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TITLE:

A Direct, Regioselective and Atom-Economical Synthesis of 3-Aroyl-*N*-hydroxy-5-nitroindoles by Cycloaddition of 4-Nitronitrosobenzene with Alkynones

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KEYWORDS:

3-aroylindoles, *N*-hydroxyindoles, nitrosoarenes, alkynones, annulation, cycloaddition, alkynols, anilines

SUMMARY:

3-Aroyl-*N*-hydroxy-5-nitroindoles were synthesized by cycloaddition of 4-nitronitrosobenzene with a conjugated terminal alkynone in a one-step thermal procedure. Preparation of the nitrosoarene and of the alkynones were adequately reported and respectively through oxidation procedures on the corresponding aniline and on the alkynol.

ABSTRACT:

We introduced a regioselective and atom-economical procedure for the synthesis of 3-substituted indoles by annulation of nitrosoarenes with ethynyl ketones. The reactions were carried out achieving indoles without any catalyst and with excellent regioselectivity. No traces of 2-aroylindole products were detected. Working with 4-nitronitrosobenzene as starting material, the 3-aroyl-*N*-hydroxy-5-nitroindole products precipitated from the reaction mixtures and were isolated by filtration without any further purification technique. Differently from the corresponding *N*-hydroxy-3-aryl indoles that, spontaneously in solution, give dehydrodimerization products, the *N*-hydroxy-3-aroyl indoles are stable and no dimerization compounds were observed.

INTRODUCTION:

Aromatic *C*-nitroso compounds[1] and alkynones[2] are versatile reactants that are continuously and deeply used and studied as starting materials for the preparation of high valuable compounds. Nitrosoarenes play an ever-growing role in the organic synthesis. They are used for many different

purposes (e.g., hetero Diels-Alder reaction[3,4], Nitroso-Aldol reaction[5,6], Nitroso-Ene reaction[7], synthesis of azocompounds[8-10]). Very recently they were even used as starting materials to afford different heterocyclic compounds[11-13]. In the last decades, conjugated ynones were investigated for their role as very interesting and useful scaffolds in the achievement of many high valuable derivatives and heterocyclic products[14-18]. *C*-Nitrosoaromatics can be afforded by oxidation reactions of the corresponding and commercially available anilines using different oxidizing agents as potassium peroxymonosulfate ($KHSO_5 \cdot 0.5KHSO_4 \cdot 0.5K_2SO_4$)[19], Na_2WO_4/H_2O_2[20], Mo(VI)-complexes/H_2O_2[21-23], selenium derivatives[24]. Alkynones are easily prepared by the oxidation of the corresponding alkynols using various oxidants (CrO_3[25] even known as Jones' reagent or mild reactants as MnO_2[26] and Dess-Martin periodinane[27]). The alkynols can be achieved by direct reaction of ethynylmagnesium bromide with commercially available arylaldehydes or heteroarylaldehydes[28].

Indole is probably the most studied heterocyclic compound and indole derivatives have wide and various applications in many different research fields. Both medicinal chemists and material scientists produced many indole-based products that cover different functions and potential activities. Indole compounds have been investigated by many research groups and both naturally occurring products and synthetic derivatives containing the indole framework show relevant and peculiar properties[29-32]. Among the plethora of indole compounds, the 3-aroylindoles have a relevant role among molecules that show biological activities (**Figure 1**). Different indole products belong to diverse classes of pharmaceutical candidates to become potential novel drugs[33]. Synthetic and naturally occurring 3-aroylindoles are known to play a role as antibacterial, antimitotic, analgesic, antiviral, anti-inflammatory, antinociceptic, antidiabetic and anticancer[34,35]. The '1-hydroxyindole hypothesis' was provocatively introduced by Somei and coworkers as an interesting and stimulating supposition to support the biological role of *N*-hydroxyindoles in the biosynthesis and functionalization of indole alkaloids[36-39]. This assumption was recently reinforced by the observation of many endogen *N*-hydroxy heterocyclic compounds that show relevant biological activities and an interesting role for many purposes as pro-drugs[40]. In the recent years, the search for novel active pharmaceutical ingredients revealed that different *N*-hydroxyindole fragments were detected and discovered in natural products and bioactive compounds (**Figure 2**): Stephacidin B[41] and Coproverdine[42] are known as antitumor alkaloids, Thiazomycins[43] (A and D), Notoamide G[44] and Nocathacins[45-47] (I, III, and IV) are deeply studied antibiotics, Opacaline B[48] is a natural alkaloid from ascidian Pseudodistoma opacum and Birnbaumin A and B are two pigments from *Leucocoprinus birnbaumii*[49]. New and efficient *N*-hydroxyindole-based inhibitors of LDH-A (Lactate DeHydrogenase-A) and their ability to reduce the glucose to lactate conversion inside the cell were developed[50-56]. Other researchers repeated that indole compounds, that did not show biological activities, became useful pro-drugs after the insertion of a *N*-hydroxy group[57].

A motif of debate was the stability of *N*-hydroxyindoles and some of these compounds gave easily a dehydrodimerization reaction that leads to the formation of a class of novel compounds, subsequently renamed as kabutanes[58-61], by the formation of a new C-C bond and two new C-O bonds. Due to the importance of stable *N*-hydroxyindoles the study of different synthetic approaches for the easy preparation of such compounds becomes a fundamental topic. In a previous research by some of us, an intramolecular cyclization by a Cadogan-Sundberg-type reaction was reported using nitrostyrenes and nitrostilbene as starting materials[62]. In the last decades we developed a novel cycloaddition between nitro- and nitrosoarenes with different alkynes in an intermolecular fashion affording indoles, *N*-hydroxy- and *N*-alkoxyindoles as major products (**Figure 3**).

At the beginning, using aromatic and aliphatic alkynes[63-67] the reactions were carried out in large excess of alkyne (10 or 12-fold) and sometimes under alkylative conditions to avoid the formation of kabutanes. 3-Substituted indole products were achieved regioselectively in moderate to good yields. Using electron poor alkynes, like 4-ethynylpyrimidine derivatives as privileged substrates we could carry out the reactions for this one-pot synthetic protocol using a 1/1 nitrosoarene/alkyne molar ratio[68]. With this protocol, an interesting class of kinase inhibitors as meridianins, marine alkaloids isolated from *Aplidium meridianum*[69], was prepared showing a different approach to meridianins through an indolization procedure (**Figure 4**)[68]. Meridianins were generally produced so far with synthetic tools starting from preformed indole reactants. To the best of our knowledge, only a couple of methodologies reported the total synthesis of meridianins or meridianin derivatives through an indolization procedure[68, 70].

In a more recent development on the use of electron poor alkynes it was worthwhile to test the employ of terminal alkynones as substrates for the indolization procedure and this led us to disclose an intermolecular synthetic technique to afford 3-aroyl-*N*-hydroxyindole products[71,72]. Analogously to the process studied for the preparation of meridianins, using terminal arylalkynone compounds the 1/1 Ar-N=O/Ar-(C=O)-C≡CH molar ratio was used (**Figure 5**). Working with alkynones as privileged starting materials, the general indole synthesis was performed with different reactants exploring a wide substrate survey and changing the nature of the substituents both on nitrosoarenes and on the aromatic ynones. Electron-withdrawing groups on the *C*-nitrosaromatic compound led us to observe an improvement both in reaction times and in products yields. An interesting synthetic approach that makes easily available a stable library of these compounds could be very useful and, after a preliminary study, we optimized our synthetic protocol using this stoichiometric reaction between alkynones and 4-nitronitrosobenzene to afford stable 3-aroyl-*N*-hydroxy-5-nitroindoles. Basically, this easy access to *N*-hydroxyindoles led us to evidence as the cycloaddition reaction between nitrosoarene and alkynone is a very atom-economical process.

PROTOCOL:

1. Preliminary preparation of the Jones Reagent

1.1 Add 25 g (0.25 mol) of chromium trioxide using a spatula in a 500 mL beaker that contains a magnetic stirring bar.

1.2 Add 75 mL of water and keep the solution under magnetic stirring.

1.3 Add slowly 25 mL of concentrated sulfuric acid with careful stirring and cooling in an ice-water bath.

NOTE: Now the solution is ready and is stable and usable for many oxidation procedures; the concentration of the solution prepared by this procedure is 2.5 M.

2. Synthesis of 1-phenyl-2-propyne-1-one

2.1 Add 75 mL of acetone in an open-air round bottom flask that contains a magnetic stirring bar.

2.2 Add 2.0 g (15.13 mmol) of 1-phenyl-2-propyne-1-ol via a glass Pasteur pipette.

2.3 Keep the reaction mixture at 0 °C and under magnetic stirring.

2.4 Add a solution of Jones reagent dropwise till the presence of a persistent orange color.

2.5 Add 2-propanol dropwise till the excess of Cr(VI) reactant is consumed to the point of a green color.

2.6 Filter the solution through a pad of diatomaceous earth.

2.7 Concentrate the washings by rotary evaporation obtaining an oil.

2.8 Dissolve the oil in 100 mL of CH_2Cl_2 and put in a separatory funnel.

2.9 Wash this organic phase with a saturated solution of $NaHCO_3$ (2 x 125 mL).

2.10 Wash the organic layer with brine (125 mL).

2.11 Dry the organic solution over anhydrous Na_2SO_4 and filter it.

2.12 Evaporate the solution obtaining 1.77 g of 1-phenyl-2-propyne-1-one as a yellow solid (quantitative yield).

2.13 Leave the solid to dry in vacuum.

2.14 Analyze and characterize by ^{1}H-NMR.

3. Preparation of 4-nitronitrosobenzene

3.1 Add 16 g of potassium peroxymonosulfate ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) (26 mmol) using a spatula in a beaker, open to air that contains a magnetic stirring bar.

3.2 Add 150 mL of water and keep the solution at 0 °C under magnetic stirring.

3.3 Add 3.6 g of 4-nitroaniline (26 mol) using a spatula.

3.4 Stir the suspension at room temperature.

3.5 Check the reaction by TLC till the complete conversion of 4-nitroaniline ($Rf_{4\text{-Nitroaniline}}$ = 0.44, $Rf_{4\text{-Nitronitrosobenzene}}$ = 0.77; CH_2Cl_2 as eluent).

3.6 Filter the crude reaction mixture on a Buchner after 48 h.

3.7 Put the solid in a one-neck round bottom flask.

3.8 Recrystallize the solid in methanol (50 mL).

3.9 Warm the suspension using a heat gun till boiling point of methanol and filter immediately the hot suspension.

3.10 Discard the solid and reuse it eventually for another recrystallization.

3.11 Filter the second precipitate formed in the Erlenmeyer flask when the solution reaches room temperature.

3.12 Leave the solid to dry in vacuum on a Buchner funnel.

3.13 Characterize the solid by ^{1}H-NMR.

4. Synthesis of 3-benzoyl-1-hydroxy-5-nitroindole

4.1 Connect all the oven dried glassware (a 250 mL two neck round bottom flask containing a magnetic stirring bar, a stopcock, a refrigerant and a joint to connect to vacuum/nitrogen system) and put under vacuum for 30 min.

4.2 At room temperature, after some cycles of vacuum/nitrogen, flush all the glassware with nitrogen and leave it under inert atmosphere.

4.3 Add 1.52 g (10 mmol) of 4-nitronitrosobenzene under inert atmosphere.

4.4 Add 1.30 g (10 mmol) of 1-phenyl-2-propyne-1-one.

4.5 Add 80 mL of toluene via a syringe and keep the reaction mixture under magnetic stirring at 80 °C.

4.6 After few minutes, check the complete solubilization of the reactants.

4.7 Verify the formation of an orange precipitate after about 30-40 min at 80 °C.

4.8 After the complete precipitation of an orange solid (about 2.5 h), turn off the heating and leave the reaction to reach room temperature.

4.9 Filter the mixture and collect 3-benzoyl-1-hydroxy-5-nitroindole as an orange solid on a Buchner funnel.

4.10 Keep under vacuum to dryness.

4.11 Analyze and characterize the solid product by ^{1}H- and ^{13}C-NMR, FT-IR, and HRMS.

REPRESENTATIVE RESULTS:

The preparation of 4-nitronitrosobenzene **2** was achieved by oxidation of 4-nitroaniline **1** by reaction with potassium peroxymonosulfate as reported in **Figure 6**. The product **2** was obtained in 64% yield after recrystallization in MeOH (twice) with 3-5% contamination of 4,4'-bis-nitro-azoxybenzene **6**. The structure of product **2** was confirmed by ^{1}H-NMR (**Figure 7**). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H).

The preparation of 1-phenyl-2-propyne-1-one **4** was afforded by oxidation of 1-phenyl-2-propyne-1-ol **3** with Jones reagent as reported in **Figure 8**. The product **4** was isolated as a yellow solid in 90% yield and the structure was confirmed by ^{1}H-NMR (**Figure 9**). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 7.4 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 2H), 3.36 (s, 1H).

The synthesis of 3-benzoyl-1-hydroxy-5-nitroindole was accomplished by thermal reaction of 4-nitronitrosobenzene **2** and 1-phenyl-2-propyne-1-one **4** in toluene at 80 °C as reported in **Figure 10**. Indole compound **5** was isolated in 58% yield by filtration after 2.5 h. The azoxy derivative **6** was isolated in 22% yield as the major product of the mother liquor after chromatography (Rf = 0.36) using CH_2Cl_2/hexane = 6/4 as eluent. The structure of product **6** was confirmed by ^{1}H-NMR (**Figure 11**). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 9.2 Hz, 2H), 8.35 (d, *J* = 9.2 Hz, 2H), 8.30 (d, *J* = 9.2 Hz, 2H), 8.23 (d, *J* = 9.2 Hz, 2H). The structure of compound **5** was determined by FT-IR, ^{1}H-NMR (**Figure 12**), ^{13}C-NMR (**Figure 13**) and HRMS (**Figure 14** and **Figure 15**).

FT-IR (KBr disk): 1619, 1560, 1518, 1336, 850, 817, 740, 700 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.68 (s, 1H, bs), 9.16 (d, *J* = 2.3 Hz, 1H), 8.38 (s, 1H), 8.22 (dd, *J* = 9.0 Hz, *J* = 2.3 Hz, 1H), 7.85 (d, *J* = 7.2 Hz, 2H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 2H). ^{13}C-NMR (400 MHz, DMSO-d_6): δ = 188.94, 143.24, 139.19, 136.58, 136.40, 131.81, 128.61, 128.53, 122.05, 118.81, 118.25, 110.96, 110.19. HRMS (ESI^-) calcd for $C_{15}H_{10}N_2O_4$: 281.0562 ([M-1]); found: 281.0565. HRMS (ESI^+) calcd for $C_{15}H_{10}N_2O_4$: 283.0719 ([M+1]), 305.0538 [M+Na]; found: 283.0713, 305.0532.

^{1}H-NMR spectra were obtained for compounds **2**, **4**, **5** and **6**; ^{13}C-NMR were obtained for compound **5**. Unless differently stated, all the spectra were collected at room temperature. High Resolution Mass spectra were obtained for compound **5** with ESI ionization (positive and negative). IR spectrum was obtained for compound **5**.

FIGURE AND TABLE LEGENDS:

Figure 1. Different 3-aroylindole compounds showing biological activities. Clometacin (anti-inflammatory drug), Pravadoline (analgesic), JWH-018 (agonist of CB1 and CB2 receptors) and BPR0L075 (antimitotic and antivascular agent).

Figure 2. Some example of natural and synthetic *N*-hydroxy indoles. Birnbaumins A and B are two toxic yellow pigment compounds, Lactate DeHydrogenase inhibitors, Coproverdine a cytotoxic marine alkaloid from a New Zealand ascidian, Stephacidin B an antitumor alkaloid isolated from the fungus *Aspergillus ochraceus*.

Figure 3. Previous research results in the intermolecular indolization procedure. Synthesis of indoles, *N*-hydroxyindoles and *N*-alkoxyindoles by cycloaddition of nitro- and nitrosoarenes with alkynes

Figure 4. Application of the synthetic approach to the preparation of natural products. Synthesis of Meridianins and analogues through the annulation of *C*-nitrosoaromatics with ethynylpyrimidine compounds.

Figure 5. Recent developments using alkynones. Synthesis of 3-aroyl-1-hydroxy-5-nitroindoles by cyclization of 4-nitronitrosobenzene with conjugated ynones.

Figure 6. Preparation of 4-Nitro-nitrosobenzene by oxidation of 4-Nitroaniline. A selective oxidation of the amino group to nitroso group.

Figure 7. ^{1}H-NMR spectrum of 4-nitronitrosobenzene (2). A typical AA'BB' splitting pattern is shown here.

Figure 8. Preparation of 1-Phenyl-2-propyne-1-one by oxidation of 1-Phenyl-2-propyne-1-ol. A selective oxidation of the alcohol to a ketone.

Figure 9. ^{1}H-NMR spectrum of 1-phenyl-2-propyne-1-one (4). A spectrum of a monosubstituted aromatic compound with a single of a terminal alkyne.

Figure 10. Synthesis of 3-Benzoyl-1-hydroxy-5-nitroindole (5) by cycloaddition of 2 and 4. The regioselective synthesis of indoles starting from a terminal ynone and a nitrosoarene.

Figure 11. ^{1}H-NMR spectrum of 4,4'-bis-nitroazoxybenzene (6). A typical double AA'BB' splitting pattern is shown here for the major byproduct.

Figure 12. ^{1}H-NMR spectrum of 3-benzoyl-1-hydroxy-5-nitroindole (5). The spectrum shows the aromatic substitution pattern of a 3,5-disubstituted-*N*-hydoxyindole.

Figure 13. ^{13}C-NMR spectrum of 3-benzoyl-1-hydroxy-5-nitroindole (5). Six signals for quaternary carbon atoms and seven signals for tertiary carbon atoms.

Figure 14. HRMS (ESI^{-}) spectrum of 3-benzoyl-1-hydroxy-5-nitroindole (5). Negative ionization mode mass spectrometry of the target compound.

Figure 15. HRMS (ESI^{+}) spectrum of 3-benzoyl-1-hydroxy-5-nitroindole (5). Positive ionization mode mass spectrometry of the target compound.

DISCUSSION:

The reaction for the indole synthesis between nitrosoarenes and alkynones shows a very high versatility and a strong and wide application. In a previous report, we could generalize our synthetic protocol working with different *C*-nitrosoaromatics and substituted terminal arylalkynones or heteroarylalkyones[72]. The procedure shows a deep substrate survey and a high functional group tolerance and both electron-withdrawing groups and electron-donor groups were present both in nitrosoarene and in the alkynone.

A single procedure for the indolization by cycloaddition of 4-nitro-nitrosobenzene with 1-phenyl-2-propyne-1-one was here reported as a representative reaction. After a partial survey, toluene, was found as the best solvent. Carrying out our protocol, 3-benzoyl-1-hydroxy-5-nitroindole **5** precipitated from the reaction mixture. The indole product was the only compound found in the solid that was isolated by filtration without any further purification. The analysis of the mother liquors led us to find and detect the only presence of 4,4'-dinitroazoxybenzene **6** as a major nitrogen-containing byproduct together with the unreacted alkynone **4** and the products were isolated and purified by chromatography ($Rf_{azoxyarene}$ = 0.36 and $Rf_{alkynone}$ = 0.30 using CH_2Cl_2 / Hexane = 6/4 as eluent). Azoxybenzenes are typical side products of the reactions with

nitrosoarenes as starting materials. Very recently it was reported as this class of compounds can be selectively obtained as the major products of thermal reactions carried out in a wide variety of organic solvents through a reductive deoxygenative coupling of *C*-nitrosoaromatics[73]. In the procedure introduced by us[72], using 4-nitronitrosobenzene with different alkynones the precipitation of 3-aroyl(heteroaroyl)-*N*-hydroxy-5-nitroindoles was always observed obtaining more than a dozen compounds. Other *C*-nitrosoaromatics showing strong electron withdrawing substituents gave prevalently the formation of 3-aroyl-1-hydroxyindoles and/or 3-aroylindole products. Employing electron rich nitrosoarenes, only 3-aroylindoles were detected. All the indoles were produced in moderate to good yields. A parallel study recently started in our lab devoted to the investigation of the reaction mechanism and to the optimization of the conditions trying to afford target compounds in higher yields. It could be possible to rise the product yields, after the filtration of the first precipitate, and adding another equivalent of 4-nitronitrosobenzene to the mother liquors of the reaction and heating the mixture. This addition and a second run lead to the formation of further precipitation, achieving another aliquote of indole product. It is well known that nitrosoarenes, both in solution and even as solids, could be present as dimers[74]. This is probably the way that favors the formation of azoxyarenes. The formation of this side product subtracts two equivalents of nitrosoarene to the cycloaddition with the alkynone. A mechanistic hypothesis for the preparation of azoxy compounds was proposed by Chuang and coworkers[73]. In principle, the indolization procedure works probably better in high dilution of nitrosoaromatic compound. The high concentration could be an Achille's heel for the competitive dimerization that is strongly connected with the formation of the azoxy compound. On this topic we are planning to try to run the reaction with slow addition of nitrosoarene and it could be useful to set an apparatus to experimentally carry out a flow reaction procedure. Further experiments will be carried out in the near future. We did not build yet a solid mechanistic conjecture to explain the formation of 3-aroylindoles. Nevertheless, in a previous report, working with arylacetylenes, we could study the mechanism of the formation of 3-arylindoles determining that the most plausible intermediate is probably a diradical specie[67]. The carbon-nitrogen bond forms first, followed by the cyclization through the formation of a carbon-carbon bond.

The use of the alkynone is a key point for our current study and the preparation of terminal ynones is an easy procedure. 1-Phenyl-2-propyne-1-ol is the only commercially available arylalkynol. The preparation of different arylalkynones and heteroarylalkynones was easily carried out starting from different commercially available aromatic and heteroaromatic aldehydes. These last compounds were treated with ethynyl magnesium bromide to generate alkynols by reactions often carried out at -78 °C. The obtained secondary propargyl alchohols were oxidized by reaction with different agents[25-27]. This procedure led us to afford terminal ynones as stable and solid compounds. Nitrosoarenes, differently from the corresponding nitroaromatics and anilines, are not easily commercially available and were prepared by the oxidation of the corresponding anilines[19-24]. It could be useful to study our synthetic approach by an in situ formation of nitroso compounds by oxidation or by reduction. Recent studies by Ragaini and coworkers reported the formation of *C*-nitrosoaromatics starting from nitroaromatic precursors[75-78]. The discovery, introduction, study and application of novel indolization protocols that could produce indoles regioselectively and with very high atom-economy, are relevant topics in synthetic organic chemistry and we are confident that this methodology through cyclization between nitrosoarenes and alkynones could be useful for different research groups.

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DISCLOSURES:

The authors have nothing to disclose.

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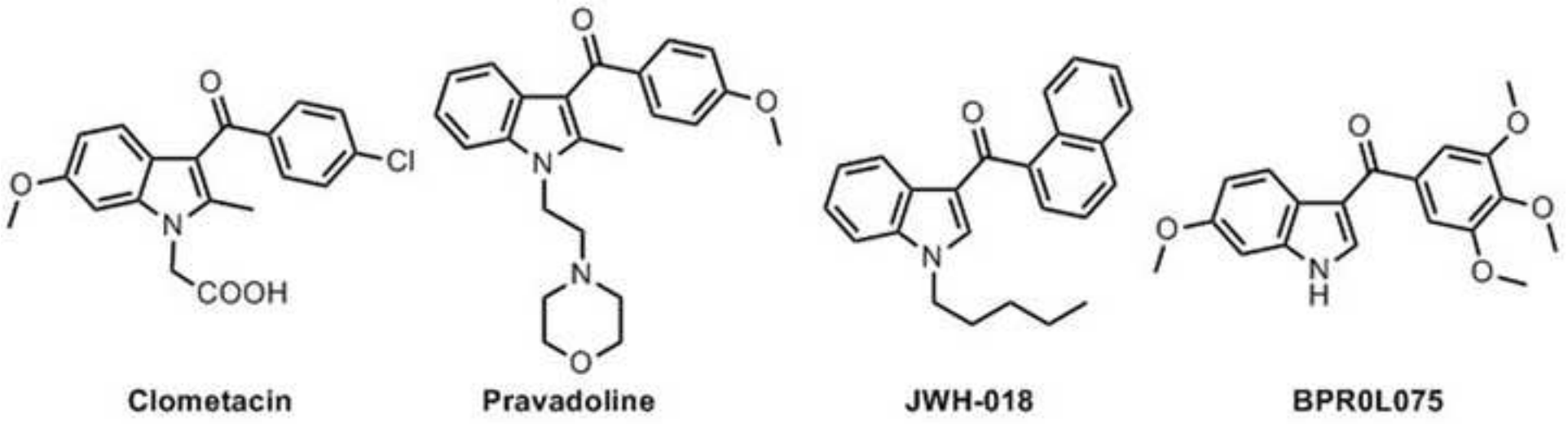
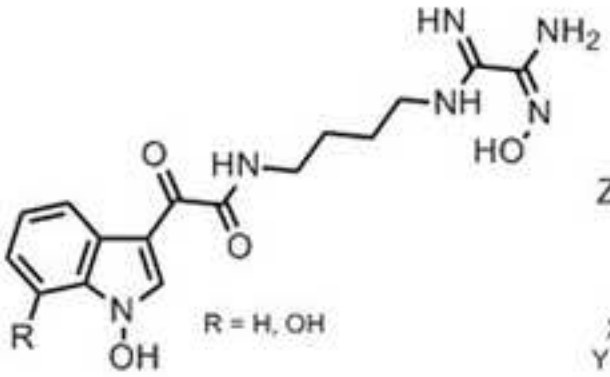
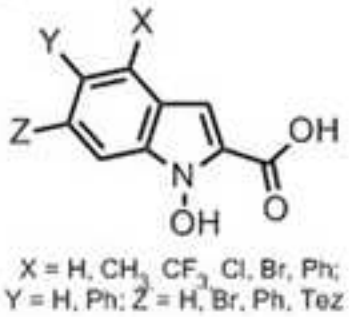
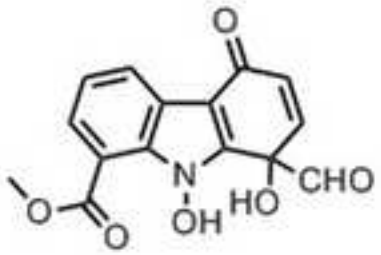




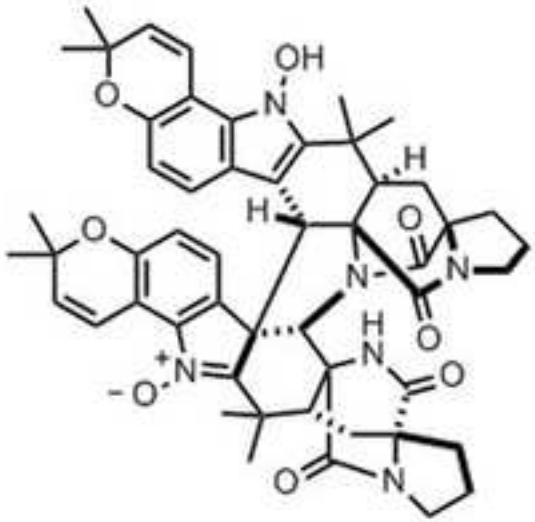
Birnbaumin A and B



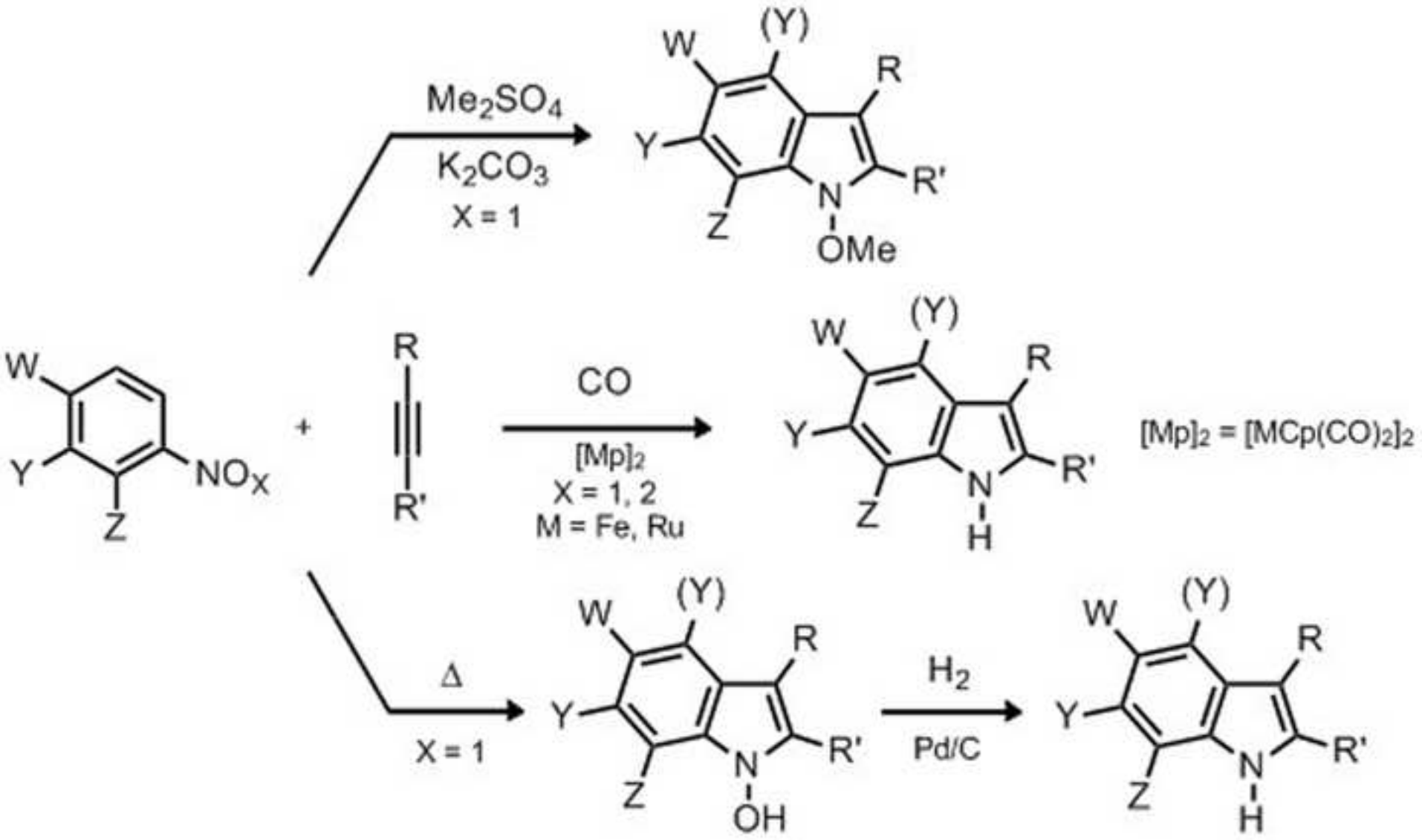
LDH-A inhibitors

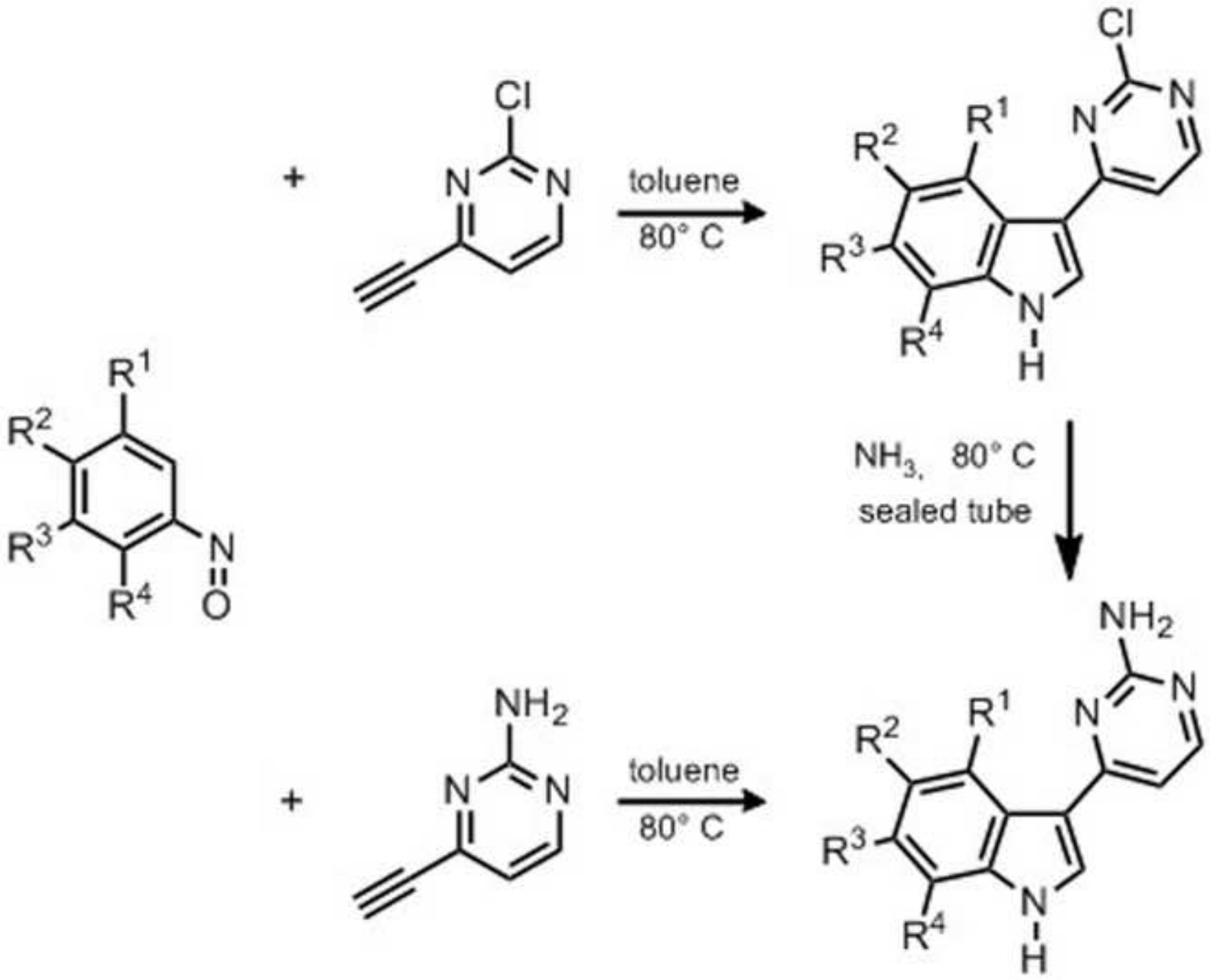


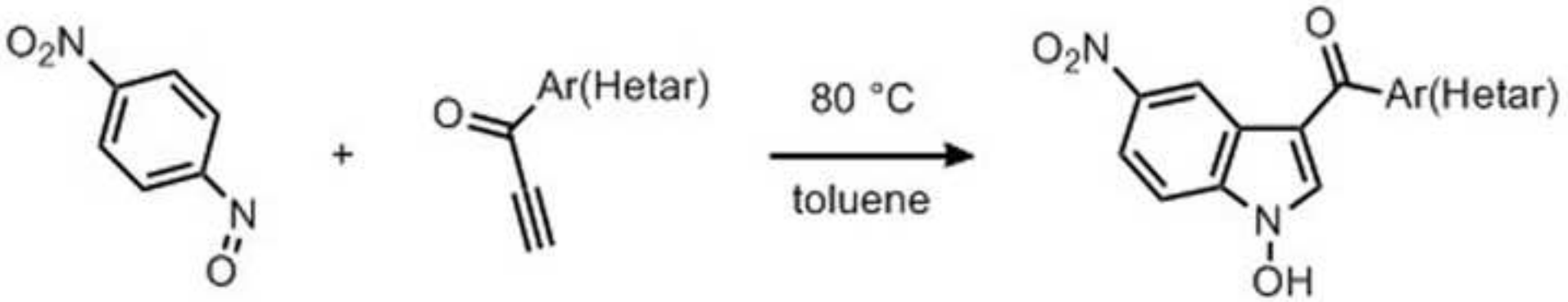
Coproverdine

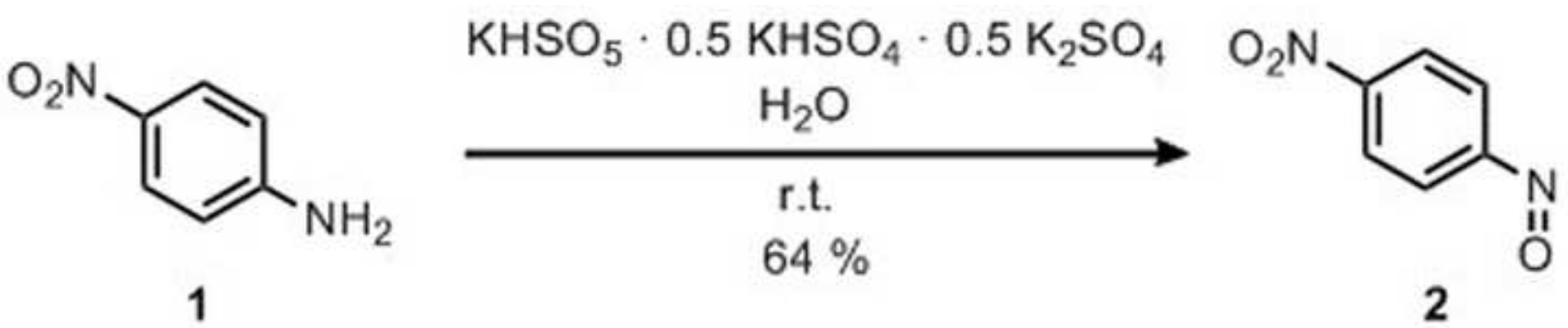


Stephacidin B









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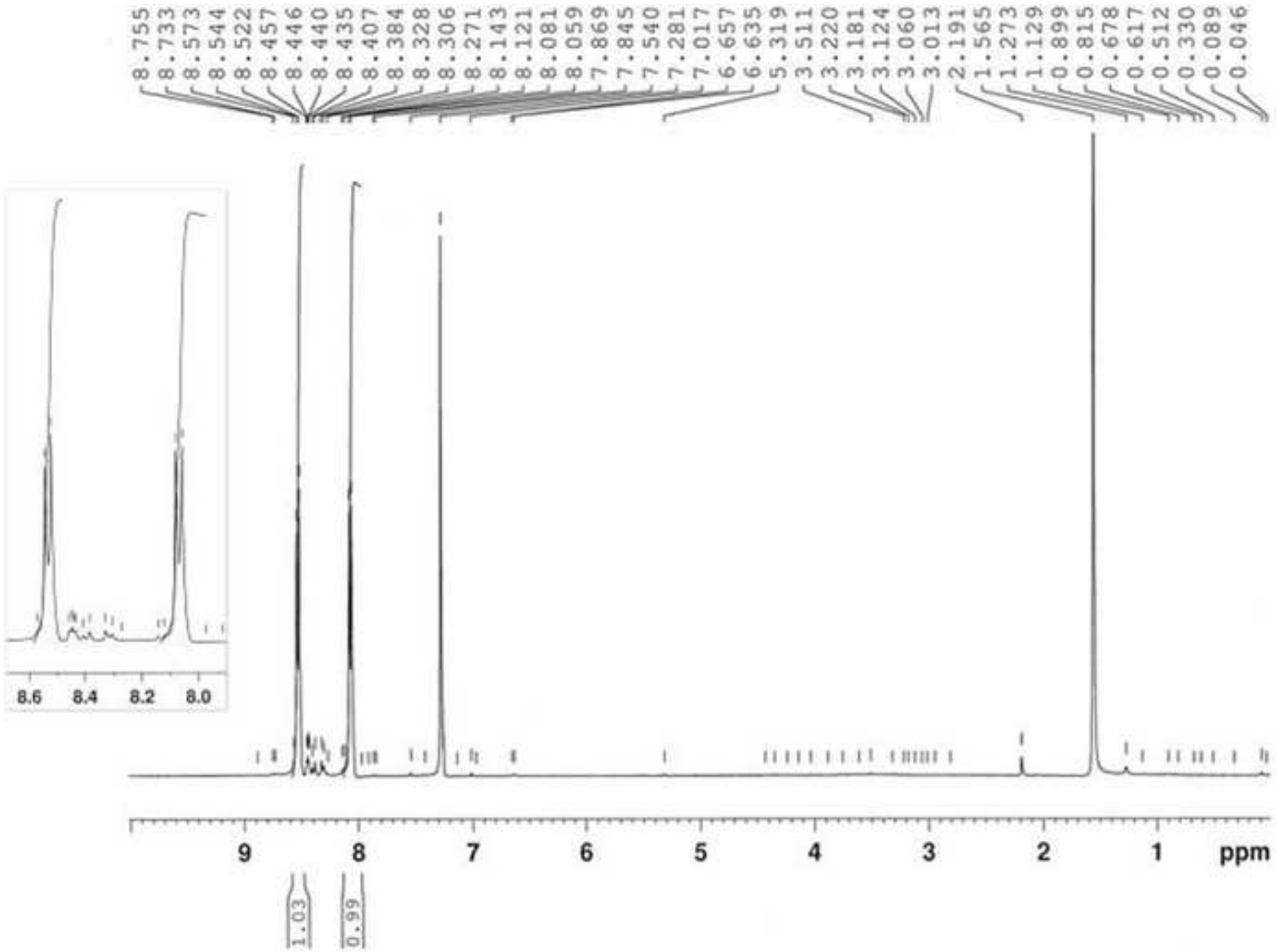
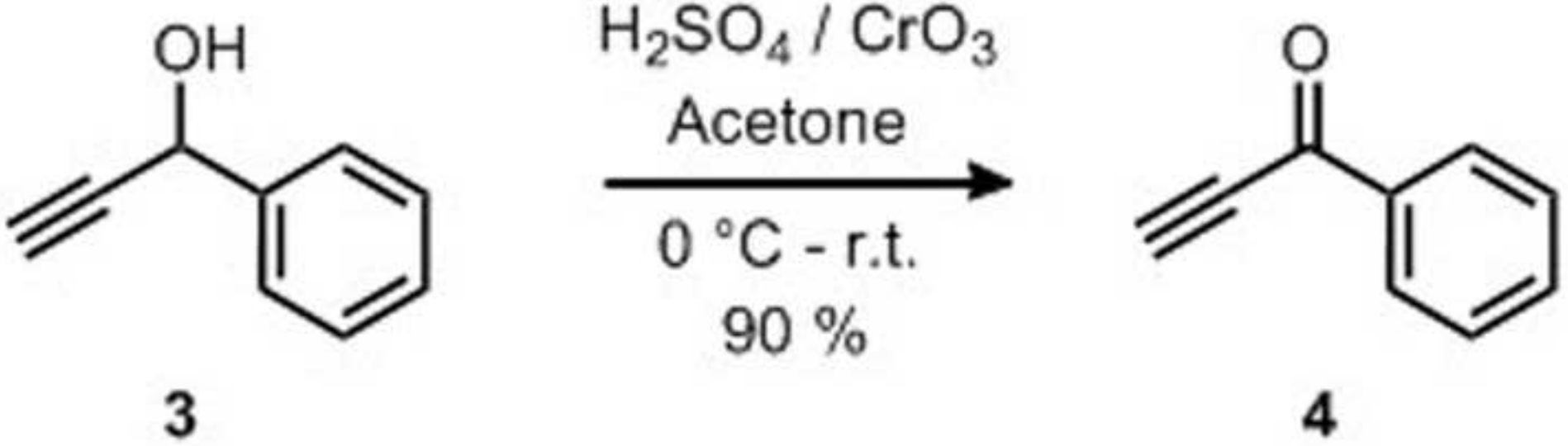
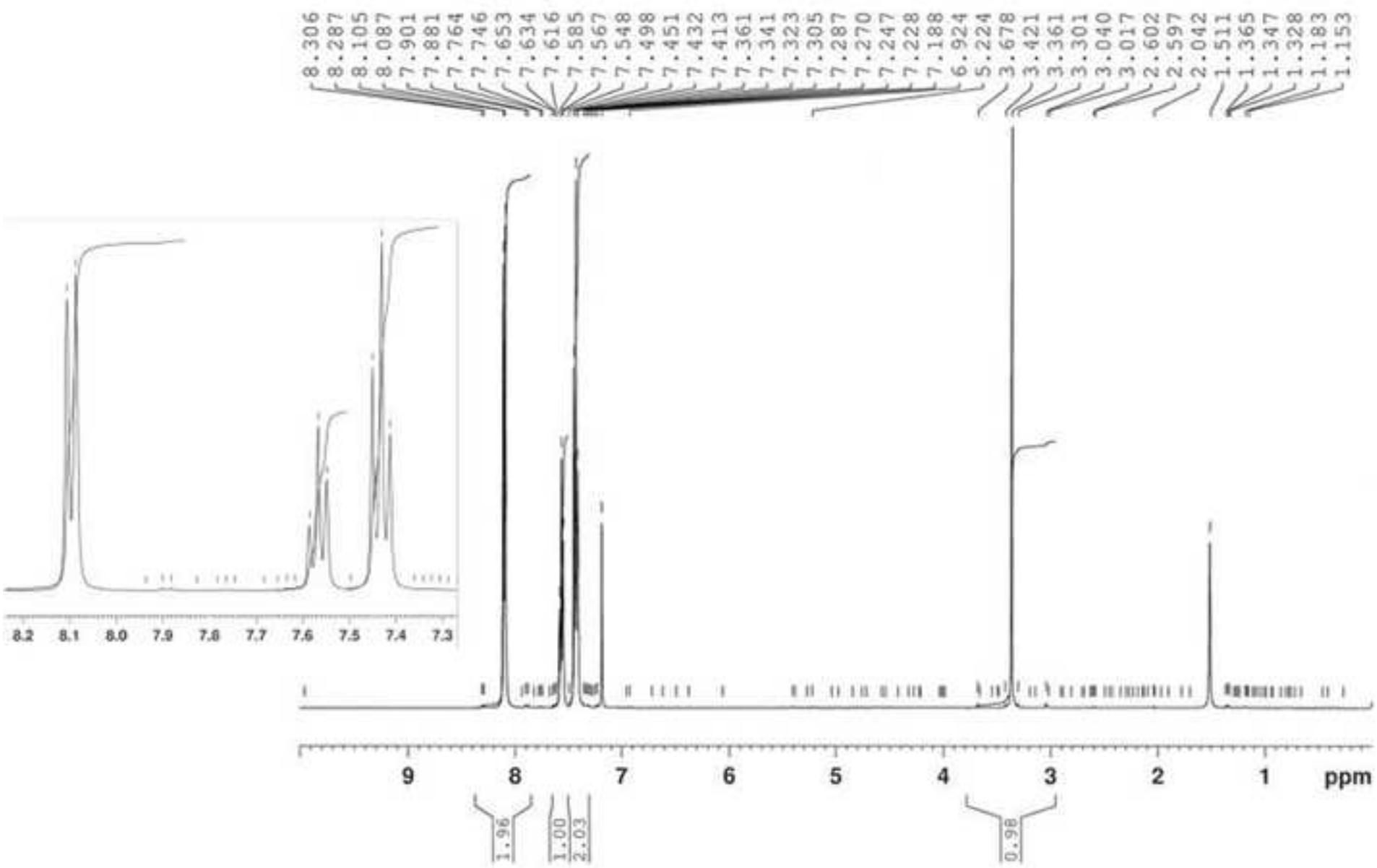
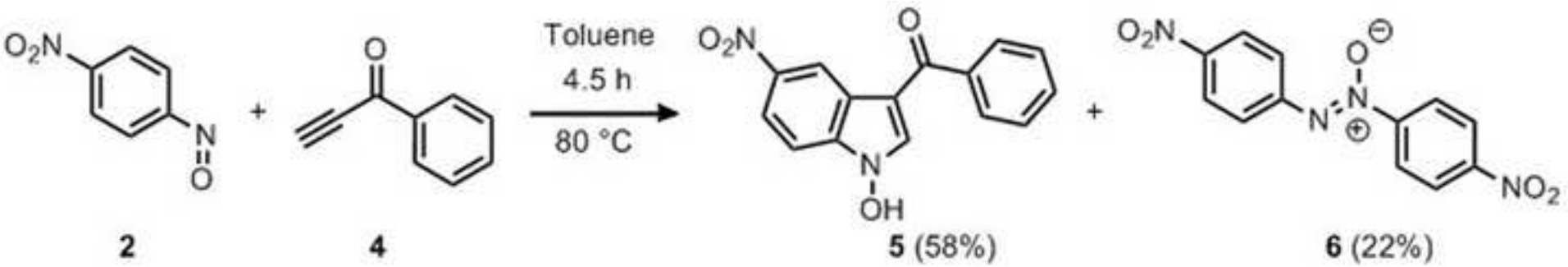
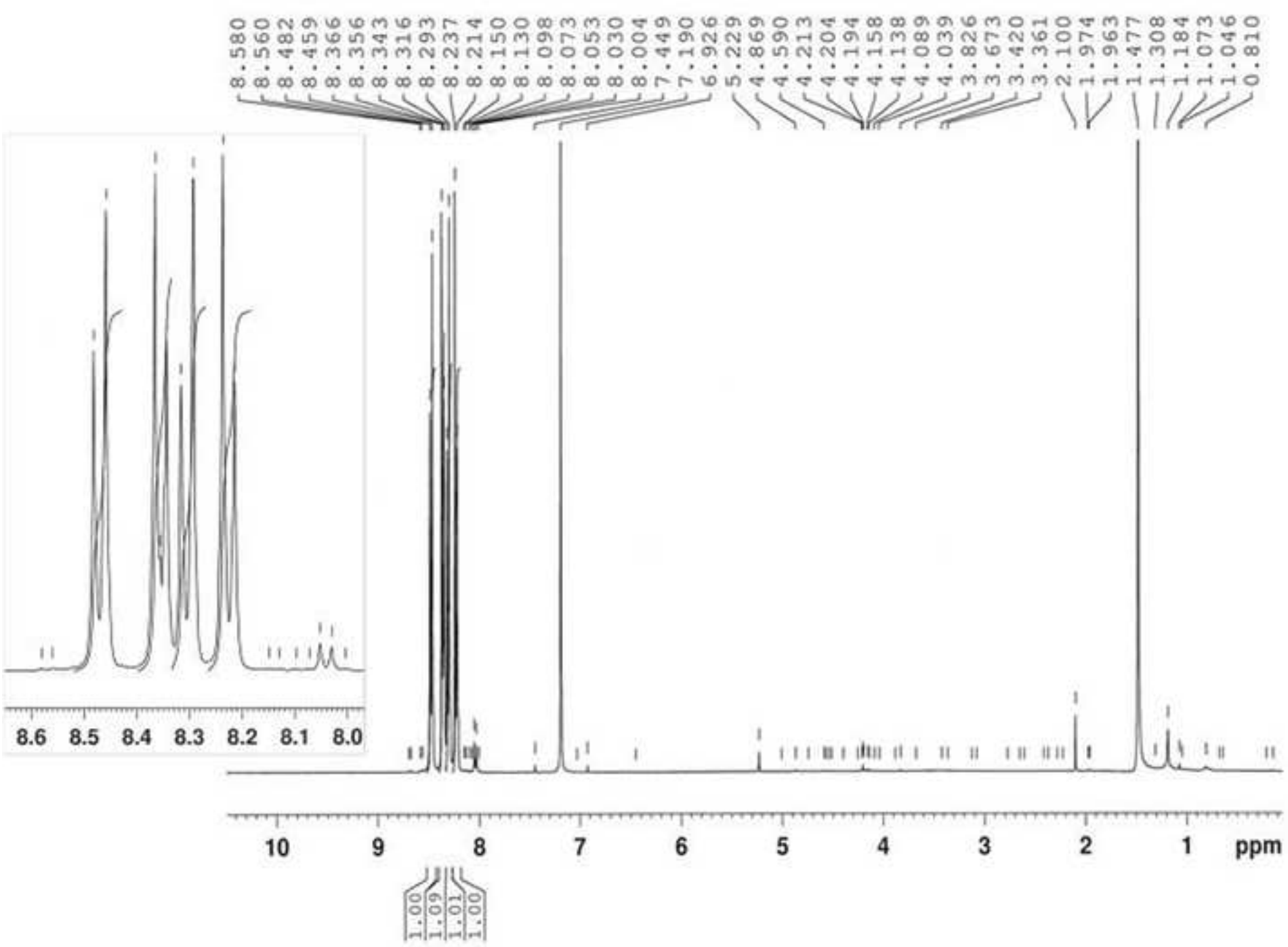


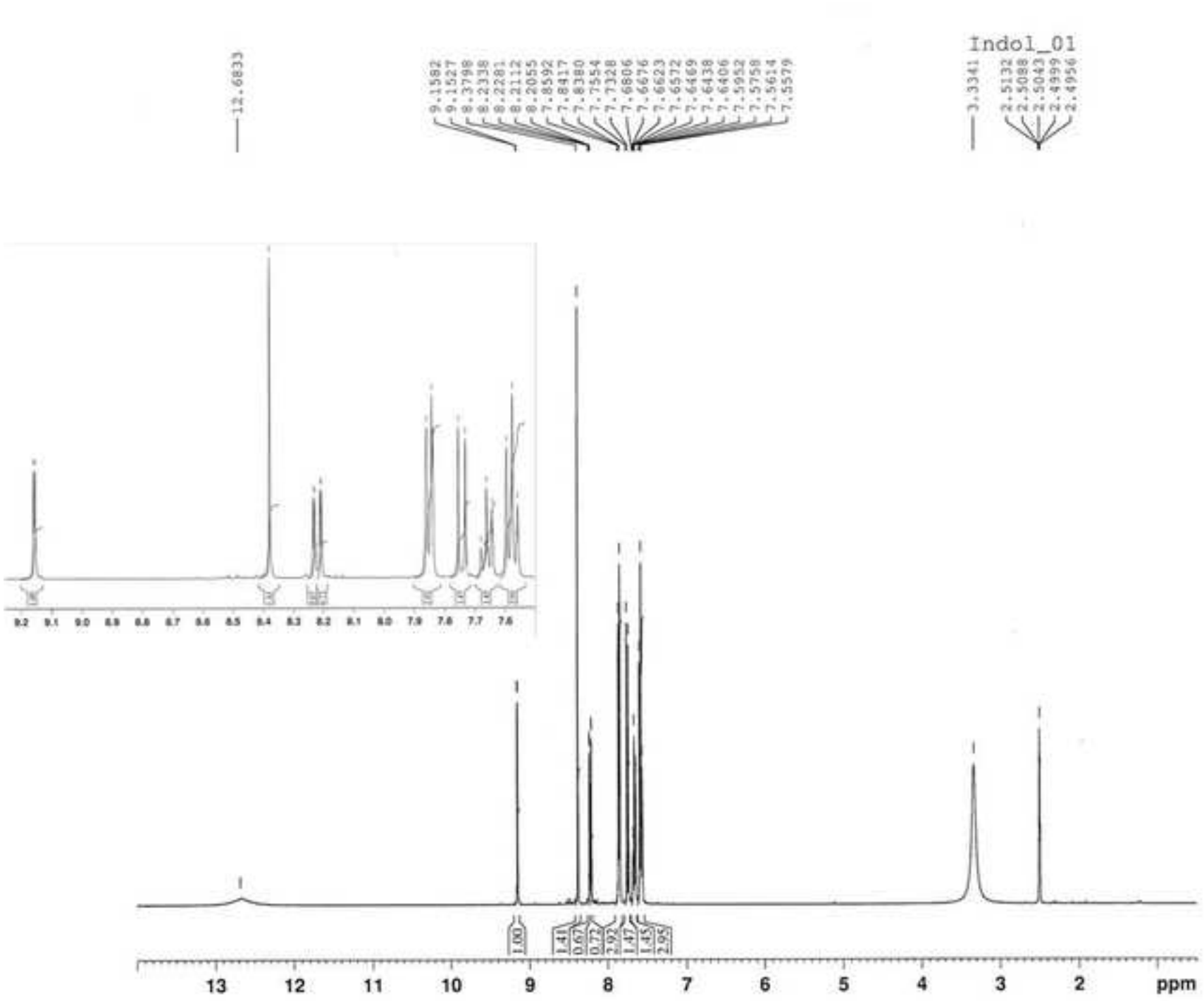


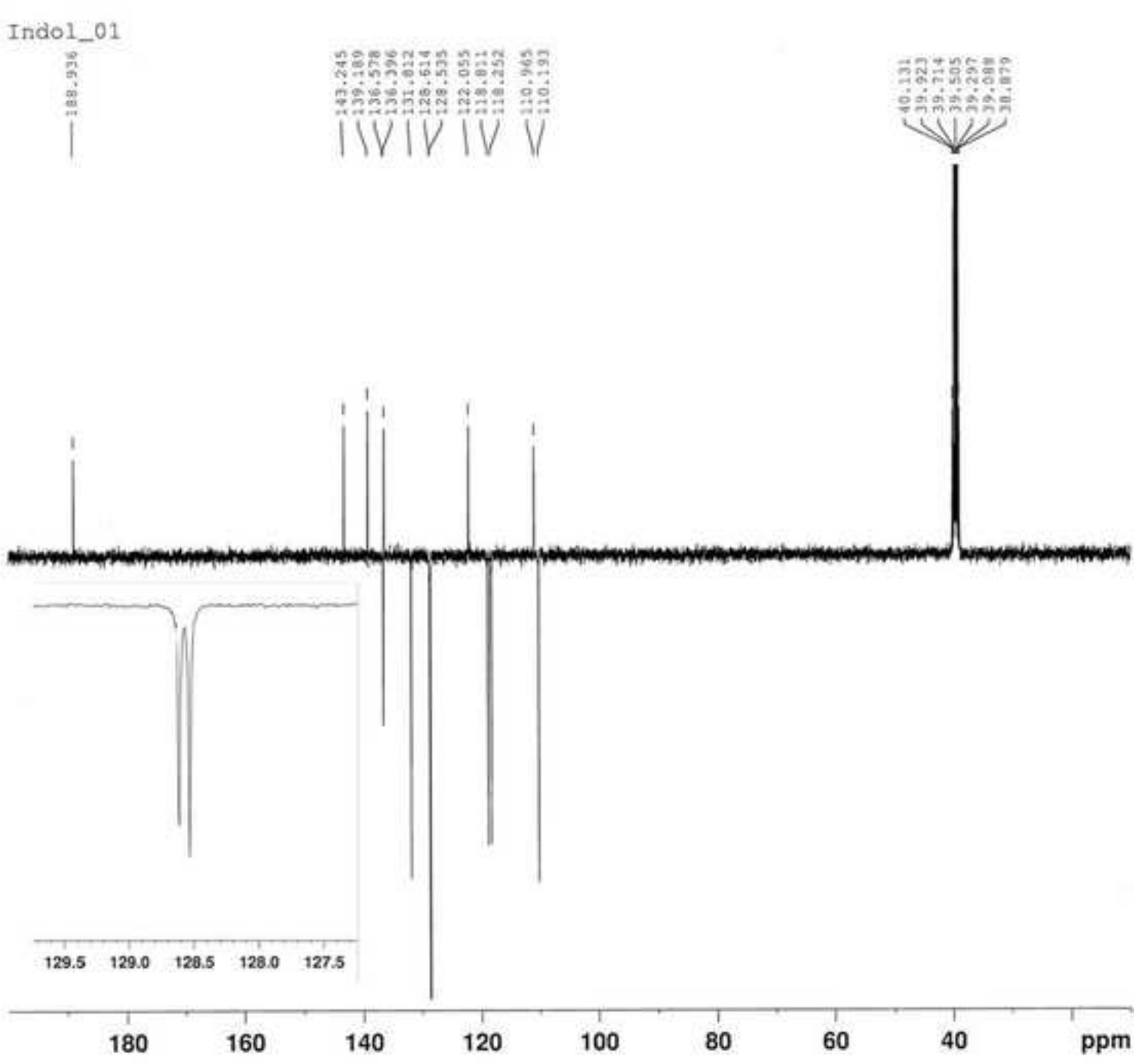


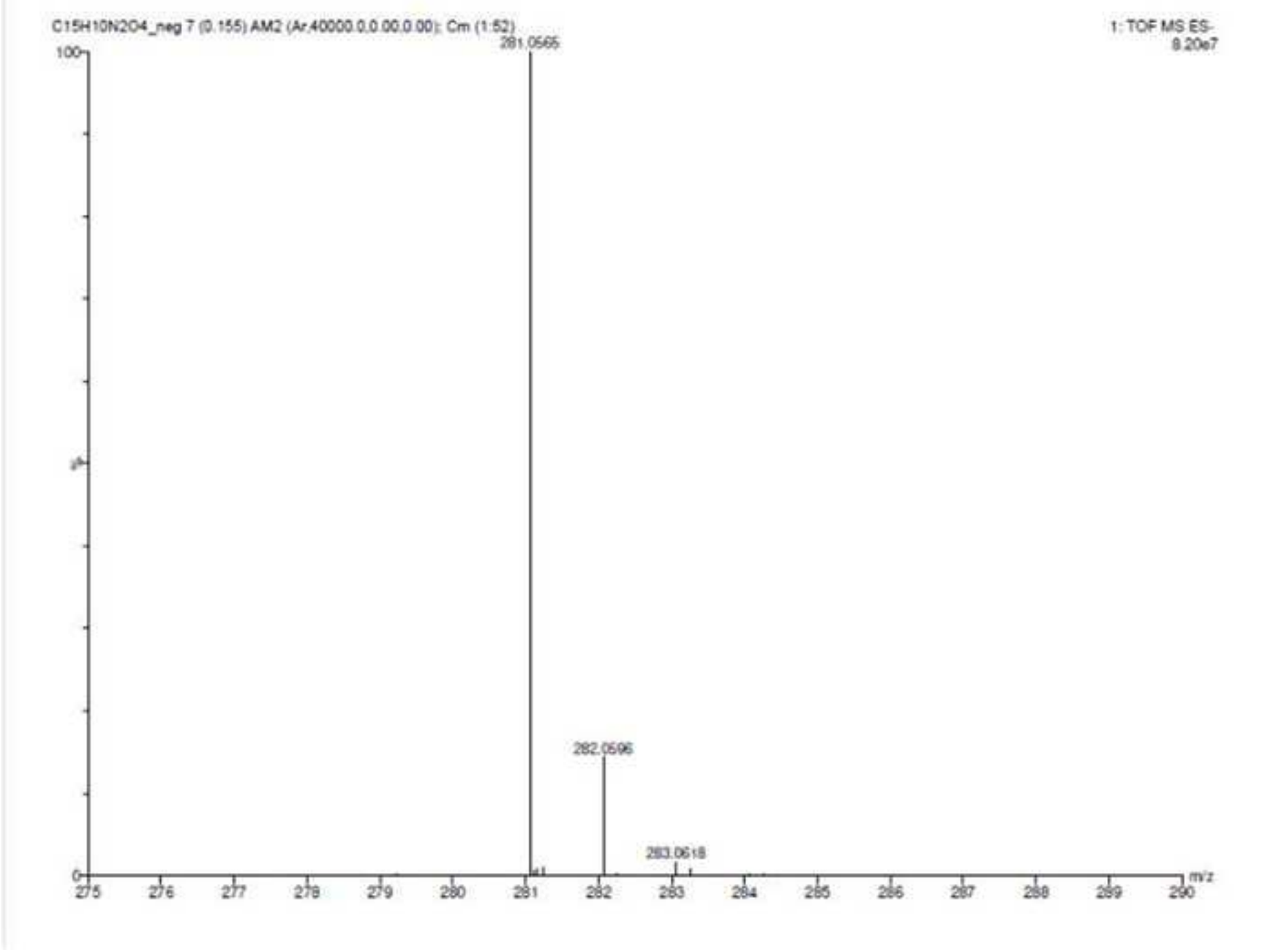


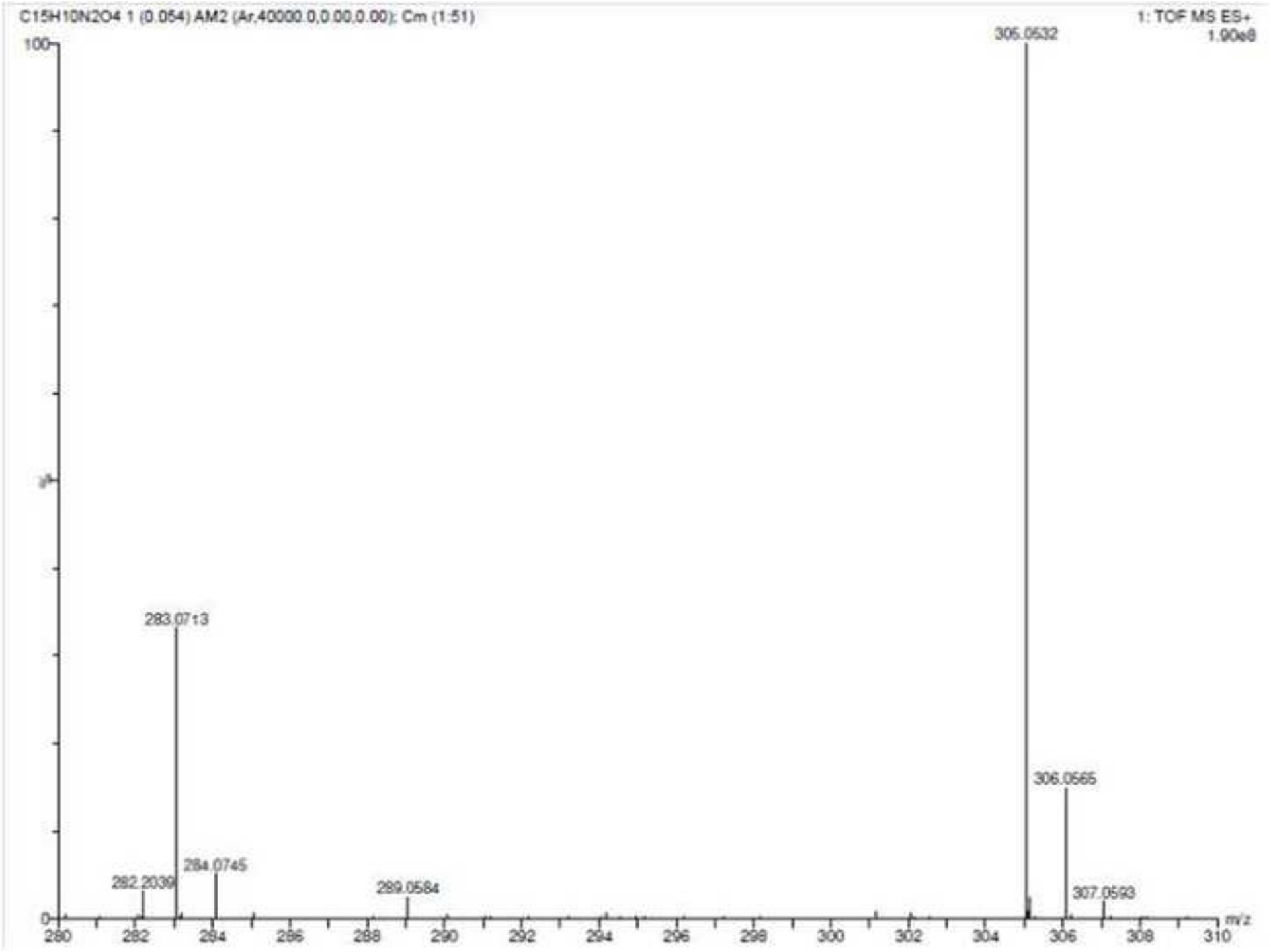
2 **4** **5** (58%) **6** (22%)











Name of Material/Equipment	Company	Catalog Number	Comments/Description
4-Nitroaniline	TCI Chemicals	N0119	
Acetone	TCI Chemicals	A0054	
1-Phenyl-2-propyne-1-ol	TCI Chemicals	P0220	
Celite 535	Fluorochem	44931	
Dichloromethane	TCI Chemicals	D3478	
Sodium hydrogen carbonate	Sigma Aldrich	S5761	
Sodium chloride	Sigma Aldrich	746398	
Sodium sulfate anhydrous	Sigma Aldrich	239313	
Oxone	TCI Chemicals	O0310	
Methanol	TCI Chemicals	M0628	
Toluene	TCI Chemicals	T0260	
Chromium Trioxide	Sigma Aldrich	236470	
Dichloromethane anhydrous	TCI Chemicals	D3478	
Hexane anhydrous	TCI Chemicals	H1197	

REBUTTAL DOCUMENT

Answers to Editorial comments

- The manuscript was entirely checked to avoid spelling or grammar errors and some redundant sentences were erased
- Some further descriptions were added to Figures 6-15
- As requested title of the legend of the figures was written in bold
- The figures were numbered in the order of their appearance
- All the references were checked and reported as suggested; for some journal the volume is not used by the editorial choice of the journal