4.1 Introduction

Heterocyclic compounds have a crucial function in facilitating biological function in cancer and deserve more attention [1-3]. According to current data, cancer ranks second among global killers. Creating an effective anticancer treatment without any unintended side effects was a major focus and difficulty for medicinal chemists. Some nitrogen heterocyclic compounds, such pyrazolo[3,4-b] pyridine, have been discovered to be more effective than others at boosting biological activity [4-10]. Heterocyclic compounds such as derivatives of pyrazolo-pyridine and pyrazolo-pyrimidine are privileged bioactive compounds [11-12]. The pyrazolo [3,4-b] pyridine ring system is an intriguing example of heterocyclic chemistry, and its derivatives have been shown to be effective for cancer treatments [13]. The compound pyrazolo [3,4-b] pyridine is an important structural motif found in a wide variety of natural products and bioactive molecules. The number of these molecules have shown useful as antiretroviral drugs, antimalarial drugs, anticancer drugs and kinase inhibitors. As a result, the efficient construction of these molecules has been a topic of intense interest among the organic chemist, medicinal chemist and contemporary organic synthesis [14,15].

Geraldo *et al.,* just recently described a novel class of pyrazolo-pyridine compounds. In addition, the pharmaceutical uses of the pyrazolo-pyridine nucleus include anxiolytic, antiviral, antileishmanial, and anti-inflammatory drugs [16]. Since β-keto esters contain both an electrophilic carbonyl and a nucleophilic carbon, they can be used as multicoupling reagents in the synthesis of complex compounds. Natural products such as serricornine, thiolactomycin, trichodiene, polyoximic acid, chokol, prostaglandin PGF2a, ar-pseudotsugonoxide, syncarpic acid, diplodialide , and podophyllotoxin all use β-keto esters as a building block in their total synthesis [17].

Pyrazole is a versatile lead compound that was created using chemical design to produce highly efficient and physiologically active compounds. Developing reactions involving pyrazoles presents a significant potential in medicinal chemistry, and there are several synthetic approaches that may be taken to yield a new molecule. As pyrazoles are widely used as medicines and protein ligands, there has been a rise in interest in developing novel synthetic techniques for their synthesis. Here, we offer a conceptually novel method that makes use of the synthetic logic afforded by direct C-H bond functionalization, in which new substituents are connected directly to specific places on the heteroarene nucleus [18].

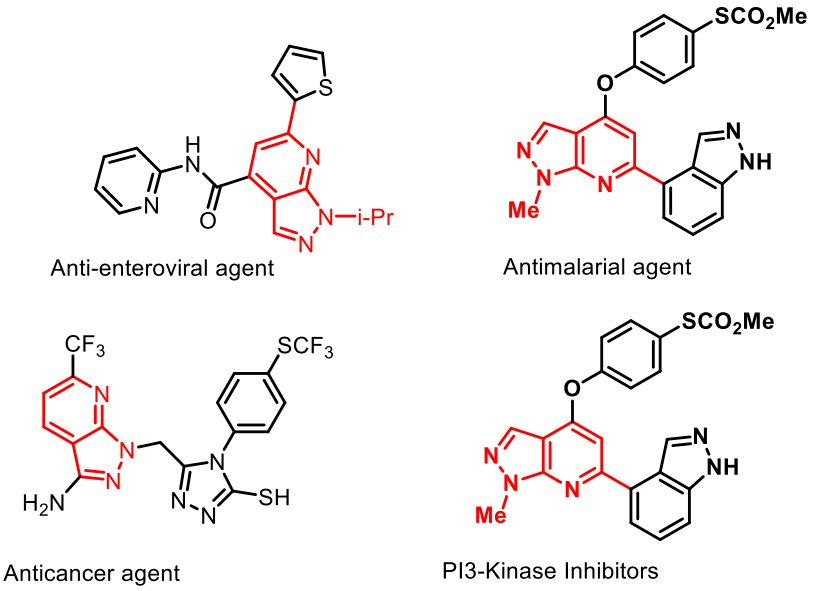


Figure 4.1 Structure of biologically relevant pyrazolo-pyridine.

In order to construct complicated cyclic molecules quickly, cycloadditions (including dipolar cycloadditions) are among the most elegant methods. Pyrazolo-pyridine and similar fused heterocycles are of interest as possible bioactive compounds. Some derivatives of the pyrazolo[3,4-b] pyridine ring system are important as low-toxicity anticancer medicines, and the class has proven to be an attractive scaffold in heterocyclic and medicinal chemistry. Many chemical compounds have been produced and investigated for inhibitory activity in the therapy of cancer. Anti-proliferation effect of these synthetic substituents

was evaluated on cancer cells after a library of chalcone analogues was generated. Para-methoxy substituted compound showed better activity comparison to fluoro- compound [19].Also, the compounds with pyrazole-ring having para-position methoxy group showed satisfactory activity. Para methoxy group contributes to improved conjugation of this molecule, which explains its potent performance. However, the final compound without any substitutions was just moderately active.

The study of cancer is a dynamic area of study today. Clinical studies are now underway to explore new treatments including immunotherapy and targeted medicines. While there is still much to be discovered about cancer, researchers are making progress in understanding the illness and developing innovative strategies to treat it. Thus, the primary focus of medicinal and organic chemists is the development of new molecules for more effective anticancer medication candidates to the treatment of cancer illnesses [20]. Thus, the design and efficient synthesis of pyrazolo [3,4-b] pyridine starting from β-keto esters is presented in this chapter.

4.2 Result and discussion

Initially, we commenced our strategy for the synthesis of various pyrazolo[3,4-b] pyridines starting from β-keto esters followed by propargylation of pyrazolo pyridine-7-ol was planned, and the retrosynthetic route is presented in **Figure 4.2** to achieve the synthesis of designed, targeted compounds.

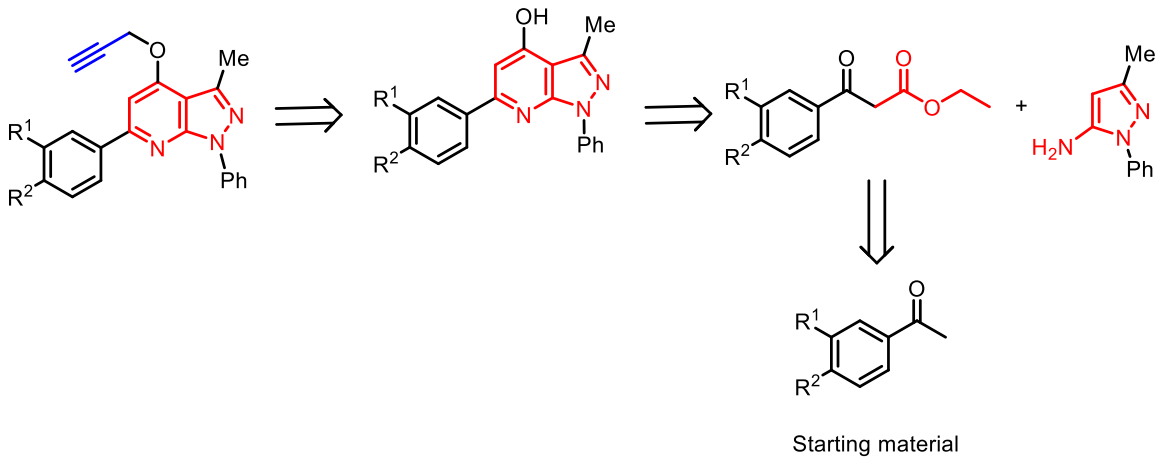
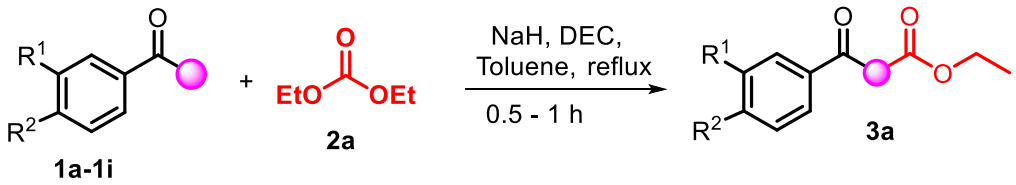


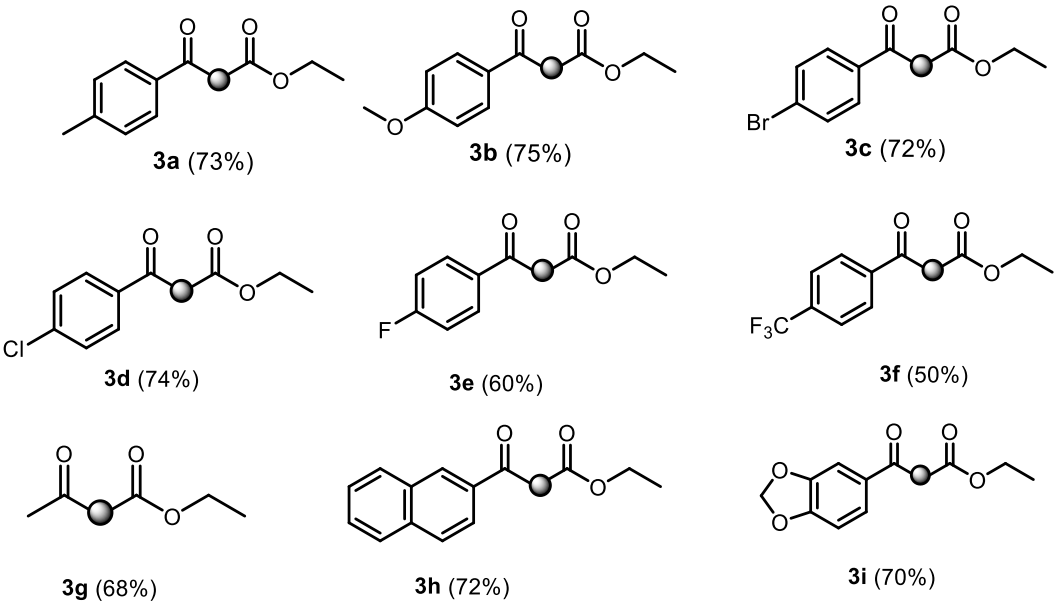
Figure 4.2 Retrosynthesis for the synthesis of propargylated pyrazolo[3,4-b] pyridines.

In order to optimize the experimental parameter, we recognized commercially available diverse acetophenone **1a-1i** as a starting material that can be converted to several β- keto esters **3a-3i**. Esterification of acetophenones **1a-1i** with diethyl carbonate in the presence of a strong base yields the β-keto esters **3a–3i** in good yields. The diverse β-keto ester with substitutes variations were synthesized, and it was observed that the product yield changed with each aryl ring replacement. We found that the yield of β-keto esters was diminished when an electron-withdrawing group was substituted for the aryl ring, as in the case of fluoro- and trifluoro-methyl. On the other hand, the process was aided by the introduction of an electron-donating group, as in the case of methyl- and methoxy-substitution for the aryl ring, furnishing a higher product yields[21].

Table 4.1 Transformation of functionalized acetophenone in to β-keto esters.[a,b]



R^1 = H
R^2 = CH_3, OCH_3, Br, Cl, F,
CF_3, -C_4H_4-, -OCH_2O-



[a]Reaction conditions: (10 mmol,1.34 gm, 1.0 equiv.) **1a-1i** and diethyl carbonate (20 mmol, 3.16 gm, 2.0 equiv.), NaH (28 mmol,0.72 gm, 3.0 equiv.) base in a solvent toluene (10 mL) at reflux condition. [b]Isolated yields.

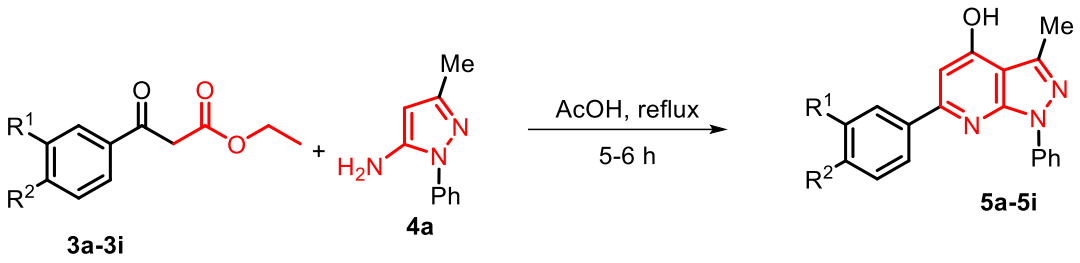
After successfully preparing the various β-kitoesters, we attempted to synthesize various pyrazolo[3,4-b] pyridines as pyrazolo-pyridin-4-ol **(5a-5i)** using the developed transamidation method. The reaction of β-ketoester with 5-amino-3-methyl-1-phenyl pyrazole gave the desired product pyrazolo-pyridine-4 ol in 68% yield at reflux condition **(Table 4.3)**.

Table 4.2 Reaction of β-ketoester **(3a-3i)** with 5-amino-3-methyl-1-phenyl pyrazole in different solvents.

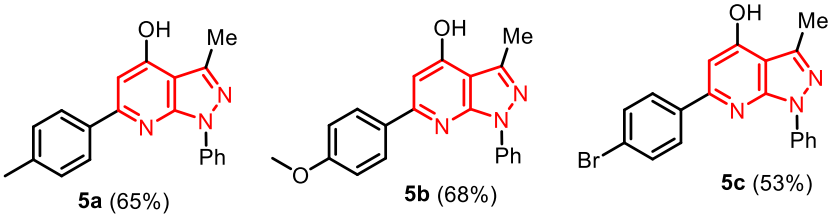
S.No.	Reaction conditions	Time h	Yield%
1.	Toluene, reflux	12	NA
2.	DMF, reflux	12	NA
3.	DMSO, reflux	12	NA
4.	Acetonitrile, reflux	12	NA
5.	MeOH, reflux	12	20
6.	EtOH, reflux	12	40
7.	**CH_3COOH, reflux**	6	**68**

With optimized conditions in our end, a variety of functionalized β-ketoester **(3a-3i)** were tested for the 5-amino-3-methyl-1-phenyl pyrazole **(Table 4.3).** To our delight, the substrates bearing electron-donating groups (e.g., methyl, methoxy) good to excellent yields comparison to electron-withdrawing groups (e.g., fluoro, chloro, etc) at the para position underwent coupling reaction smoothly and provided the corresponding pyrazolo-pyridine-4-ol within 5-6 hours. Further, the reaction of para-substituted trifluoromethyl successfully converted into corresponding pyrazolo[3,4-b] pyridine **5f** in 45% yield. Thus diverse pyrazolo[3,4-b] pyridines derivatives **5a**-**5h** were prepared in good to very good yields (**Table 4.3**).

Scheme 4.1 Transformation of functionalized β-ketoester with 5-amino-3-methyl-1-phenyl pyrazole.[a,b]



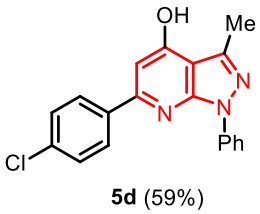
3a-3i 4a 5a-5i



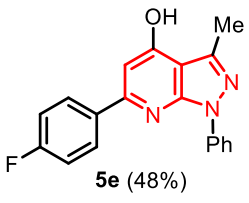
5a (65%)

5b (68%)

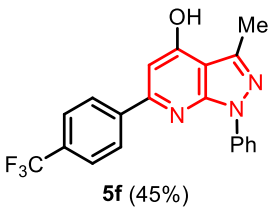
5c (53%)



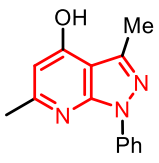
5d (59%)



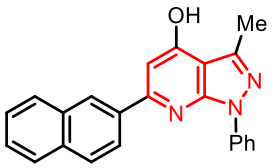
5e (48%)



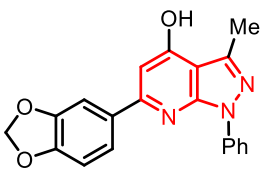
5f (45%)



5g (60%)



5h (55%)

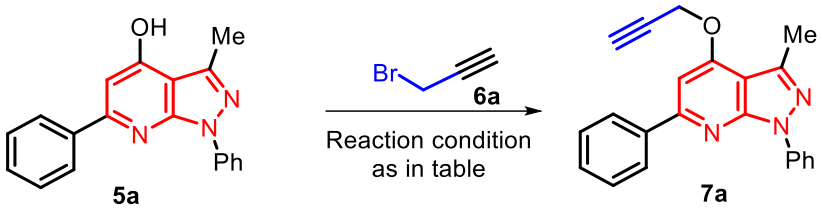


5i (57%)

[a]Reaction conditions: ethyl 3-oxo-3-(p-tolyl) propanoate (1.0 g, 5.20 mmol,1.0 equiv.) **3a-3i**, 5-amino-3-methyl-1phenyl pyrazole (1.17 g, 6.76 mmol, 1.3 equiv.) were stirred in acetic acid (10 mL) at reflux medium. [b]Isolated yields.

We further investigated the transformation of various activated pyrazolo-pyridine -7-ol **(5a-5i)** and propargyl bromide in acetone using K_2CO_3. In this context, we believe that although NaH and K_2CO_3 have comparable basicity, their poor solubility in organic solvents would be one of the reasons for observing low yields. It was observed that the reaction proceeds better in acetone when compared with other solvents, including DMF, THF and 1,4-dioxane. The optimized reactions and their outcomes are shown in (**Table 4.4**).

Table 4.3 Optimization of the reaction condition.[a,b]

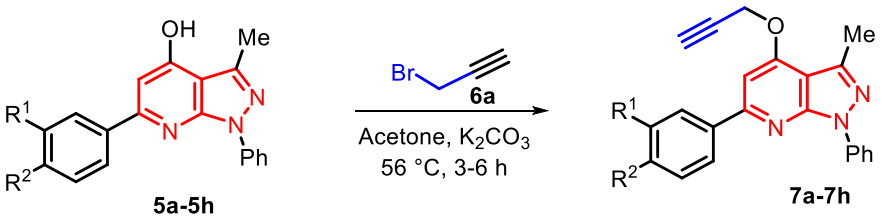


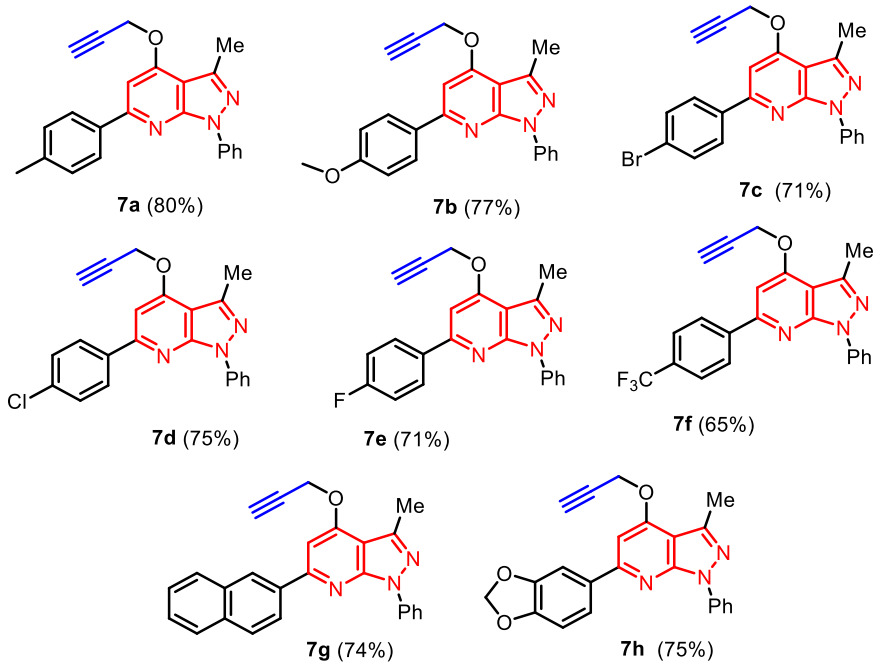
Entry	Reaction condition	Yield (%)
1	DMF, K_2CO_3, 60℃, 3 h	70
2	DMF, K_2CO_3, RT, 3 h	22
3	DMF, NaH, 0 ℃, 3 – 6 h	44
4	THF, K_2CO_3, 60 ℃, 3 h	NA
5	THF, NaH, 0 ℃, 3 h	NA
6	1,4-dioxane, K_2CO_3, RT, 3 h	45
7	1,4-dioxane, K_2CO_3, 60 ℃, 3 h	65
8	**Acetone**, K_2CO_3, 56 ℃, 3 h	**80**

[a]Reaction conditions: Substrate (0.1gm, 0.331 mmol, 1.0 equiv.) **5a,** Propargyl bromide (0.30 mL, 0.398mmol,1.2 equiv.) and K_2CO_3 (0.045gm, 0.33 mmol,1.0 equiv.) base in acetone (5 mL) at 56 ℃. [b]Isolated yields.

O-propargylated pyrazolo[3,4-b] pyridine **(7a-7i)** is of interest, hence research into its synthesis from propargylation of different pyrazolo-pyrimidin-4-ols under diverse reaction circumstances is a priority. We came up with a new synthetic approach to get the desired product, an *O*-propargylated form of pyrazolo [3,4-b] pyridine. We found that an excellent isolated yield (80%) of *O*-propargylated pyrazolo [3,4-b] pyridine could be obtained by treating pyrazolo-pyrimidin-7-ol with propargyl bromide in acetone using K_2CO_3 as a base.

Scheme 4.2 Transamidation of various activated of pyrazolo-pyridine -4-ol with propargyl bromide.[a,b]





[a]Reaction conditins: Substrate (0.1g, 0.331 mmol,1.0 equiv.) **5a-5h**, Propargyl bromide (0.30 mL, 0.398 mmol, 1.2 equiv.) and K_2CO_3 (0.045 g, 0.331mmol, 1.0 equiv.) in acetone at 56 °C. [b]Isolated yields.

4.3 Fabrication carbon paste electrode-To prepare the carbon paste electrode (CPE) the graphite powder (size < 20µm) was used. The nujul oil was used as a binder. The ratio of

graphite powder and nujol oil was used 70:30. The paste was filled in a glass capillary; the prepared electrode was manually polished butter paper to get the smooth surface [22].

4.4 Open Circuit Potential- The open circuit potential (OCP) is an essential quantity in cyclic voltammetry that may be used to learn about the initial electrochemical state of the system, the redox potentials present, the condition of the electrodes, and the kinetics and reversibility of the reactions being studied. It is essential for the analysis of CV data as a reference point in the CV experiment.

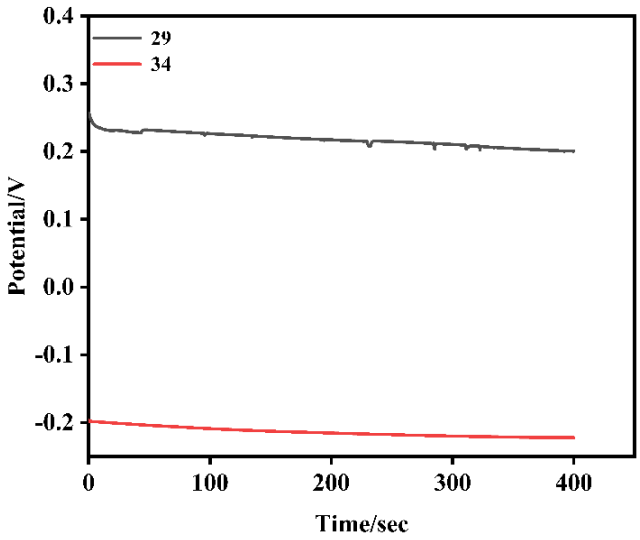


Figure 4.3 Graph to OCP evaluation of propargylated pyrazolopyridine (electron donating and electron withdrawing).

4.5 Cyclic voltammetry- The electrochemical technique of cyclic voltammetry (CV) is widely used to study the reduction and oxidation processes of molecular species [23]. (0.1 M $NaClO_4$ + C_2H_5OH) was utilized as the supporting electrolyte, and a carbon paste electrode (CPE; d = 0.03 cm^2) was employed as the working electrode. Other components included a Pt counter electrode (1 cm^2), an aqueous Ag/AgCl reference electrode.

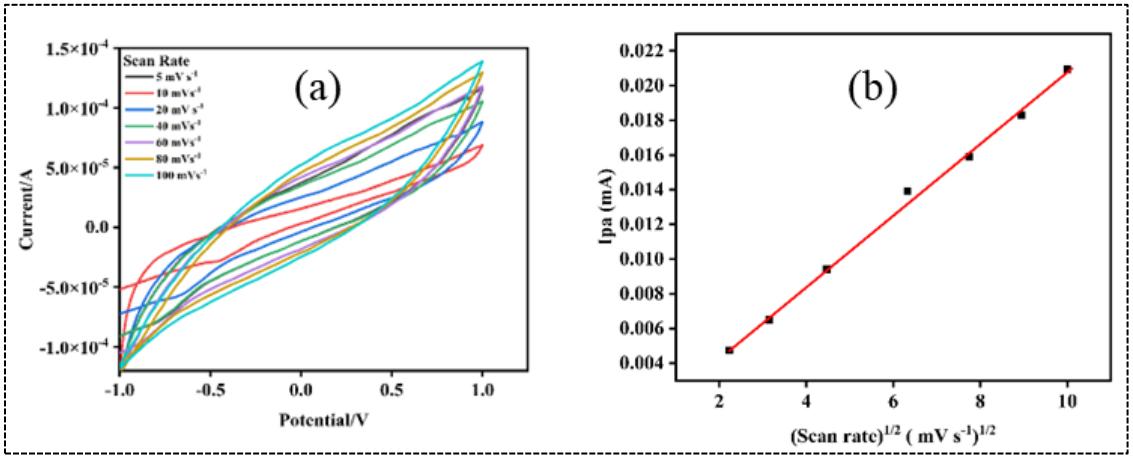


Figure 4.4 (a) Cyclic voltammograms of **5a** at different scan rate. **(b)** The linear plot of Ipa vs square root of scan rate.

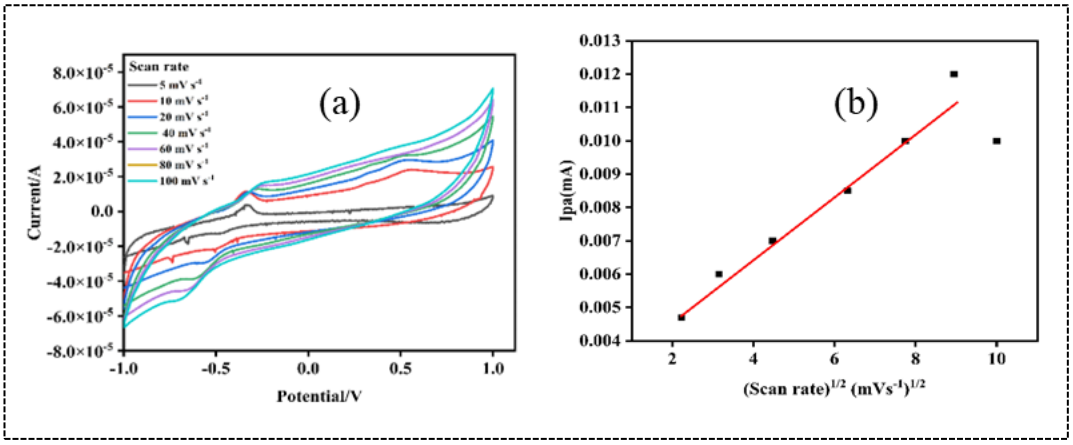


Figure 4.5 (a) Cyclic voltammograms of **7a** at different scan rate. **(b)** The linear plot of Ipa vs square root of scan rate.

The study was carried out under a potential range between -1.0 to +1.0 V. The 4-substituted derivatives propargylated pyrazolo pyridines (**7a-7h**) showed well-defined diffusion-controlled quasi-reversible redox peaks. A typical irreversible signal was seen for 4-substituted derivatives, with a negligible reduction in all instances and an oxidation peak for **7a**.

4.6 Electrochemical Impedance Spectroscopy-

In conclusion, Electrochemical Impedance Spectroscopy (EIS) is a flexible and potent instrument in electro-organic synthesis, helping researchers better understand, optimize,

and regulate electrochemical reactions and processes. It has the potential to greatly improve the safety, selectivity, and efficiency of electro-organic synthesis techniques.

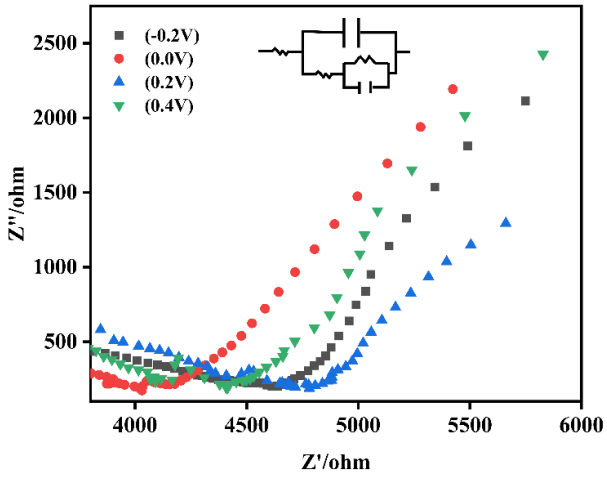


Figure 4.6 Electrochemical impedance spectroscopy EIS study of **7a** at different potential.

The kinetic and mechanistic data of different electrochemical systems are provided by electrochemical impedance spectroscopy (EIS), which is widely utilized in corrosion studies, semiconductor science, energy conversion and storage technologies, chemical and biological sensing, noninvasive diagnostics, etc. EIS is based on the application of a sinusoidal signal (ac voltage or current) over a wide range of frequencies to perturb an electrochemical system in equilibrium or instead state, and the observation of the system's sinusoidal response (current or voltage, respectively) to the applied perturbation. The obtained data was best fitted on using circuit R(C(R(CR))). The data as shown above graph reveals that our processes is diffusion controlled.

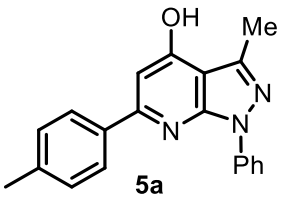
4.7 Conclusion

In conclusion, an efficient and promising strategy for the synthesis of *O*-propargylated pyrazolo [3,4-b] pyridine via transformation of pyrazolo-pyridine -4-ol with propargyl bromide in the presence of K_2CO_3. Broad substrate scope and excellent functional group tolerance are the merits of the developed methodology. We believe that methodology will

be highly useful for combinatorial synthesis *O*-propargylated pyrazolo [3,4-b] pyridine in a short span of time.

4.8 Experimental Procedure and Spectral data of all compounds

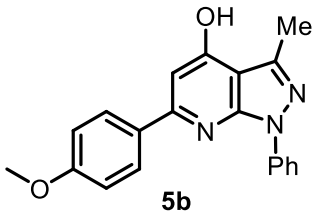
4.8.1 General procedure for the synthesis of pyrazolo [3,4-b] pyridine as pyrazolo-pyridine-4-ol 5a-5i: After adding (1.17 gm, 6.76 mmol, and 1.3 equiv.) of 5-amino-3-methyl-1-phenyl pyrazole **4a** to a stirring solution, the mixture was then dissolved in 20 milliliters of acetic acid in an oven-dried 100 mL round-bottom flask while the environment was N_2. Subsequently, ethyl 3-oxo-3-(p-tolyl) propanoate **3a** was added to the reaction mixture in the amount of (1.0 gm, 5.20 mmol, and 1.0 equiv.) Following this, the mixture was heated to reflux at 118℃ for a period of 12 to 14 hours. Following the evaporation of the solvent from the reaction mixture with the help of toluene, which is an azeotropic solvent, the mixture was then triturated with diethyl ether. In conclusion, it was dried under a high vacuum in order to get solid product **5a**, which had a yield of 68% and was utilized in subsequent processes without any additional purification methods. A similar procedure was followed in order to synthesis compounds **5a-5i**, which resulted in yields that ranged from mediocre to excellent.



5a

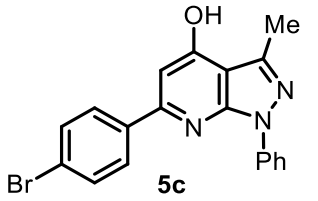
3-methyl-1-phenyl-6-(p-tolyl)-1*H*-pyrazolo[3,4-b] pyridin-4-ol (5a). The product was purified by silica column chromatography (Ethyl acetate:Hexane 1:9), light brown solid: m.p. (220 °C); Yield (65%), **^{1}H NMR** (500 MHz, DMSO-d_6) δ = 11.44 (s, 1H), 8.21 (d, *J* = 7.8 Hz, 2H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 6.43 (s, 1H), 2.40 (s, 3H), 2.14 (s, 3H). **^{13}C NMR** (126 MHz,

DMSO-d_6) δ = 163.46, 149.93, 148.42, 142.22, 139.24, 138.31, 134.11, 128.95, 128.67, 125.29, 120.47, 109.10, 105.96, 20.85, 15.15 ppm;



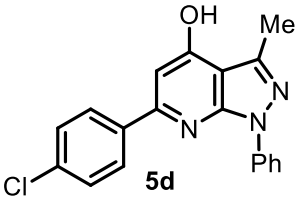
5b

6-(4-methoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-b] pyridin-4-ol (5b). The product was purified by silica column chromatography (Ethyl acetate:Hexane 1:9), white coloured solid: m.p. (235 °C); Yield (68%), **^{1}H NMR** (500 MHz, DMSO-d_6) δ = 11.43 (s, 1H), 8.21 (d, *J* = 7.8 Hz, 2H), 7.54 – 7.47 (m, 4H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.43 (s, 1H), 3.84 (s, 3H), 2.17 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ = 163.64, 159.96, 150.16, 148.36, 142.42, 139.44, 130.34, 129.12, 125.43, 120.63, 113.97, 109.35, 106.04, 55.40, 15.44 ppm;



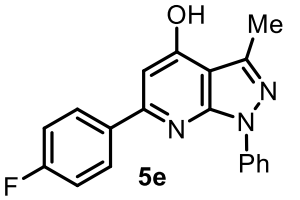
5c

6-(4-bromophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-b] pyridin-4-ol (5c). The product was purified by silica column chromatography (Ethyl acetate:Hexane 1:9), light brown coloured solid: m.p. (48 °C); Yield (53%), **^{1}H NMR** (500 MHz, DMSO-d_6) δ = 11.55 (s, 1H), 8.20 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 7.8 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 4H), 7.29 (t, *J* = 7.8 Hz, 1H), 6.47 (s, 1H), 2.12 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ = 163.81, 160.12, 150.33, 148.52, 142.59, 139.61, 130.51, 129.29, 125.60, 120.80, 114.13, 109.52, 106.21, 15.60 ppm;



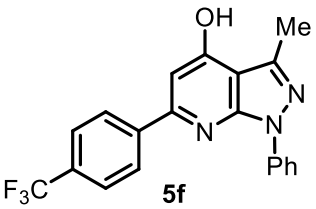
5d

6-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-b] pyridin-4-ol (5d). The product was purified by silica column chromatography (Ethyl acetate:Hexane 1:9), light brown coloured solid: m.p. (53 °C); Yield (59%), **^{1}H NMR** (500 MHz, DMSO-d_6) δ = 11.55 (s, 1H), 8.20 (d, *J* = 6.9 Hz, 2H), 7.58 (s, 4H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 1H), 6.47 (s, 1H), 2.12 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ = 163.81, 147.26, 142.39, 139.50, 136.11, 134.09, 130.99, 129.31, 128.75, 125.72, 120.85, 109.23, 106.48, 15.43 ppm;



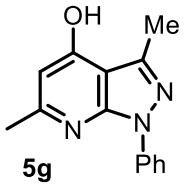
5e

6-(4-chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-b]pyridin-4-ol (5e). The product was purified by silica column chromatography (Ethyl acetate:Hexane 1:9), brown coloured solid: m.p. (60 °C); Yield (48%), **^{1}H NMR** (500 MHz, DMSO-d_6) δ = 11.50 (s, 1H), 8.20 (d, *J* = 8.0 Hz, 2H), 7.61 (t, *J* = 5.8 Hz, 2H), 7.52 (d, *J* = 7.9 Hz, 2H), 7.36 (t, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 7.7 Hz, 1H), 6.46 (s, 1H), 2.13 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ = 163.82, 147.57, 142.47, 139.54, 133.67, 131.36, 131.29, 129.32, 125.71, 120.86, 115.75, 115.58, 109.44, 106.54, 15.41 ppm;



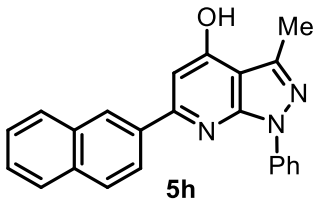
5f

3-methyl-1-phenyl-6-(4-(trifluoromethyl)phenyl)-1*H*-pyrazolo[3,4-b]pyridin-4-ol (5f). The product was purified by silica column chromatography (Ethyl acetate:Hexane 1:9), light brown coloured solid: m.p. (85 °C); Yield (45%), **^{1}H NMR** (500 MHz, DMSO-d_6) δ = 11.63 (s, 1H), 8.20 (d, *J* = 8.1 Hz, 2H), 7.89 (d, *J* = 7.9 Hz, 2H), 7.79 (d, *J* = 7.3 Hz, 2H), 7.53 (t, *J* = 7.9 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 6.52 (s, 1H), 2.09 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ = 163.11, 149.49, 146.21, 141.58, 140.70, 138.77, 129.35, 128.75, 128.67, 128.60, 125.06, 124.87, 120.21, 108.38, 105.93, 14.61 ppm;



5g

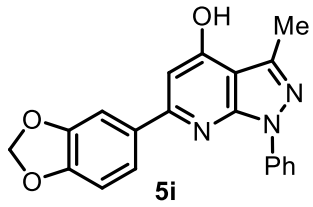
3,6-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-b] pyridin-4-ol (5g). The product was purified by silica column chromatography (Ethyl acetate:Hexane 1:9), light brown coloured solid: m.p. (90 °C); Yield (60%), **^{1}H NMR** (500 MHz, DMSO-d_6) δ = 11.19 (s, 1H), 8.19 (d, *J* = 7.9 Hz, 2H), 7.49 (t, *J* = 7.9 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 6.36 (s, 1H), 2.58 (d, *J* = 8.2 Hz, 6H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ = 164.18, 149.99, 146.18, 143.22, 139.75, 129.25, 125.34, 120.45, 111.21, 106.58, 19.05, 15.09 ppm;



5h

3-methyl-6-(naphthalen-2-yl)-1-phenyl-1*H*-pyrazolo[3,4-b] pyridin-4-ol (5h). The product was purified by silica column chromatography (Ethyl acetate:Hexane 1:9), light brown coloured solid: m.p. (118 °C); Yield (60%), **^{1}H NMR** (500 MHz, DMSO-d_6) δ = 11.56 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 2H), 8.12 (s, 1H), 8.05 (d, *J* = 8.1 Hz, 2H), 8.01 (d, *J* = 4.5 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.61 – 7.58 (m, 2H), 7.53 (t, *J* = 7.9 Hz, 2H), 7.29 (t,

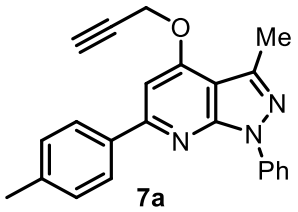
J = 7.4 Hz, 1H), 6.59 (s, 1H), 2.12 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ = 124.73, 111.98, 111.20, 110.95, 110.40, 105.56, 102.28, 93.93, 91.64, 88.12, 85.46, 83.46, 73.54, 72.07, 70.98, 69.32, 64.20, 16.72 ppm;



5i

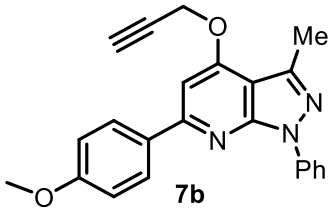
6-(benzo[d][1,3]dioxol-5-yl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-b]pyridin-4-ol (5i). The product was purified by silica column chromatography (Ethyl acetate: Hexane 1:9), white coloured solid: m.p. (135 °C); Yield (57%), **^{1}H NMR** (500 MHz, DMSO-d_6) δ = 11.49 (s, 1H), 8.21 (d, *J* = 8.0 Hz, 2H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.15 (s, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 6.44 (s, 1H), 6.12 (s, 2H), 2.18 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ = 163.31, 147.88, 147.67, 147.16, 142.08, 139.12, 130.56, 128.82, 125.14, 122.63, 120.32, 109.07, 108.05, 105.87, 101.29, 15.10 ppm;

4.8.2 Synthesis of propargylated derivatives of pyrazolo-pyridine-4-ol 7a-7h: In an oven dried 100 mL two necked round bottom flask taken pyrazolo-pyridine-4-ol (0.1g, 0.331 mmol, 1.0 equiv.) and K_2CO_3 (0.045 g, 0.331mmol, 1.0 equiv.) in acetone (5mL) was added and stirred for half an hour. After that propargyl bromide (0.30 mL, 0.398 mmol, 1.2 equiv.) was added dropwise and reaction mixture refluxed for 2 hours. The completion of reaction was monitored by TLC, after completion of reaction the reaction mixture was quenched by aqueous solution of $NaHCO_3$ and extracted with EtOAc. The organic layer dried over Na_2SO_4 and the solvent from the mixture was evaporated under vacuum. After that the crude mixture was subjected for column chromatography to afford purified solid product **7a**. The similar protocol followed to synthesize compounds **7a –7h**, which give moderate to good yield.



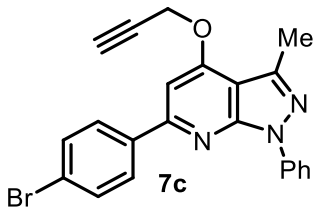
7a

3-methyl-1-phenyl-4-(prop-2-yn-1-yloxy)-6-(p-tolyl)-1*H*-pyrazolo[3,4-b]pyridine (7a). The product was purified by silica column chromatography (Ethyl acetate:Hexane 1:9), yellow coloured solid: m.p. (250 °C); Yield (80%), **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 8.30 (d, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.3 Hz, 2H), 7.32 – 7.27 (m, 3H), 6.60 (s, 1H), 5.10 (s, 2H), 2.52 (s, 1H), 2.45 (s, 3H), 2.25 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 162.13, 149.36, 149.12, 143.11, 139.72, 135.88, 134.65, 129.14, 129.02, 128.88, 125.45, 120.84, 110.96, 106.72, 79.14, 54.09, 21.46, 15.52 ppm;



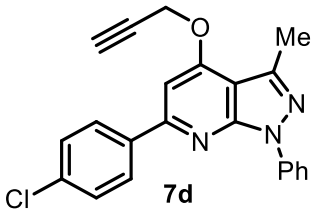
7b

6-(4-methoxyphenyl)-3-methyl-1-phenyl-4-(prop-2-yn-1-yloxy)-1*H*-pyrazolo[3,4-b] pyridine (7b). The product was purified by silica column chromatography (Ethyl acetate: Hexane 1:9), yellow coloured solid: m.p. (265 °C); Yield (80%), **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 8.23 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.33 (d, *J* = 7.4 Hz, 2H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.51 (s, 1H), 5.02 (s, 2H), 3.81 (s, 3H), 2.45 (s, 1H), 2.20 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 162.13, 149.36, 149.12, 143.11, 139.72, 138.88, 134.65, 129.14, 129.02, 128.88, 125.45, 120.84, 110.96, 106.72, 79.14, 74.53, 54.09, 21.46, 15.52 ppm;



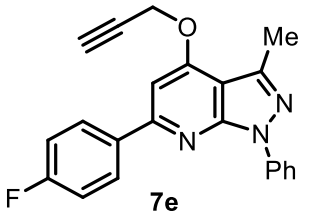
7c

6-(4-bromophenyl)-3-methyl-1-phenyl-4-(prop-2-yn-1-yloxy)-1*H*-pyrazolo[3,4-b]pyridine (7c). The product was purified by silica column chromatography (Ethyl acetate: Hexane 1:9), light brown coloured solid: m.p. (40 °C); Yield (71%), **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 8.28 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 6.58 (s, 1H), 5.10 (s, 2H), 2.53 (s, 1H), 2.24 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 162.34, 149.57, 147.79, 142.97, 139.82, 136.69, 131.98, 130.78, 129.31, 125.87, 123.62, 121.12, 110.83, 106.97, 74.90, 54.44, 15.74 ppm;



7d

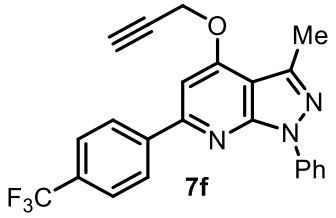
6-(4-chlorophenyl)-3-methyl-1-phenyl-4-(prop-2-yn-1-yloxy)-1*H*-pyrazolo[3,4-b] pyridine (7d). The product was purified by silica column chromatography (Ethyl acetate: Hexane 1:9), light brown coloured solid: m.p. (45 °C); Yield (75%), **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 8.28 (d, *J* = 8.1 Hz, 2H), 7.52 – 7.47 (m, 4H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 14.9 Hz, 1H), 6.58 (s, 1H), 5.10 (s, 2H), 2.53 (d, *J* = 2.6 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 161.83, 149.06, 147.29, 142.46, 139.32, 135.71, 134.93, 130.00, 128.80, 128.51, 125.37, 120.62, 110.40, 106.53, 74.38, 53.92, 15.22 ppm;



7e

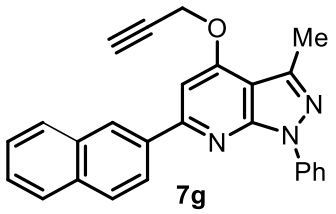
6-(4-fluorophenyl)-3-methyl-1-phenyl-4-(prop-2-yn-1-yloxy)-1*H*-pyrazolo[3,4-b] pyridine (7e). The product was purified by silica column chromatography (Ethyl acetate: Hexane 1:9), light brown coloured solid: m.p. (60 °C); Yield (71%), **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 8.29 (d, *J* = 7.4 Hz, 2H), 7.51 (t, *J* = 7.9 Hz, 2H), 7.45 (d, *J* = 5.7 Hz, 2H), 7.29

(d, *J* = 6.9 Hz, 1H), 7.22 – 7.17 (m, 2H), 6.59 (s, 1H), 5.10 (s, 2H), 2.53 (s, 1H), 2.23 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 161.86, 149.07, 147.58, 142.56, 139.36, 130.48, 130.41, 128.82, 125.36, 120.64, 115.42, 115.25, 110.62, 106.64, 74.36, 53.91 ppm;



7f

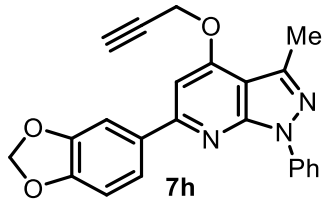
3-methyl-1-phenyl-4-(prop-2-yn-1-yloxy)-6-(4-(trifluoromethyl)phenyl)-1*H*-pyrazolo[3,4-b]pyridine (7f). The product was purified by silica column chromatography (Ethyl acetate:Hexane 1:9), light brown coloured solid: m.p. (70 °C); Yield (65%), **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 8.28 (d, *J* = 7.6 Hz, 2H), 7.77 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.53 – 7.49 (m, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 6.61 (d, *J* = 2.1 Hz, 1H), 5.10 (s, 2H), 2.54 (s, 1H), 2.21 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 161.84, 149.04, 146.91, 142.35, 140.90, 139.28, 129.13, 128.87, 125.50, 125.29, 125.26, 120.67, 110.26, 106.68, 78.68, 74.50, 54.03, 15.21ppm;



7g

3-methyl-6-(naphthalen-2-yl)-1-phenyl-4-(prop-2-yn-1-yloxy)-1*H*-pyrazolo[3,4-b]pyridine (7g)- The product was purified by silica column chromatography (Ethyl acetate: Hexane 1:9), light brown coloured solid: m.p. (110 °C); Yield (74%), **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 8.32 (d, *J* = 8.0 Hz, 2H), 7.99 – 7.91 (m, 4H), 7.61 – 7.56 (m, 3H), 7.52 (d, *J* = 4.8 Hz, 2H), 7.29 (d, *J* = 7.2 Hz, 1H), 6.72 (s, 1H), 5.13 (s, 2H), 2.54 (s, 1H), 2.24 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 161.93, 149.16, 148.72, 142.87, 139.46, 134.76, 133.14,

132.83, 128.85, 126.73, 126.70, 126.52, 125.33, 120.67, 110.83, 106.85, 74.39, 53.95, 15.33 ppm;



7h

6-(benzo[d][1,3]dioxol-5-yl)-3-methyl-1-phenyl-4-(prop-2-yn-1-yloxy)-1*H*-pyrazolo[3,4-b]pyridine (7h). The product was purified by silica column chromatography (Ethyl acetate:Hexane 1:9), light brown coloured solid: m.p. (140 °C); Yield (75%), **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 8.29 (d, *J* = 7.5 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 1H), 6.93 (s, 3H), 6.58 (s, 1H), 6.06 (s, 2H), 5.09 (s, 2H), 2.52 (s, 1H), 2.30 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 166.31, 153.00, 142.46, 134.71, 133.71, 131.26, 129.64, 129.13, 128.64, 128.29, 127.98, 50.48, 48.59, 27.33ppm;

^{1}H NMR and ^{13}C NMR of pyrazolo[3,4-b] pyridin-4-ol derivatives (5a):

^{1}H-NMR & ^{13}C-NMR (500 MHz, DMSO-*d*6)

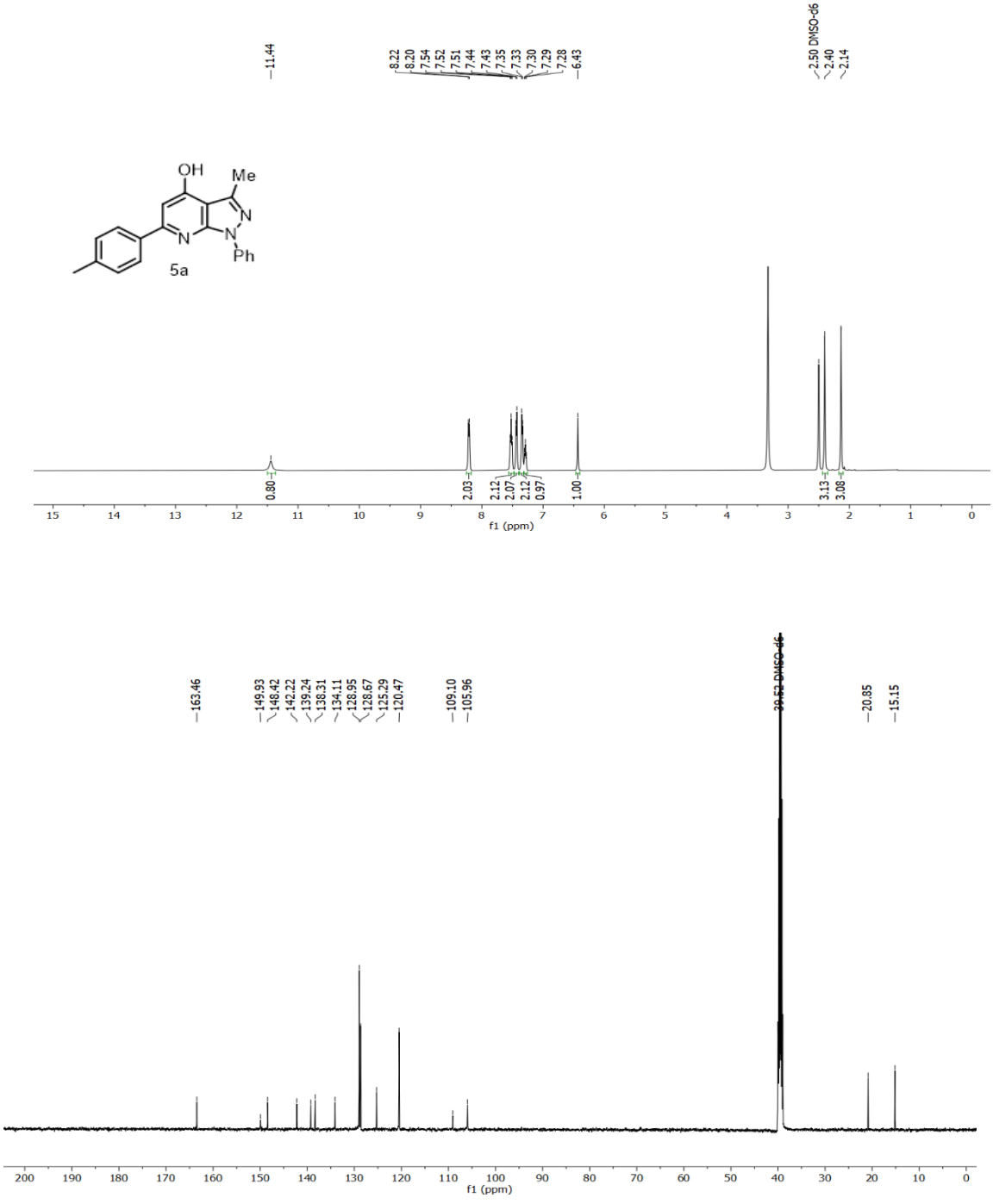


Figure 4.7 ^{1}H NMR and ^{13}C NMR spectra of compound 5a in DMSO

^{1}H NMR and ^{13}C NMR of pyrazolo[3,4-b] pyridin-4-ol derivatives (5b):

^{1}H-NMR & ^{13}C (500 MHz, DMSO-d6)

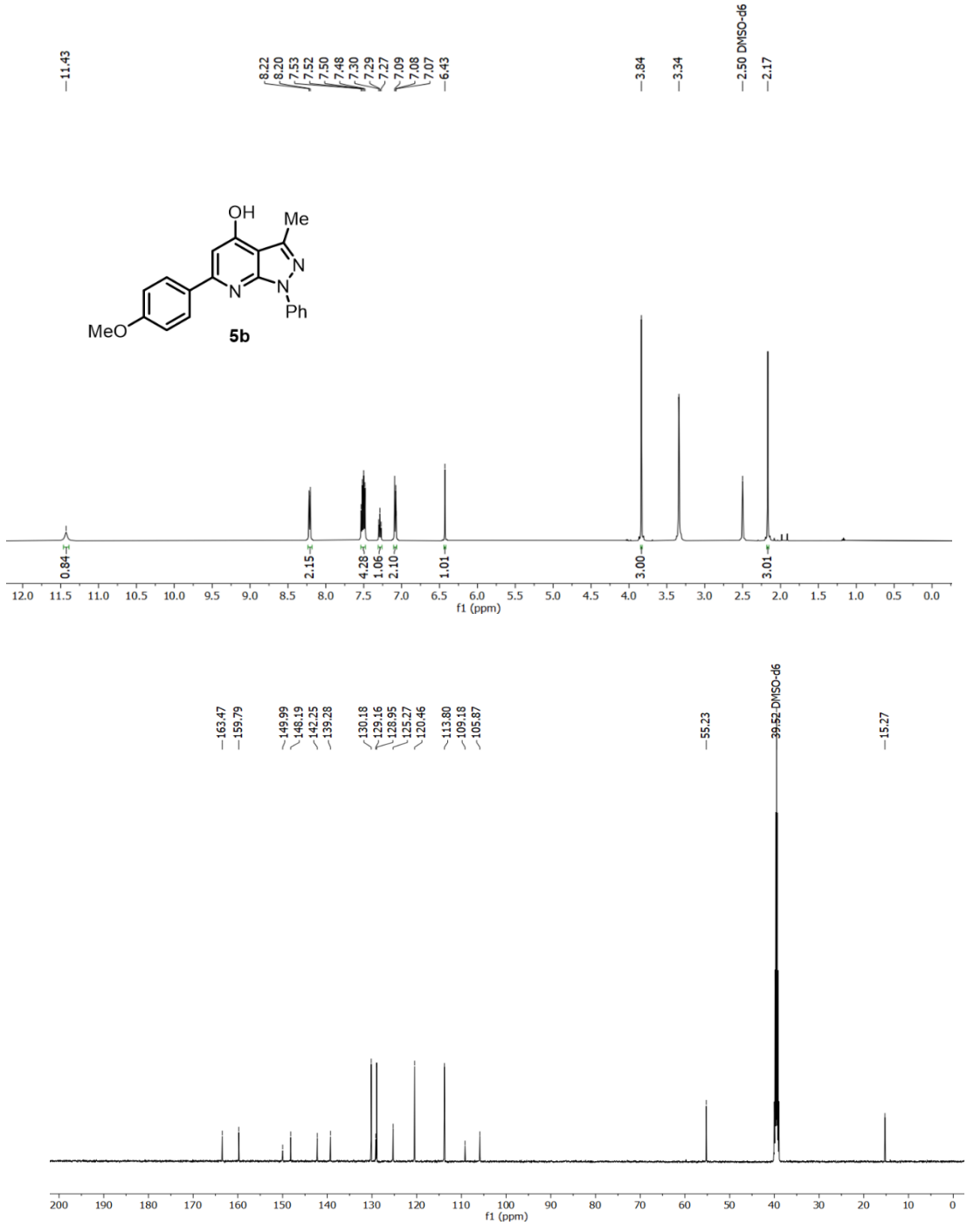


Figure 4.8 ^{1}H NMR and ^{13}C NMR spectra of compound 5b in DMSO.

^{1}H NMR and ^{13}C NMR of propargylated derivatives of pyrazolo[3,4-b] pyridine (7a):

^{1}H-NMR & ^{13}C (600 MHz, $CDCl_3$)

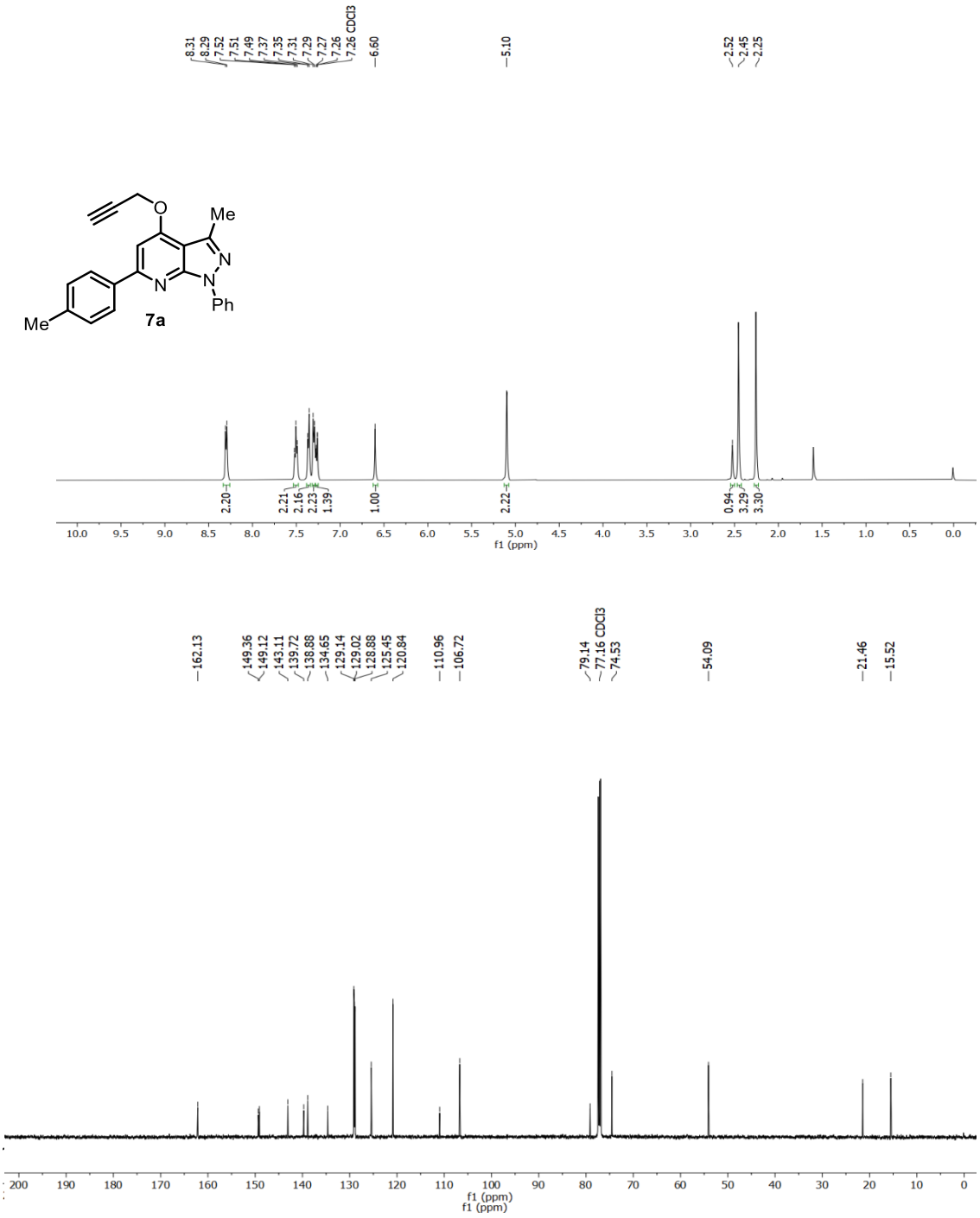


Figure 4.9 ^{1}H NMR and ^{13}C NMR spectra of compound 7a in $CDCl_3$

^{1}H NMR and ^{13}C NMR of propargylated derivatives of pyrazolo[3,4-b] pyridine (7b):

^{1}H-NMR & ^{13}C (600 MHz, $CDCl_3$)

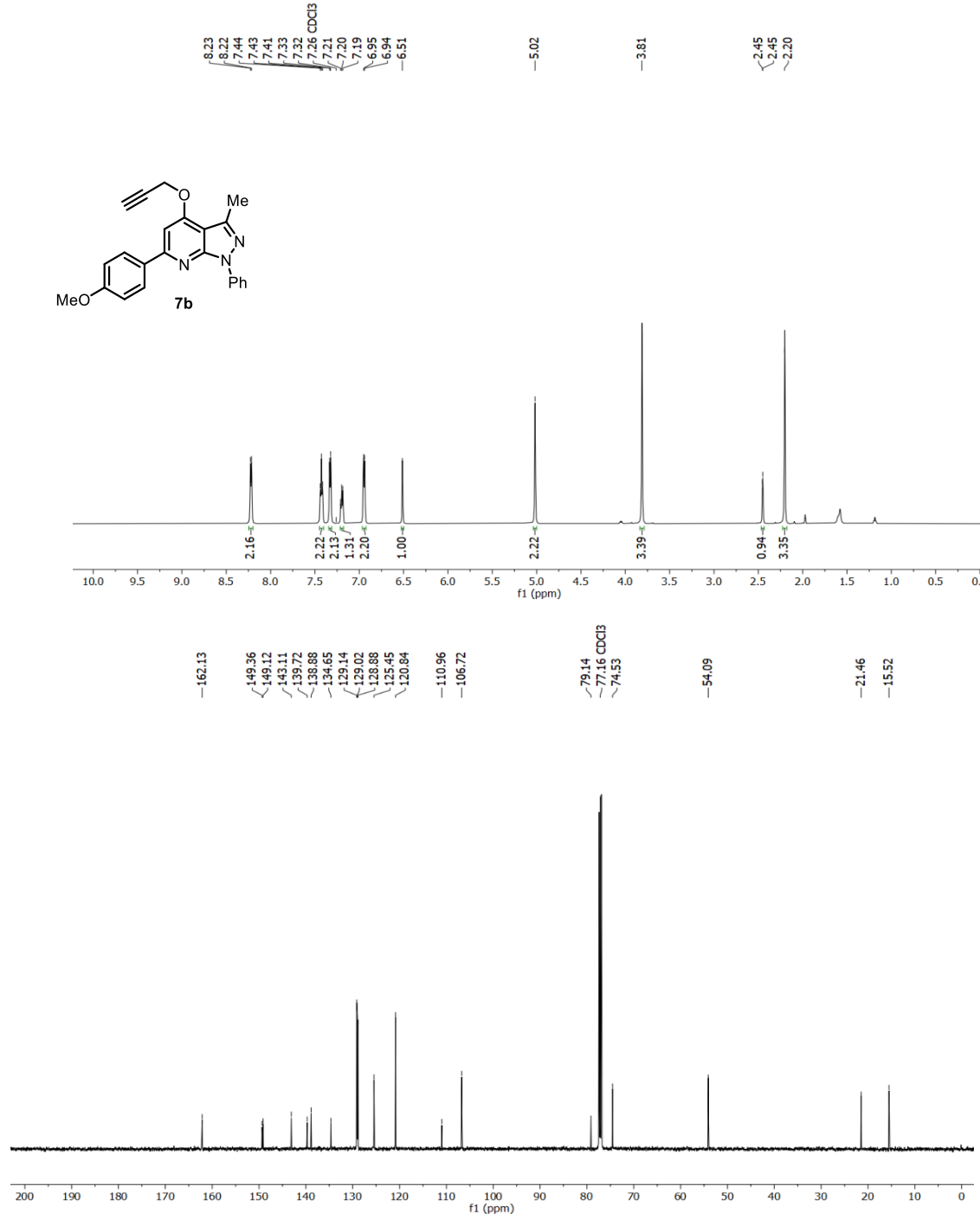


Figure 4.10 ^{1}H NMR and ^{13}C NMR spectra of compound 7a in $CDCl_3$

4.9 References

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