 1H), 3.46 (bs, 0.2H), 3.30 (s, 0.16H), 3.19 (s, 2H), 2.91 (dd, *J* = 14.6, 7.6 Hz, 0.16H), 1.38 (s, 1.34H), 1.32 (s, 7.8H); ^{13}C{1H} NMR (126 MHz,) δ 169.36, 168.65, 155.22, 154.92, 132.99, 132.98, 132.58, 132.53, 131.60, 131.38, 123.61, 123.56, 81.14, 80.30, 75.75, 66.18, 63.67, 61.20, 60.58, 60.54, 52.56, 52.50, 50.11, 46.73, 28.64, 28.52, 21.19, 14.31. Chemical Formula: $C_{17}H_{21}BrN_2O_3$.



10e

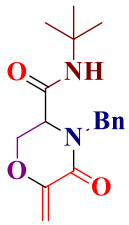
N-(2-(tert-butylamino)-2-oxo-1-(3,4,5-trimethoxyphenyl)ethyl)-N-(2-hydroxyethyl) propiolamide:

6:1 mixture of rotamers, white solid, 53% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (s, 1.8H), 6.52 (s, 0.2H), 6.13 (s, 0.13H), 5.85 (s, 0.16H), 5.68 (s, 0.86H), 5.52

(s, 0.85H), 3.91 (d, *J* = 5.4 Hz, 1H), 3.86 (s, 3.2H), 3.83 (s, 5.9H), 3.77 – 3.66 (t, 2H), 3.47 (s, 0.19H), 3.29 (s, 0.14H), 3.18 (s, 2H), 2.93 (s, 0.15H), 1.39 (s, 1.35H), 1.35 (s, 8H); $^{13}C\{1H\}$ NMR (126 MHz,) δ 169.87, 169.38, 155.14, 154.93, 154.18, 153.74, 138.48, 128.90, 128.68, 107.01, 106.79, 80.83, 80.06, 75.95, 64.31, 61.42, 61.03, 60.84, 56.31, 52.43, 49.86, 28.66, 28.55. Chemical Formula: $C_{20}H_{28}N_2O_6$.

3.3. Procedure for the cyclizations of Ugi adducts to morpholines 11 and 12

To Ugi adducts **7a** and **10c** (0.3 mmol), 20 mol% PPh_3 (0.03 mmol) was added as a catalyst and dissolved in isopropyl alcohol (6 ml). All reagents were loaded into a thermo sealed tube with a stopper and equipped with a magnetic stirrer. The reaction took place at 80°C in an oil bath for 3 hours. The resulting mixture was transferred to a round bottom flask together with silica gel and evaporated on a rotary evaporator. The chromatographic column was performed in the EtOAc/Hex system (50% / 50%) and consequently provided **11 a,b** (61-66%) and **12 a-d** (83-89%).

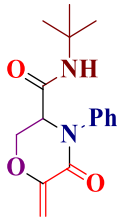


11a

4-benzyl-N-(tert-butyl)-6-methylene-5-oxomorpholine-3-carboxamide:

white solid, 66% yield. ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 5.63 (d, J = 0.7 Hz, 1H), 5.60 (bs, 1H), 5.01 (d, J = 14.4 Hz, 1H), 4.92 (d, J = 0.9 Hz, 1H), 4.38 (dd, J = 11.3, 1.3 Hz, 1H), 4.36 (d, J = 14.4 Hz, 1H), 3.94 (dd, J = 11.4,

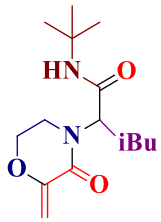
3.3 Hz, 1H), 3.77 (dd, J = 3.2, 1.5 Hz, 1H), 1.23 (s, 9H); $^{13}C\{1H\}$ NMR (126MHz, CDCl3) δ 167.1, 159.5, 150.1, 135.8, 129.2, 128.9, 128.5, 101.1, 66.8, 61.1, 52.0, 50.6, 28.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{23}N_2O_3^+$ 303.1703; Found 303.1707.



11b

N-(tert-butyl)-6-methylene-5-oxo-4-phenylmorpholine-3-carboxamide:

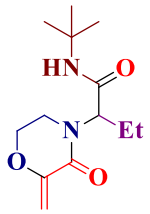
white solid, 61% yield. ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (t, 2H), 7.32 (d, 3H), 5.90 (bs, 1H), 5.67 (s, 1H), 4.99 (s, 1H), 4.56 (d, *J* = 10.1 Hz, 1H), 4.28 (d, *J* = 10.3 Hz, 2H), 1.74 (bs, 0.2 H), 1.57 (bs, 0.8H), 1.32 (s, 9H); $^{13}C\{1H\}$ NMR (126 MHz,) δ 167.04, 159.13, 150.40, 140.50, 140.35, 129.64, 127.73, 125.32, 101.56, 66.78, 64.34, 52.35, 28.74, 28.65. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{21}N_2O_3^+$ 289.1547; Found 289.1551.



12a

N-(tert-butyl)-4-methyl-2-(2-methylene-3-oxomorpholino)pentanamide:

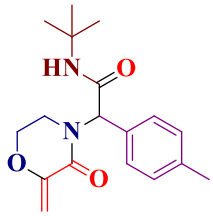
white solid, 83% yield. ^1H NMR (500 MHz, $CDCl_3$) δ 5.93 (bs, 1H), 5.49 (s, 1H), 4.99 (dd, *J* = 8.6, 6.8 Hz, 1H), 4.83 (d, 1H), 4.11 – 4.05 (m, 1H), 3.95 (ddd, *J* = 11.5, 8.3, 3.2 Hz, 1H), 3.54 (ddd, *J* = 11.9, 6.5, 3.4 Hz, 2H), 1.70 – 1.59 (m, 3H), 1.34 (s, 9H), 0.94 (dd, *J* = 9.7, 6.6 Hz, 6H). Chemical Formula: $C_{15}H_{26}N_2O_3$.



12b

N-(tert-butyl)-2-(2-methylene-3-oxomorpholino)butanamide:

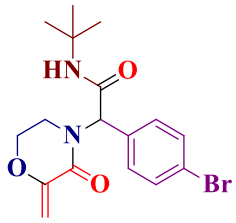
white solid, 83% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.45 (s, 1H), 4.83 – 4.75 (m, 1H), 4.06 (dd, *J* = 9.9, 5.6 Hz, 1H), 3.99 – 3.89 (m, 1H), 3.63 – 3.55 (m, 1H), 3.53 – 3.43 (m, 1H), 1.89 (dt, *J* = 14.3, 7.3 Hz, 1H), 1.67 – 1.58 (m, 1H), 1.28 (s, 9H), 0.88 (t, 3H); ^{13}C{1H} NMR (126 MHz,) δ 169.08, 160.09, 150.88, 99.53, 64.25, 58.04, 51.45, 41.88, 28.72, 20.74, 10.53, 1.10. Chemical Formula: $C_{13}H_{22}N_2O_3$.



12c

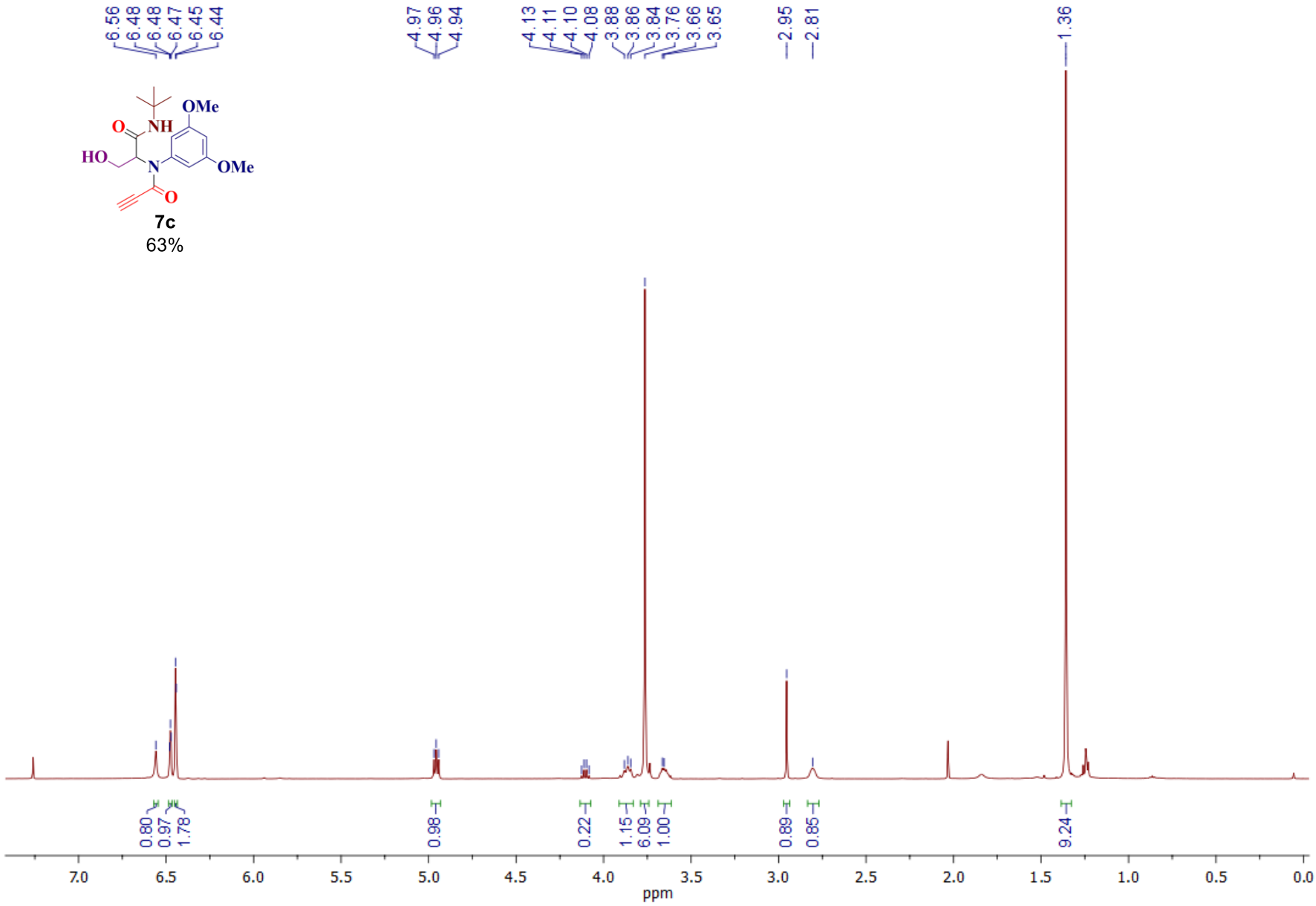
N-(tert-butyl)-2-(2-methylene-3-oxomorpholino)-2-(p-tolyl)acetamide:

white solid, 89% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 22.5, 8.0 Hz, 1H), 6.21 (s, 1H), 5.77 (s, 1H), 5.44 (s, 1H), 4.77 (s, 1H), 4.14 – 4.01 (m, 1H), 3.92 – 3.80 (m, 1H), 3.78 – 3.63 (m, 1H), 3.12 – 2.97 (m, 1H), 2.34 (s, 3H), 1.34 (ss, 9H); ^{13}C{1H} NMR (126 MHz,) δ 168.56, 159.83, 151.01, 138.70, 133.87, 133.72, 131.46, 129.78, 129.23, 128.59, 128.53, 99.21, 64.43, 59.78, 51.89, 43.53, 28.74, 21.23. Chemical Formula: $C_{18}H_{24}N_2O_3$.



12d

2-(4-bromophenyl)-N-(tert-butyl)-2-(2-methylene-3oxomorpholino)acetamide: white solid, 89% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 6.24 (s, 1H), 5.99 (s, 1H), 5.42 (s, 1H), 5.28 (s, 0.12H), 4.79 (s, 1H), 4.07 (t, *J* = 8.3 Hz, 1H), 3.94 – 3.82 (m, 1H), 3.77 – 3.73 (m, 1H), 3.09 – 3.04 (m, 1H), 1.34 (s, 9H); ^{13}C{1H} NMR (126 MHz,) δ 167.96, 159.96, 150.80, 133.61, 132.29, 130.90, 123.02, 99.73, 64.36, 59.17, 52.03, 43.60, 28.73. Chemical Formula: $C_{17}H_{21}BrN_2O_3$.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OMe
O
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6.09
1.00
0.89
0.85
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7c

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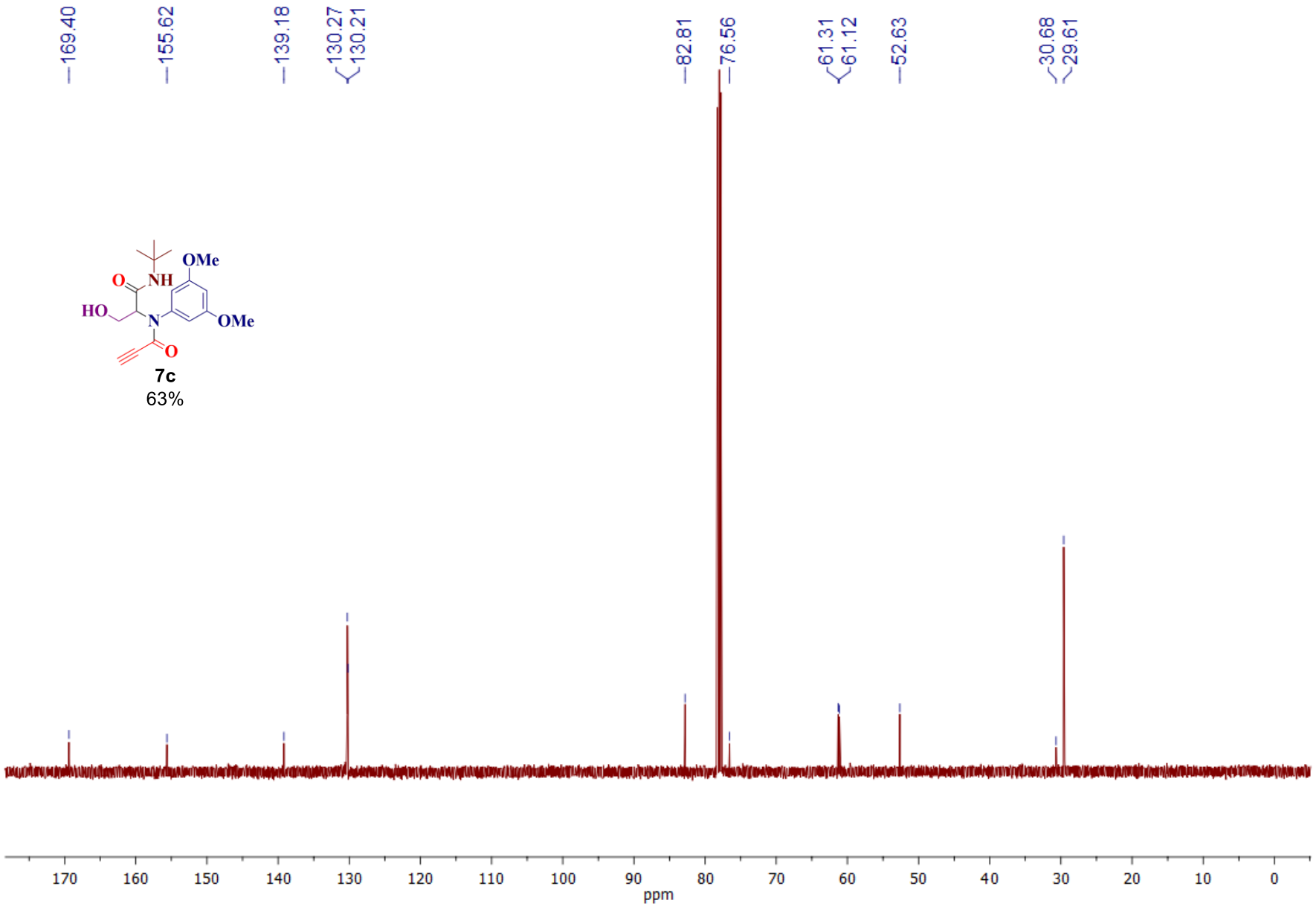
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O
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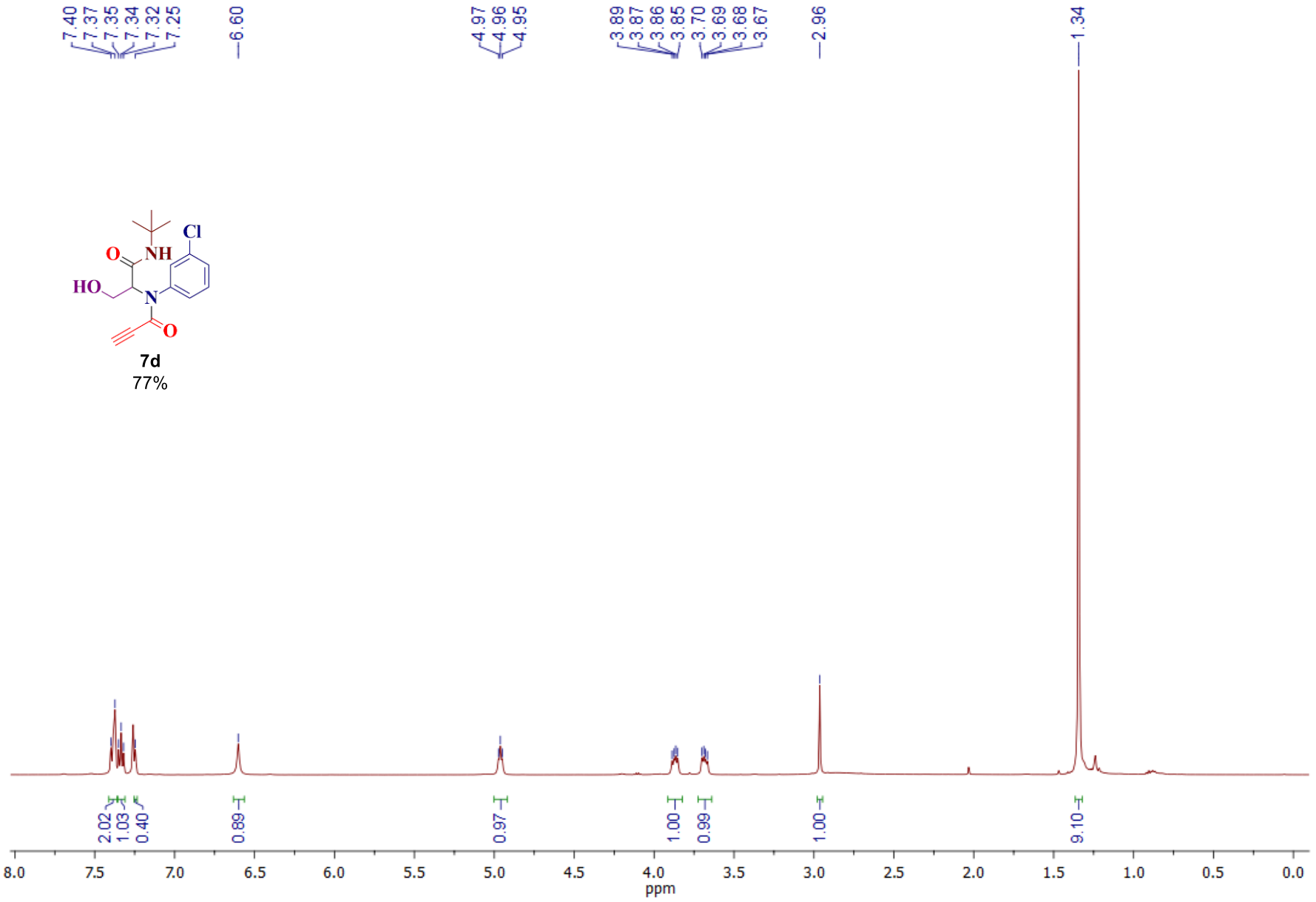
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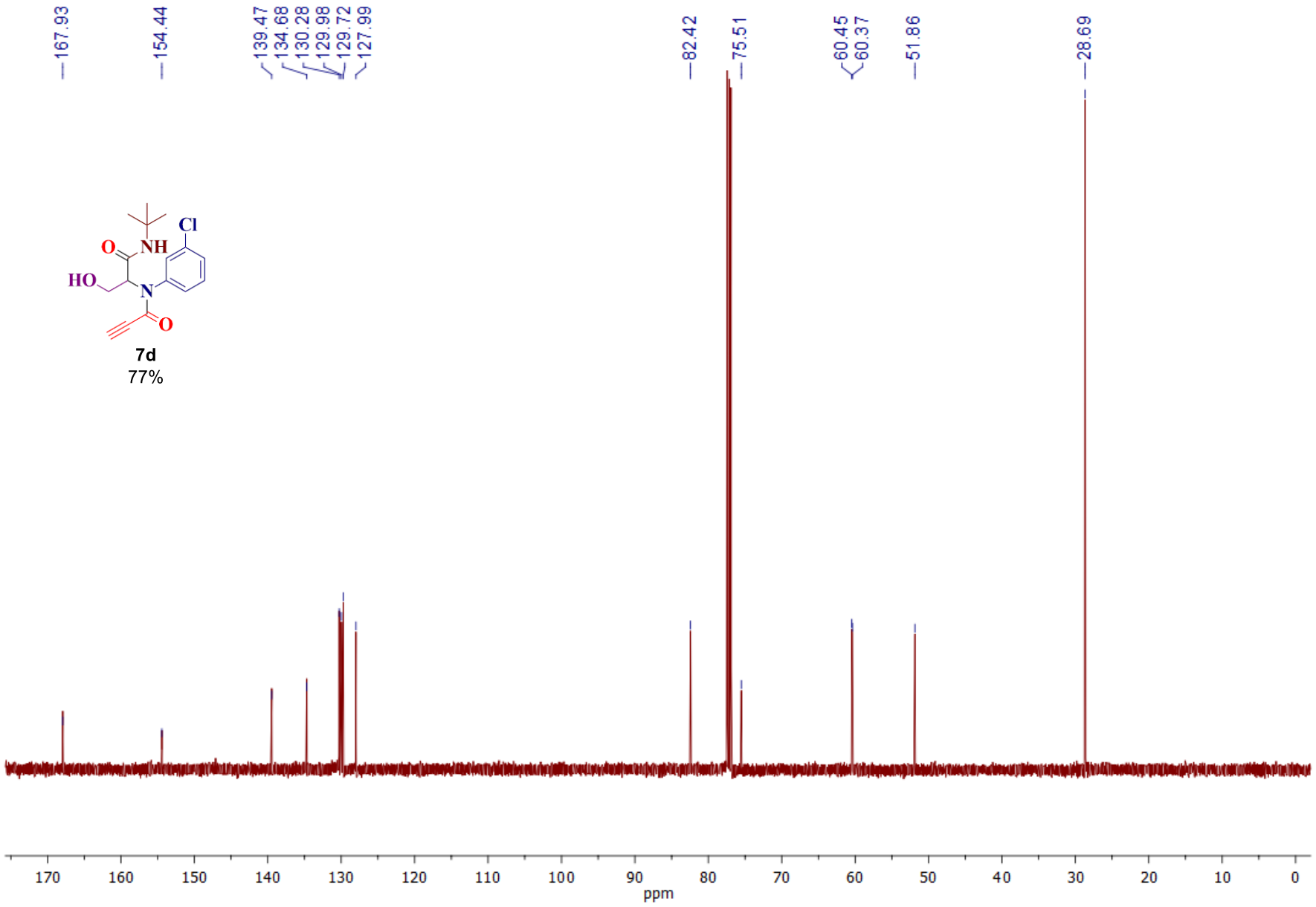
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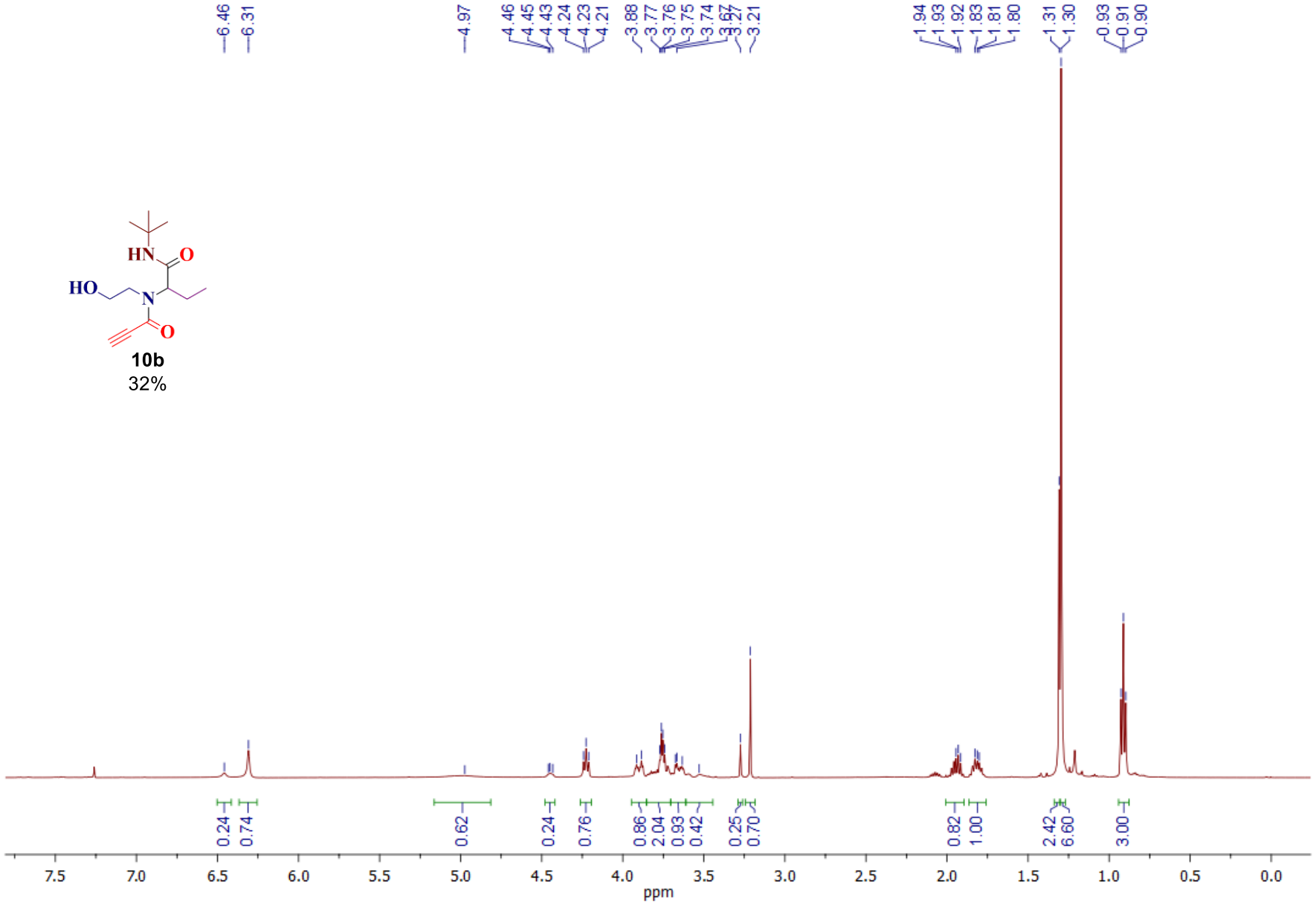
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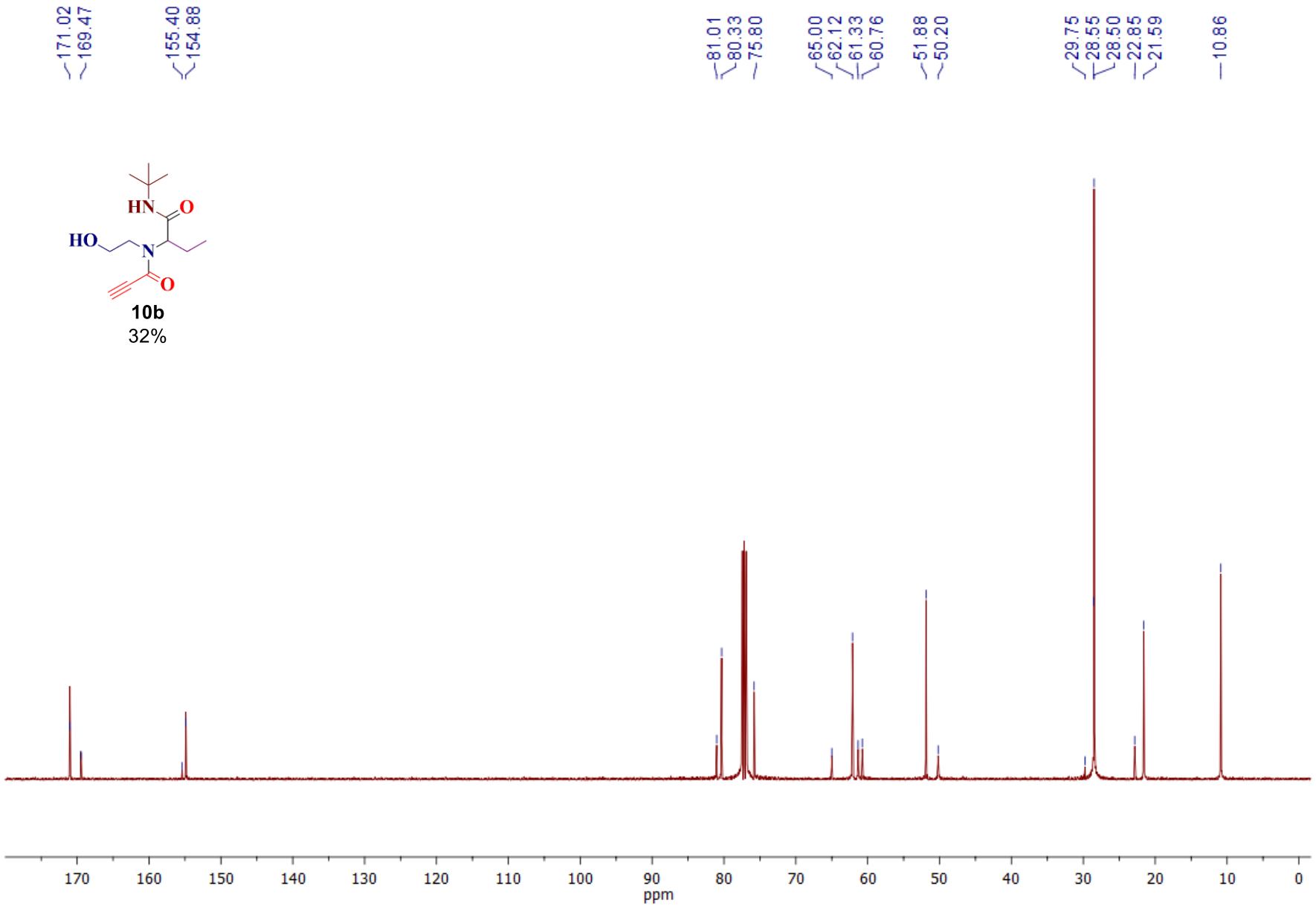
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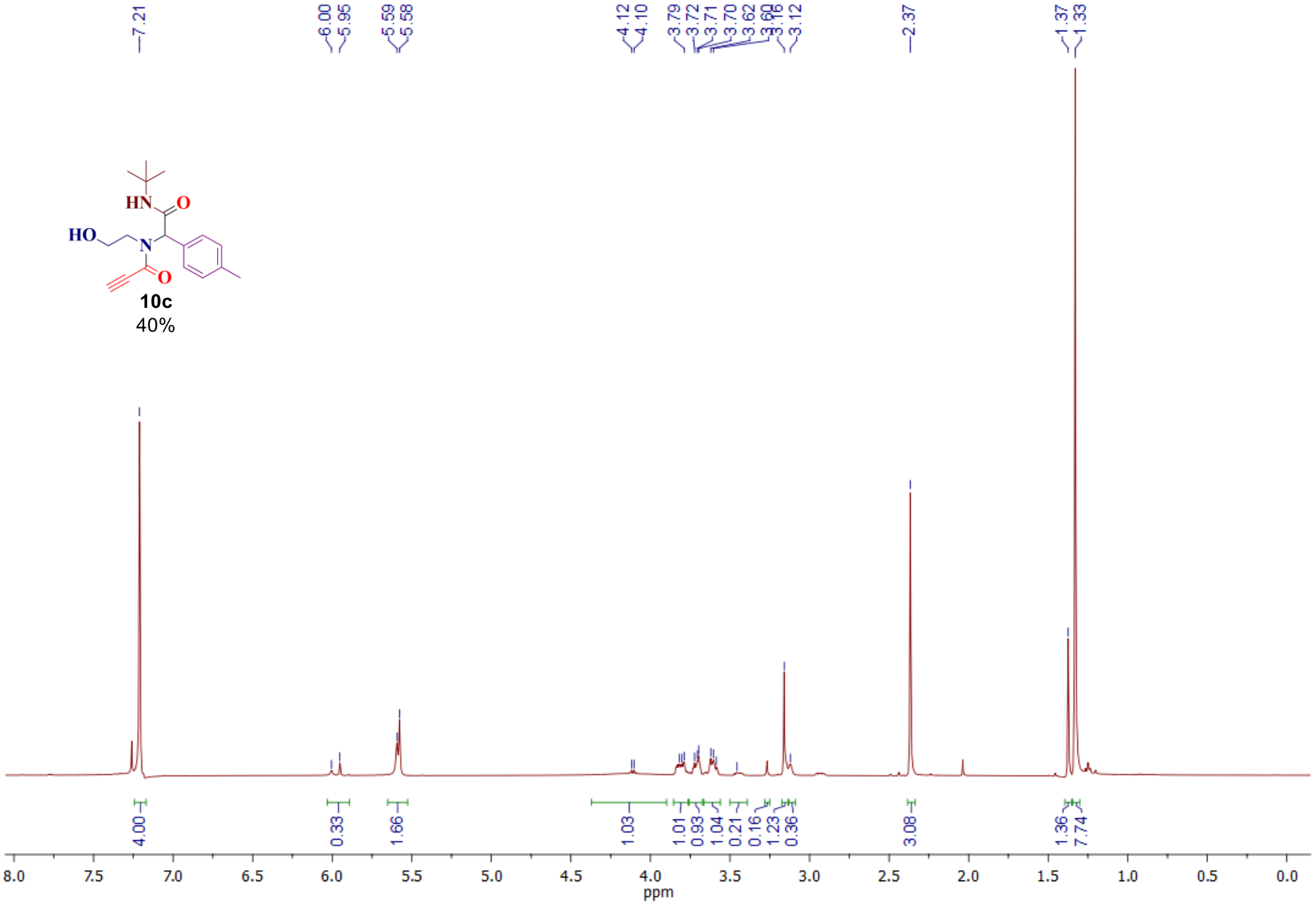
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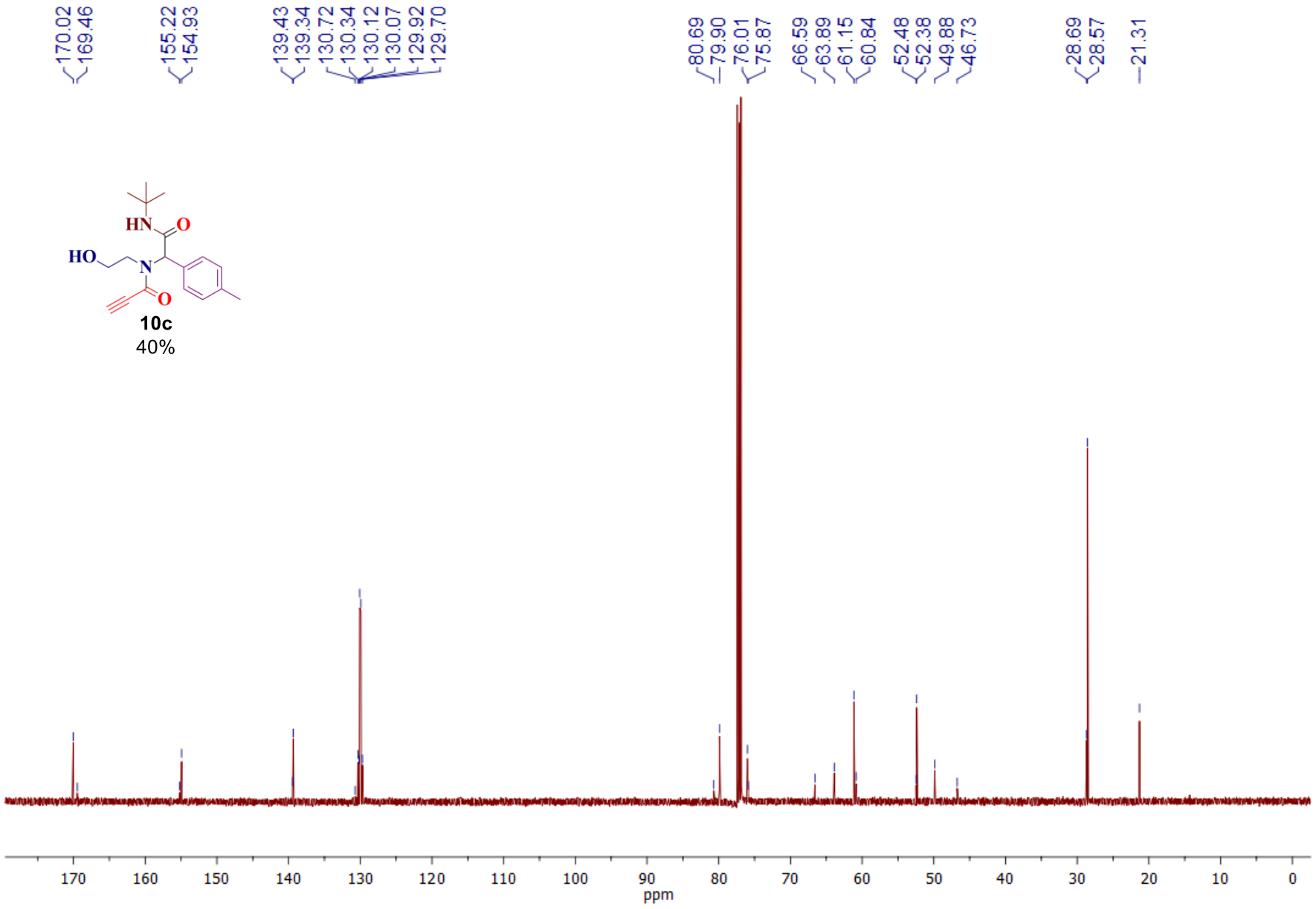
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