3CHAPTER 4
SYNTHESIS OF MANNICH BASE DERIVATIVES OF INDOLE

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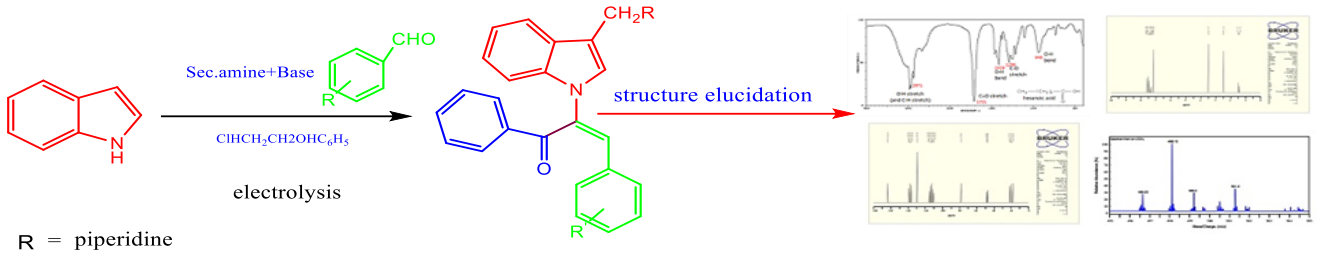
Graphical Abstract



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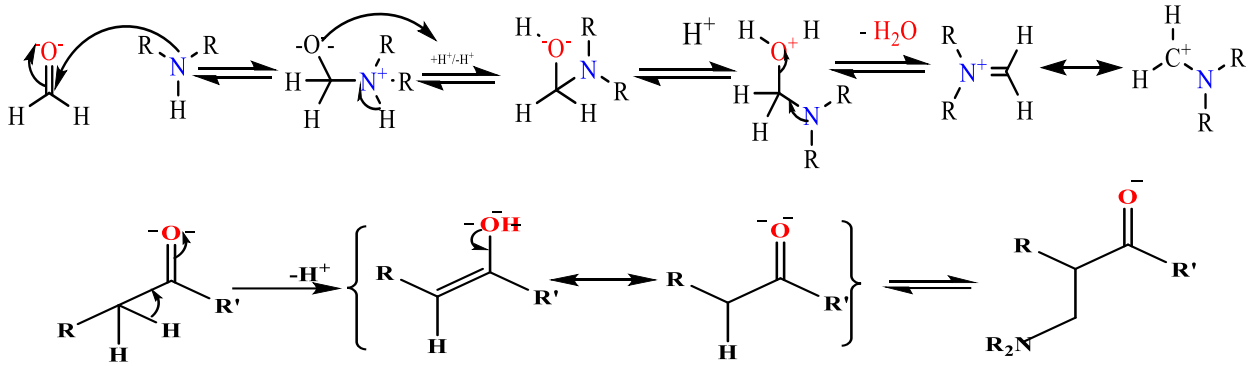
4.1 Introduction

The Mannich reaction is a highly versatile nucleophilic addition reaction that brings together a compound with active hydrogen(s), an amine (either primary or secondary), and formaldehyde (any aldehyde). Through this process, Mannich bases are created, which are beta-amino ketones with various substituents attached. This reaction allows for the preparation of a diverse range of compounds with unique and desirable properties. [1-2].

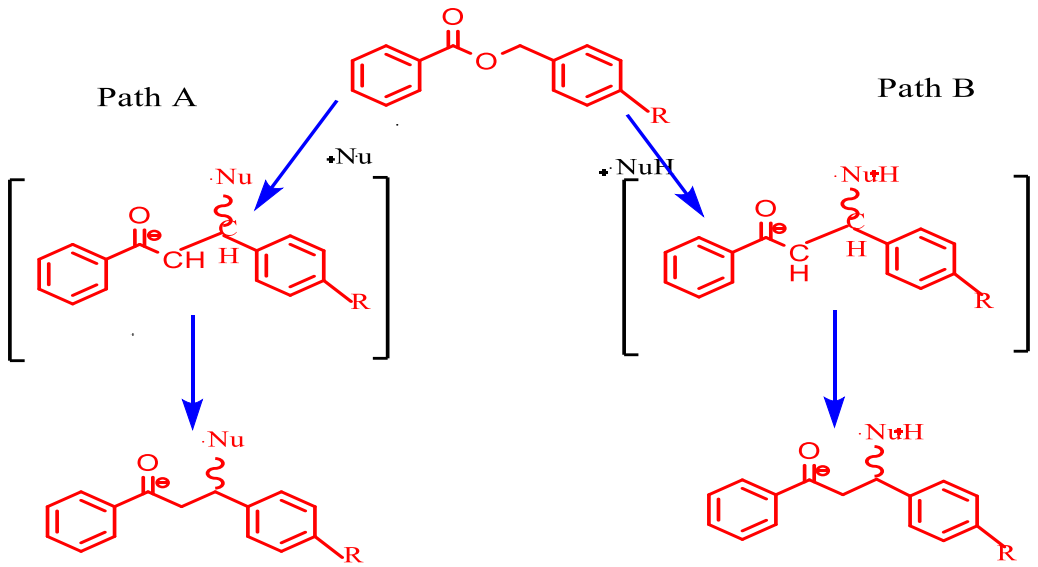
Mannich bases are commonly utilized in the production of polymer materials and the creation of diverse additives used in water treatment. By reacting a primary or secondary amine with a carbonyl compound and an aldehyde, a Mannich base is formed, resulting in an amino methylation product. This versatile compound is extensively used across industries, including materials science, agriculture, and pharmaceuticals, as well as playing a critical role in numerous organic syntheses. In addition, Mannich bases serve as valuable catalysts, chiral auxiliaries, and building blocks for the development of other useful compounds (Scheme 4.01). [3].

General reaction Mechanism of Mannich base



Chalcones, a distinctive type of compound, are abundant in nature, occurring in a variety of natural substances such as flavonoids, bioflavonoids, and anthocyanins. These compounds belong to the flavonoid group. By utilizing mannich bases of indoles and chloro-methyl ketone in the presence of a base, chalcones play an integral role in the synthesis of various classes of compounds. This process occurs under specific conditions [4].

Chalcones, a type of secondary metabolite found in both edible and medicinal plants, fall under the flavonoid family. These compounds, formally known as 1,3-diphenyl-2-propen-1-ones, consist of two aryl groups linked by an unsaturated carbonyl group in the α, β position [5]. These molecules feature a distinctive −C═O–CH═CH– ketoethylenic moiety and exhibit a delocalized π-electron arrangement within their aromatic rings. [6]. Chalcones, vibrant molecules that exude hues from golden yellow to warm orange, are predominantly composed of polyphenolic compounds. These powerful compounds possess a pivotal role in the pigmentation of select plant corollas. Interestingly, chalcones have been the subject of much fascination, thanks to their captivating properties that naturally occur in berries, herbs, teas, and even soy-based cuisine. Additionally, they can also be found in the form of plant allelochemicals, insect hormones, and pheromones, making them a truly fascinating and multifaceted presence in the natural world. [7]. Chalcones are in high demand for their versatile role in the production of heterocyclic compounds and their ability to undergo various chemical reactions. When aromatic aldehydes and aryl ketones are combined with precise amounts of condensing agents, a plethora of chalcone derivatives can be formed. [8]. The combination of aryl ketones and aromatic aldehydes, with the right condensing agents, can produce various chalcone derivatives. These chalcones are pivotal building blocks in the biosynthetic pathways for compounds such as aurones, isoflavonoids, and flavonoids. In recent years, the medicinal chemistry field has seen a surge of interest in the immense potential of chalcones, both naturally occurring and synthetic, due to their wide range of pharmacological properties. From antibacterial and anti-inflammatory to analgesic and anticholinergic, as well as antiplatelet, antiulcer, antioxidant, and antimalarial effects, chalcones have captivated researchers in the twenty-first century. [9]. (Scheme 4.02)



General mechanisms of the addition reaction of nucleophiles onto the activated double bonds of chalcones

One effective strategy for generating a diverse array of compounds involves using addition reactions of nucleophiles onto activated double bonds found in chalcones. These compounds possess significant biological and pharmacological potential, which can be modulated by introducing various functional groups through the reaction. By manipulating the properties of the nucleophile or adjusting the reaction conditions, one can transform the mechanism of the addition reaction and yield new and unique products. [10].

Extensive research has been conducted on the potential of chalcone derivatives as a versatile treatment for various afflictions. This is attributed to the presence of an α, β-unsaturated carbonyl group in their molecular makeup, which exhibits a unique ability to engage with nucleophiles such as thiols and amines in a Michael addition-like fashion, resulting in distinct pharmacological properties. [11].

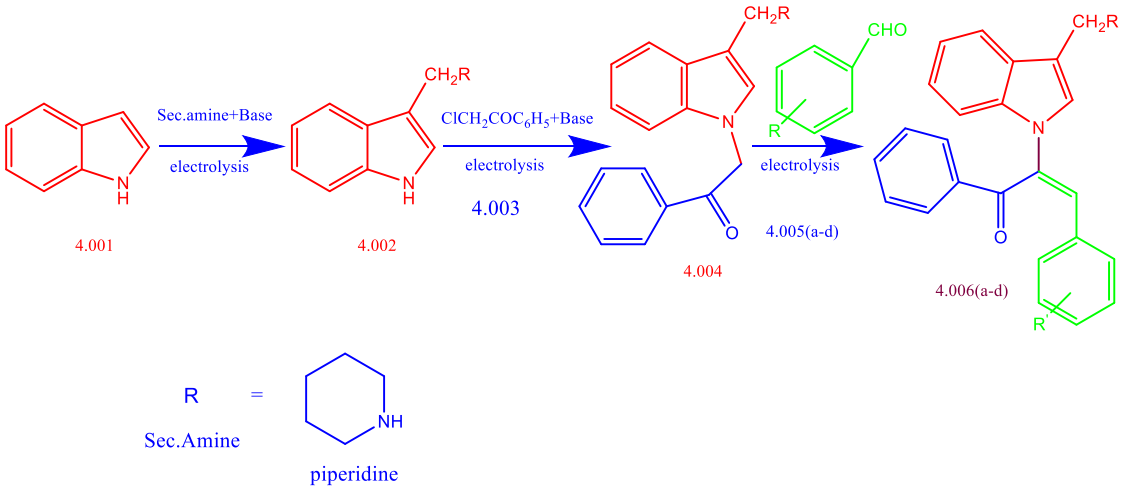
The Mannich base reaction is a highly effective method used in medicinal chemistry for producing new chemical compounds or enhancing the characteristics of potential drugs [12-14]. In addition to this, the use of heterocyclic intermediates also yields heterocyclic Mannich bases, which possess numerous advantageous qualities. Despite their potential, the majority of these compounds have been mainly studied in compassionate pharmaceuticals [15-18].

Present work

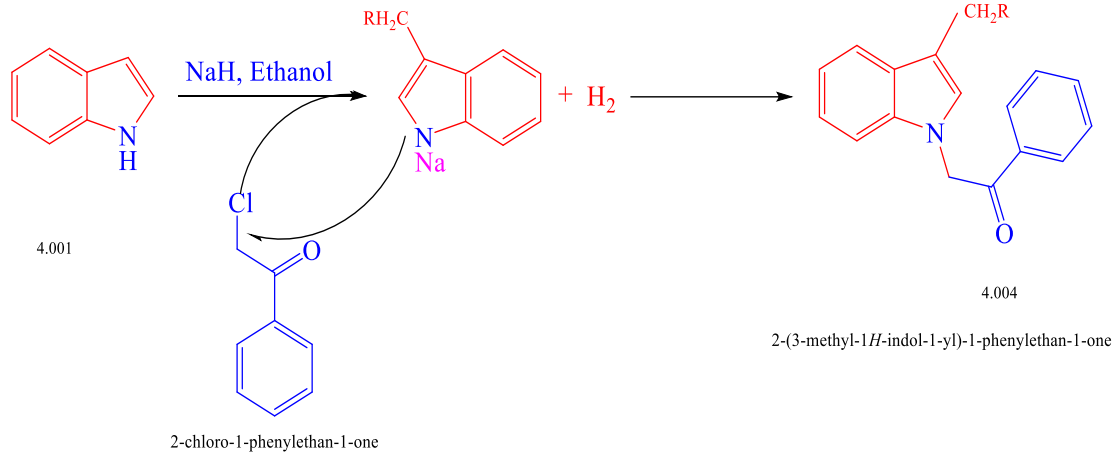
The indole nucleus, found within heterocyclic scaffolds, boasts captivating properties that make it a promising candidate for the creation of innovative synthetic medicines. The introduction of a formaldehyde and secondary amine mixture in a neutral and low-temperature setting leads to the substitution of nitrogen in indole. This reaction results in the formation of the indolyl anion, which exists in low equilibrium concentrations. However, at higher temperatures, the Mannich reaction takes place, producing a 3-substituted product with greater thermodynamic stability.It is well known fact that, electrochemical investigations are most suitable to study the redox properties of any chromatophores. Electrochemical investigations include, the study of mechanism of reaction occurring on the electrode solution interface.

In the present synthetic pathway, a mixture of indole and secondary amine were treated separately under electrochemical conditions of controlled pH and voltage, where glassy carbon electrode is working electrode, AgCl/Cl as reference electrode and Pt as counter electrode were employed, to give Mannich bases, compound 4.002. N-arylation of compound 4.002 with chloromethyl ketone in the presence of base under suitable electrochemical conditions phenyl-2-[-3-(substituted)-1-H-indole-1-yl] ethanone (compound **4.004)** was synthesized which, further react with different derivatives of Benzaldehyde 4.004(a-d) in the presence of ethanol produced desired Chalcones, 3-substituted-1-{(2E)-1-1phenyl-3-(3, 4, 5 trimethoxyphenyl) but-2-en-1-one)}indole **4.006 (a-d)** by Claisen – Schmidt condensation.

This is an environmentally friendly method to create fused indole derivatives containing active hydroxyls and carbonyl under mild reaction conditions.



Mechanism of formation of 4.004



Mechanism for the formation of 4.006(a-d)

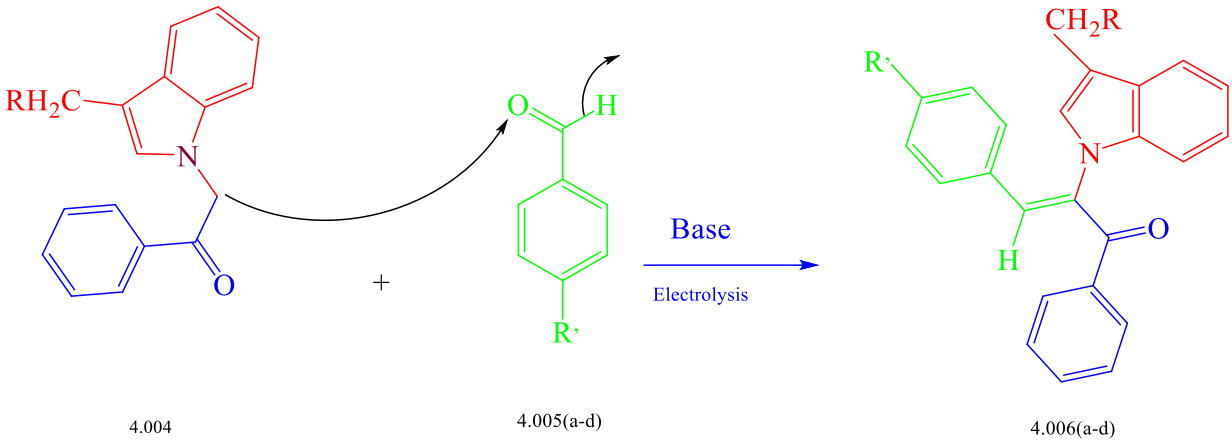
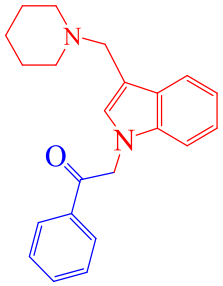


Table 4.1: Nature of R' in synthesized product

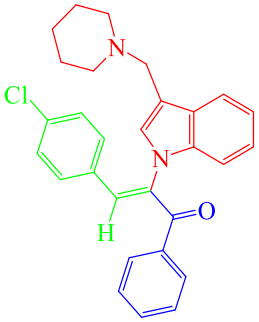
S. No.	Compound	R'
1	4.006a	Cl
2	4.006b	NO_2
3	4.006c	Br
4	4.006d	OCH_3

Structures of synthesized compounds in present experimental section



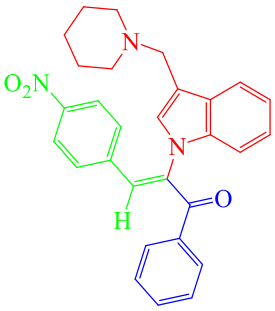
4.004

1-phenyl-2-(3-(piperidin-1-ylmethyl)-1*H*-indol-1-yl)ethan-1-one



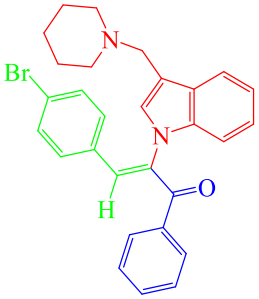
4.006a

(*Z*)-3-(4-chlorophenyl)-1-phenyl-2-(3-(piperidin-1-ylmethyl)-1*H*-indol-1-yl)prop-2-en-1-one



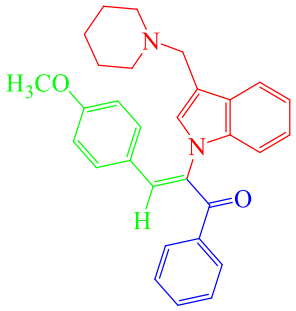
4.006b

(*Z*)-3-(4-nitrophenyl)-1-phenyl-2-(3-(piperidin-1-ylmethyl)-1*H*-indol-1-yl)prop-2-en-1-one



4.006c

(*Z*)-3-(4-bromophenyl)-1-phenyl-2-(3-(piperidin-1-ylmethyl)-1*H*-indol-1-yl)prop-2-en-1-one



4.006d

(*Z*)-3-(4-methoxyphenyl)-1-phenyl-2-(3-(piperidin-1-ylmethyl)-1*H*-indol-1-yl)prop-2-en-1-one

Table 4.2: Conditions used for the synthesis 2(1H-indol-1-yl)-1-phenyl ethanone with chloroacetophenone.

Indole (4.001)	3-(piperidine-1-ylmethy)-3H-indole 4.002	Chloroacetophenone (4.003)	Solvent	Base	Potential applied (In Volt)	Time Hrs	pH
0.2 M	0.1M	0.1 M	Ethanol	NaH	2.0	3.0	9

Table 4.3: Conditions used for the synthesis of *(2Z)-2-(1-H-indole-yl)-3-(4-subsituted)-1-phenylprop-2-en-1-one (4.006 a-d)* with 4-substituted benzaldehyde.

	2(1H-indol-1-yl)-1-phenyl ethanone (4.004)	4-substituted benzaldehyde (4.005) (a-d)	Solvent	Base	Potential applied (In Volt)	Time (Hrs.)	pH
1	0.1 M	0.2 M	Ethanol	NaH	2.5	3.0	8
2	0.1 M	0.1 M	Ethanol	NaH	2.5	3.0	9
3	0.1M	0.2 M	Ethanol	NaH	2.5	3.5	9
4	0.1 M	0.2 M	Ethanol	NaH	2.5	3.5	8

4.3: Experimental section

1. Melting points have been determined in open glass capillaries and are uncorrected.
2. The impurity of the compounds was checked by TLC on silica gel 'G' plates in solvents system hexane: ethyl acetate (9:1) as eluent. Iodine was used as visualizing agents.
3. IR spectra were recorded on PERKIN ELMER UATR range 600-4000cm^{-1}
4. ^{1}H NMR spectra were recorded on model NMR spectrometer (Bruker Avance II 400) using $CDCl_3$ as solvent and TMS as an internal reference. Chemical shifts are expressed in δ ppm
5. Mass spectra were recorded on XEVO-G2-S Q TOF in range of 10-700m/Z.
6. Before analysis, all the samples were dried for one hour under reduced pressure.
7. Physical and spectral data for all compounds are given in Table 4.4 and 4.5.
8. Chloroacetophenone (Merk) was used in the synthesis without further purification.

4.3.1: Experimental procedures for synthesis of 4.004 and 4.006(a-d)

1-phenyl-2-[1-H-indole-1-yl] ethanone (4.004)

In the Ethanol (50 ml), containing NaH, indole **4.001** (0.2 moles), secondary amine (piperidine) (1mole) we get compound 4.002, further chloroacetophenone **4.003** (0.1 mole) and was added. The mixture was subjected to electrolysis in the presence of TBAP as a supporting electrolyte at (2 V) for 3 hrs at pH 9 and then poured into ice cold water and allowed to remain for 24 hrs. Separated crystals were filtered and recrystalized from suitable solvent. (Yield 83%, M.P. 241).

(2Z)-2-(1-H-indole-yl)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (4.006a)

In (50 ml) Ethanol, 2-(1H-indol-1-yl)-1-phenyl ethenone **(4.004)** (2.10g, 0.1 mole) and p-chloro benzaldehyde **(4.005a)** (1.55g, 0.1 mole) was mixed. The mixture was subjected to electrolysis at (2.5 V) potential for 3.0 hrs using sodium hydroxide as base and TBAP as supporting electrolyte. Compound was crystallized by pouring the reaction mixture into ice cold water for 24 hrs. Separated crystals were filtered and recrystalized from suitable solvent. (Yield 76%, M.P. 310).

(2Z)-2-(1-H-indole-yl)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (4.006b)

In (50 ml) Ethanol, 2-(1H-indol-1-yl)-1-phenyl ethenone **(4.004)** (2.10g, 0.1 mole) and p-nitro benzaldehyde **(4.005b)** (3.02g, 0.1 mole) was mixed and the mixture was subjected to electrolysis at (2.5V) potential for 3 hrs using sodium hydroxide as base and TBAP as electrolyte. Compound was crystallized by pouring the reaction mixture into ice cold water for 24 hrs. Separated crystals were filtered and recrystalized from suitable solvent. (Yield 73%, M.P. 122).

(2Z)-2-(1-H-indole-yl)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one (4.006c)

In (50 ml) Ethanol, 2-(1H-indol-1-yl)-1-phenyl ethenone **(4.004)** (2.10, 0.1 mole) and p-bromo benzaldehyde **(4.005c)** (1.84g, 0.2 mole) was added. This mixture was subjected to electrolysis at (2.5 V) potential for 3.5hrs using sodium hydroxide as base and TBAP as electrolyte. Compound was crystallized by pouring the reaction mixture into ice cold water for 24 hrs. Separated crystals were filtered and recrystalized from suitable solvent. (Yield 69%, M.P. 265).

(Z)-2-(1-H-indole-yl)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (4.006d)

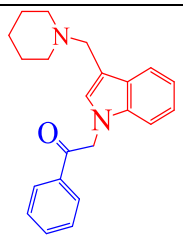
In (50 ml) Ethanol, 2-(1H-indol-1-yl)-1-phenyl ethenone **(4.004)** (2.10g, 0.1 mole) and p-methoxy benzaldehyde **(4.005d)** (2.72g, 0.010 mole) was mixed and mixture was subjected to electrolysis at (2.5 V) microwave power for 3.5hrs using sodium hydroxide as base and TBAP as electrolyte. Compound was crystallized by pouring the reaction mixture into ice cold water for 24 hrs. Separated crystals were filtered and recrystalized from suitable solvent. (Yield 77%, M.P. 121).

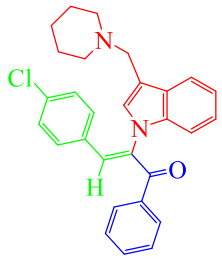
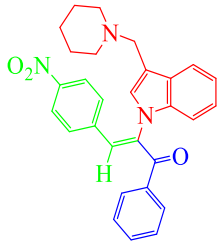
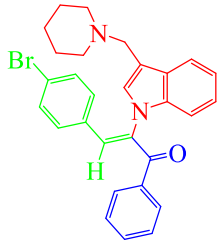
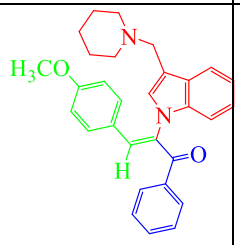
- **4.4: Characterization and structure elucidation of the compounds**

Table 4.4: Physical and Analytical data of the compounds 4.004 and 4.006(a-d) of present scheme 4.03

S. No.	Compound No.	Molecular formula	M.W.	M.P. (ºC)	Yield (%)
1.	4.004	$C_{22}H_{24}N_2O$	332.0	241	83
2	4.006a	$C_{29}H_{27}ClN_2O$	454.5	310	76
3	4.006b	$C_{29}H_{27}N_3O_3$	465.0	122	73
4	4.006c	$C_{29}H_{27}BrN_2O$	499.0	265	69
5	4.006d	$C_{30}H_{30}N_2O_2$	450.0	121	77

Table 4.5: Spectral data of select compounds 4.004-4.006(a-d)

S.No.	Comp.	IR (KBr) cm^{-1}	1H NMR $CDCl_3$ δ (ppm)	13C NMR $CDCl_3$ δ (ppm)	Mass (ESI) 784µs (Accumulation time) m/z
	 **4.004**	871.82-620.20(=C-Carom.),1078.01(C-O, str)1214.26 (C-N, str),1387.12(O-H, str),1475-1600(C=C str.),3537.33(N-H)	-----	-----	-----

2	 **4.006a**	654.50(C-C str),875.43(C-Cl),1221.47(C-O, str),1440.33 (C-H)1667.88 (C=N) 1780.74(C=O),3100-2670.11(C-H, str),3256.72(OH, str),3400.01N-H, str)	1.49-1.43(CH3),2.48(Ar-C-H),3.15(Cl-C-H),7.62-7.32(H-C=O),7.86-7.79(Ar-H),	26.10-23.99(R-CH_2),56.08(C-Cl),116.56-114.10(C=C),138.36-135.14(Ar-C),189.15(H-C=O)	454.18(100%), [M+1]at 456.12, 451.52[M-4.6] and 458.56[M+2.43]
3	 **4.006b**	701.11(C=C, bend),1341.56(N-O,str),1616.33(C=O, str),2853.53-2438.42(C-H),3401.60(N-H,str)	1.50-1.43(alkyl),2.46(CH_3-C=O),3.55(-C-N),7.83-7.96-7.58(Ar-H),	21.72-18.04(CH_3CO),48.42-47.48(CH_2),78.52(-C-Nstr),108.65-103.52(C=Cstr),157.42-136.36(Ar-C),163.63(C=O)	450.23(100%), [M+1] at 452.24, 447.32[M-4.92], and 448.92[M-3.32]
4	 **4.006c**	640.85(C-Br), 875.14-72024(C=C, bend),1013.36(C=O)1447.92(0-H, bend),2954.26-2431.90(C-H, str),3064.51(N-H,str.),3306.38(O-H,str)	2.12-2.10(Ar-CH_3),2.04-2.02(C=C),3.65-2.81(Ar-C=O),3.95(Br-C-H),6.15-6.05(C=C-H),7.60-7.40(Ar-H)	18.34-14.18(CH_2),53.44-47.12(C-C),76.64(C-Br),122.06-109.68(C=C),164.45(Ar-C)	[M+1] at 469.11, base peak at 465.21(100), fragment peaks at 461.28[M-7.83] and 462.48[M-6.63]
	 **4.006d**	698.80(C=C, str),832.67-720.39(C=C, bend),1377.87(CH_3bend),1449.20(C-C, bend),1559.76(N=O, str),305754-2856.80(C-H,str),3336.61(N-H,str),3651.42(O-H)	1.47-1.42(C-H,str),2.49(Ar-C-H),7.14(C=C),7.68-7.28(Ar-H)	21.31-18.79(CH_2, str),48.40-47.44(C-N),115.56-110.53(Ar-C),139.52-130.09(C=C, str),163.75(C=O)	501.30[M+1] base peak at 498.13(100%),496.63[M-4.67] and 499.20[M-2.1]

4.5 Explanation of spectral data for the elucidation of structure of compounds 4.004 and 4.006(a-d)

4.5.1 Infrared Spectra

In the compound ***1-phenyl-2-[1-H-indole-1-yl] ethanone (4.004)***, presence of C-N was confirmed by the peak at 1214 cm ^{1}, Sharp peaks at 1078 cm^{-1} showed the stretching for C=O bond. peaks at 2675-3332 $cm^{-1}$is due to C-H bond, peak at 3537 is due to N-H stretching are confirmed through FTIR spectra **4.01**.[19]

In the compound ***(2Z)-2-(1-H-indole-yl)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (4.006a)*** presence of peak at 875 cm^{-1} confirms C-Cl stretching, peak at 1667 cm^{-1} is showing C-N stretching, peak at 1780 cm^{-1} confirms the C=O stretching, peaks from 2670-3100 cm^{-1} are due to C-H bond, peak at 3400 cm^{-1} N-H stretching are confirmed through FTIR spectra **4.02**.[19].

In the compound ***(2Z)-2-(1-H-indole-yl)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (4.006b)*** presence of the peak at 680 cm^{-1} confirms C-N stretching, peak at 701 cm^{-1} is due C=C bending, peak of C=O shown at 1616 cm^{-1}peak from 2738-3064 cm^{-1} shows C-H bond stretching, peaks at 3401 cm^{-1} due to N-H stretching confirmed through FTIR spectra **4.03**. [20].

In the compound ***(2Z)-2-(1-H-indole-yl)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one (4.006c)*** presence peak present at 640 cm^{-1} confirms presence of C-Br bond, peak at 874 cm^{-1} is due to C=C bending, , peak at 1602 cm^{-1} is due to C=O, peak at 1593 cm^{-1} shows N-O stretching, peaks from 2531-2954 cm^{-1} are due to C-H stretching, peak at 3064 cm^{-1} confirm of bond N-H stretching confirmed through FTIR spectra **4.04.** [21].

In compound ***(Z)-2-(1-H-indole-yl)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (4.006d*)** presence of peak at 698 cm^{-1} is because of C=C stretching, peak at 832 cm^{-1} is due to O-CH stretching, peak at 1377 cm^{-1} shows presence of CH_3, 1559 cm^{-1} shows C=O stretching, peaks from 2856-3054 cm^{-1} are due to C-H stretching, peaks at 3336 shows N-H stretching Confirmed through FTIR spectra **4.05.** [22].

4.5.2 NMR Spectra

4.5.2.1 ^{1}H NMR spectra:

In the ^{1}H NMR spectra of ***(2Z)-2-(1-H-indole-yl)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (4.006 a)***, there was one peak at δ 8.05 for only one proton of pyridine ring, which was adjacent to nitrogen atom and other one was at δ 7.86-7.79 for another proton of pyridine ring. Next, for 6 protons, a multiplet at δ 7.32-7.62 was shown in the spectra, in which there was a doublet for one proton of pyrazole ring, which was adjacent to nitrogen atom and rest peaks were for four protons of the benzene ring attached to it. An attachment of one benzene ring from the nitrogen atom of indole moiety was confirmed by the peak at δ 7.18. there was one more single peak at δ H-C-Cl protons, one doublet was at δ 1.43-1.49 for the remaining proton of benzene are confirmed through ^{1}H NMR spectra 4.06.[23]

According to ^{1}H NMR spectra of ***(2Z)-2-(1-H-indole-yl)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (4.006b***) the structure was differentiated from other derivatives by a singlet which was present at δ 2.81, which was for three protons of CH_3 group attached to the phenyl group. There were one multiplet at at δ 7.58-7.83 for only proton of pyridine ring, which was adjacent to nitrogen atom and single peak at δ 7.05 for another proton of pyridine ring. There was a peak at δ 3.55 is due to nitrogen bond attached to benzene ring. Single peak at δ 2.46 is for carbonyl and lastly a doublet at δ 1.43-1.50 is due to alkyl group So, protons in the spectrum confirmed through ^{1}H NMR spectra 4.08.[23]

In ^{1}H NMR spectra of ***(2Z)-2-(1-H-indole-yl)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one (4.006c)***, there was a singlet at δ 3.95 for three protons of Br group attached to the phenyl ring. A downfield peak at δ 7.90 was there for one proton of the pyridine ring, which was adjacent to nitrogen atom. Next, there was triplet at δ 7.57-7.95 for two protons, in which there was a doublet for one proton of pyrazole ring, which was adjacent to nitrogen atom, and one was for the proton of pyridine ring. An attachment of phenyl ring to the nitrogen atom of indole ring was established by the doublet for protons at δ 6.05-6.15. This proton confirmed through ^{1}H NMR spectra 4.10.[24].

According to ^{1}H NMR spectra of ***(Z)-2-(1-H-indole-yl)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (4.006d*)**, there was a singlet at δ 3.50 for three protons of COOMe group attached to the phenyl ring. There was a multiplet at δ 7.42-7.68 for proton of pyridine ring, which was adjacent to nitrogen atom. In the range of δ 7.28-7.38, there was a multiplet shown protons, in which there was a doublet for one proton of pyrazole ring, which was adjacent to nitrogen atom and rest peaks were for two protons of the phenyl ring. Similarly, in the range of δ 6.76-7.19, there was also a single peak at δ 7.14 one proton of pyridine ring. Then we have a single peak at δ 2.49 for remaining protons of phenyl ring. At last, for four protons of benzene ring and one remaining proton of pyridine ring, there were doublet at δ 1.42-1.47 for two and three protons, respectively Confirmed through the ^{1}H NMR spectra 4.12.[25].

4.5.2.2.^{13}C NMR spectra

In ^{13}C NMR spectra of ***(2Z)-2-(1-H-indole-yl)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (4.006 a)*** there is single peak at δ 189.15 was for one carbon of ketone, triplet peaks at δ 135.14-138.36 are for carbons of the Ar-C=C bond, there is a single peak at δ 124.05 is for carbon of heteroaromatic group, then there are peaks from δ 114.10-116.56 for carbon of nitrile bond, we have single peak at δ 56.08 for carbon of chloride C-Cl, then there is a doublet at δ 23.99-26.10 for carbon of C-Ar. All these confirmed through ^{13}C NMR spectra 4.07.[23]

In ^{13}C NMR spectra of ***(2Z)-2-(1-H-indole-yl)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (4.006b***) there is one single peak at δ 163.63 for carbon of ketone, we have single peak at δ 157.42 is for carbon of amide group, there is a triplet of range δ 136.36-139.54 is for carbon of heteroaromatic C=C, there is a single peak at δ 130.10 is for C-CH_2 bond, we have a multiplate at range of δ 103.52-108.65 are for carbons of alkene, there is single peak at δ 78.52 is for carbon attached with nitro C-NO_2, there is a doublet at δ 47.48-48.52 for carbon of C-C=O bond, also there was one triplet at δ 18.04 to 21.32 for alkane C bond confirmed through ^{13}C NMR spectra 4.09.[23].

In ^{13}C NMR spectra of ***(2Z)-2-(1-H-indole-yl)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one (4.006c)***, there was doublet peak at δ 164.45-167.01 for carbon of ketone, there was single peak at δ 128.49 for heteroaromatic carbons, we have multiplate of range from δ 116.43-122.06 for nitrile group, there is single peak at δ 53.44 for C-O, there is single peak at δ 47.12 for carbon attached to bromide C-Br bond, and there are triplet peak from δ 14.18 to 18.34 for C-Ar, confirmed through ^{13}C NMR spectra 4.11.[24].

In ^{13}C NMR spectra of ***(Z)-2-(1-H-indole-yl)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (4.006d*)** there is single peak at δ 163.75 for carbon of ketone, there is a triplet from δ 136.29-139.52 for heteroaromatic carbons, we have multiplate peak range from δ 110.53-115.56 is for nitrile group, there is a single peak at δ 78.43 for C-OR bond, there is a doublet at δ 47.44-48.40 is for

OCH_3, also a triplet peaks at δ 18.79-21.31 are for CH_2, confirmed through ^{13}C NMR spectra 4.13.[25].

4.5.2.3 Mass Spectrum

4.14. The spectrum shows chemical compound is **4.006a** mass spectrum. The molecular ion, which is indicative of the compound's molecular mass, is responsible for the parent peak at about 454.18 m/z[M-1.94]. Other peaks emerge from the molecular ion's fragmentation, revealing structural information like the peak at 456.12 m/z molecular ion peak that corresponds to peak at 451.52 m/z[M-4.6] + because of hydrogen loss, another peak at [M+2.43].[24]

4.15 The molecular ion is represented by the peak at m/z 452.24 in this mass spectrum. Base peak is present at m/z 450.23, Additional peaks are produced by fragmentation, including the important peak at 447.32 m/z signal that indicates the [M-4.92] + fragment ion and fragment ion peak at 448.92m/z [M-3.32] because of hydrogen loss. These fragment ions shed light on the structure of the compound **4.006b**.[24].

4.16 The spectrum shows the compound **4.006c** mass spectrum. The molecular ion, which is essential for estimating the compound's molecular mass, is shown by the peak at 469.11 m/z. and base peak at 465.21m/z [M-3.9], Fragmentation produces peaks like 461.28 m/z ([M-7.83] and 462.48m/z[M-6.63], which denotes hydrogen loss and aids in structural comprehension.[26]

4.17 The substance, OCH_3 is the subject of this mass spectrum. The base peak is shown by the prominent signal at 498.13 m/z. Molecular ion peak is present at 501.30m/z. Peaks are produced by fragmentation, with the peak at 496.63 m/z ([M-4.67] and 499.20m/z[M-2.1] signifying hydrogen loss and the peak at 494.13 m/z signifying [M-OCH_3] + from methoxy group loss. The total data is used to calculate the molecular mass and structure of the compound **4.006d**.[26].

FTIR Spectra of synthesized compounds 1-phenyl-2-[1-H-indole-1-yl] ethanone (4.004) and (2Z)-2-(1-H-indole-yl)-3-(4-subsituted)-1-phenylprop-2-en-1-one (4.006 a-d)

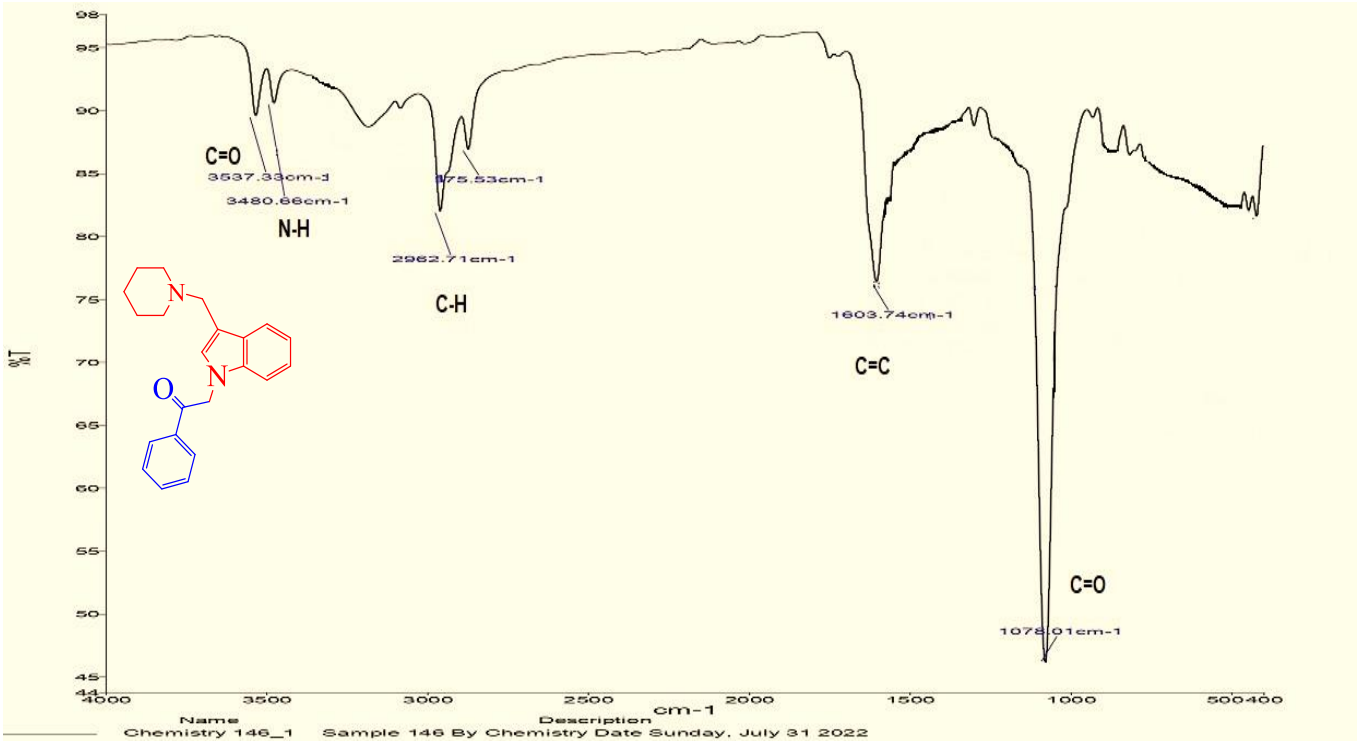


Figure 4.01 FTIR Spectra of 1-phenyl-2-[1-H-indole-1-yl] ethanone (4.004)

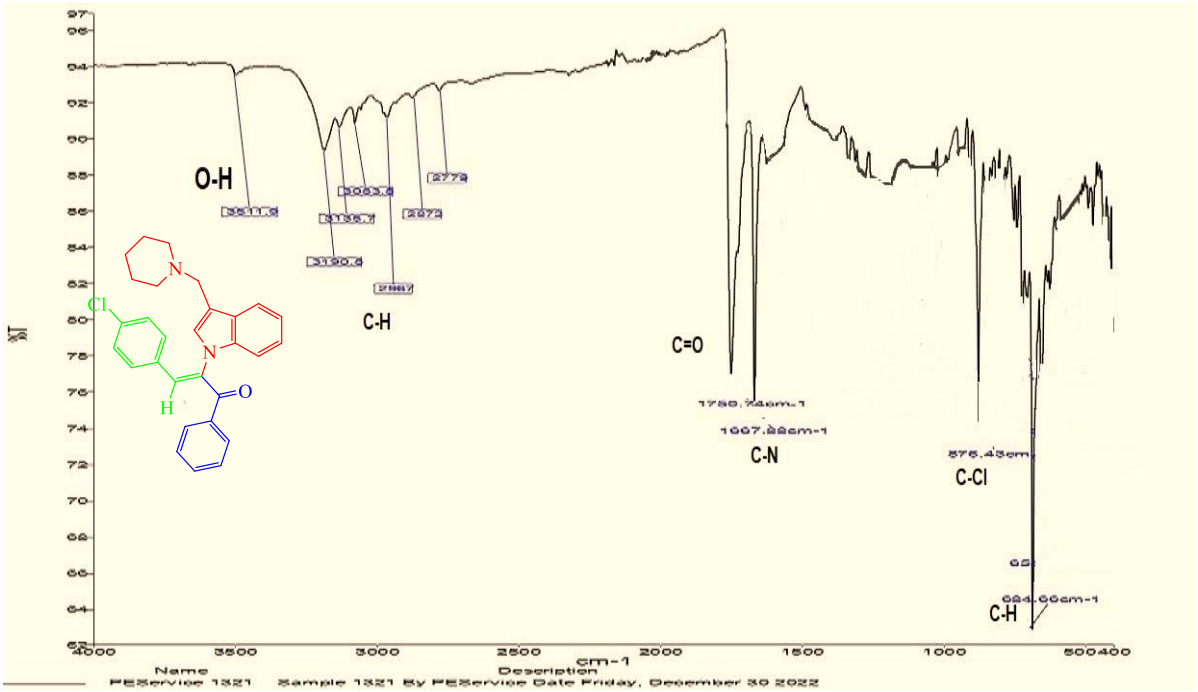


Figure 4.02 FTIR of (2Z)-2-(1-H-indole-yl)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (4.006a)

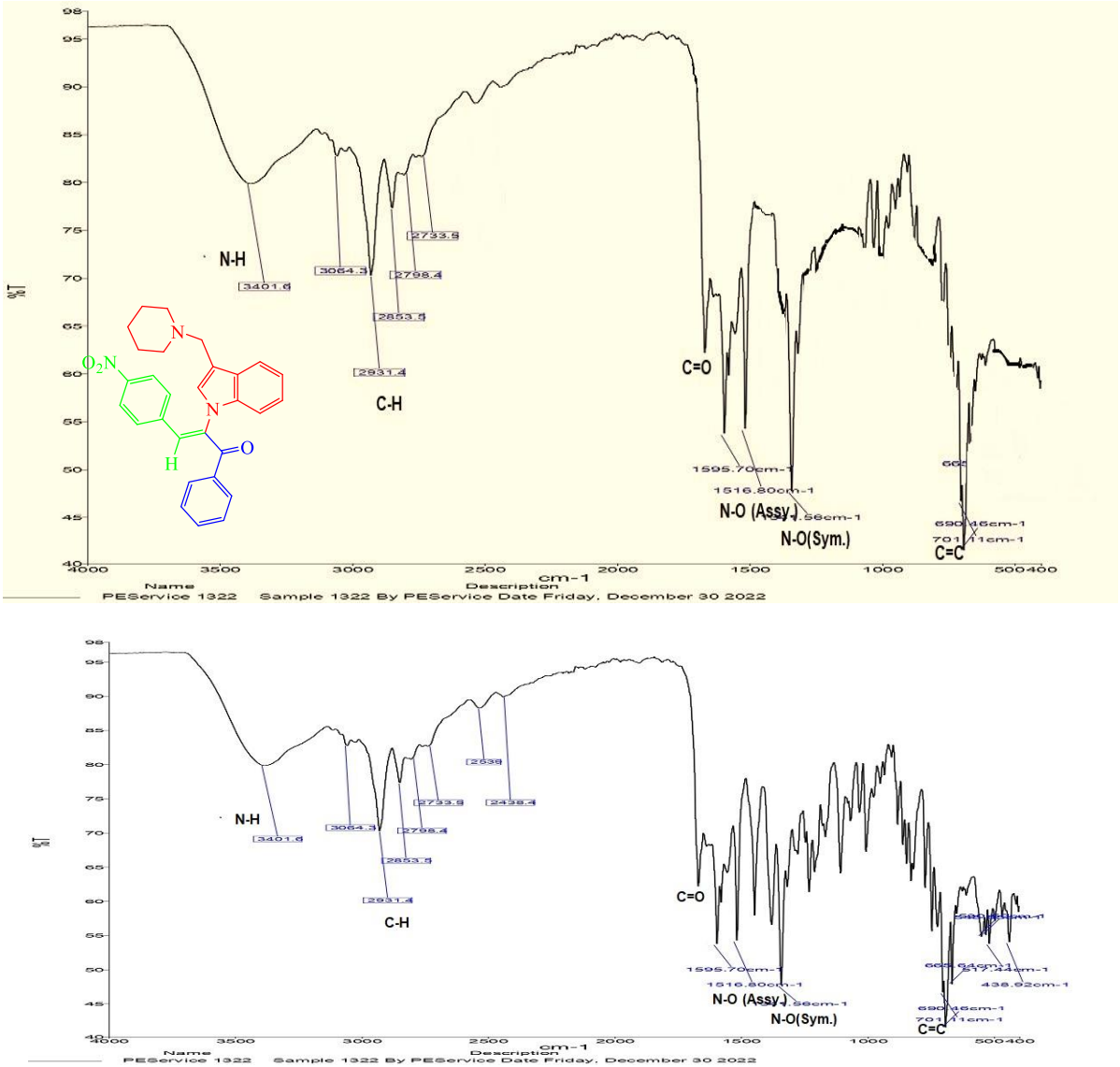


Figure 4.03 FTIR of (2Z)-2-(1-H-indole-yl)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (4.006b)

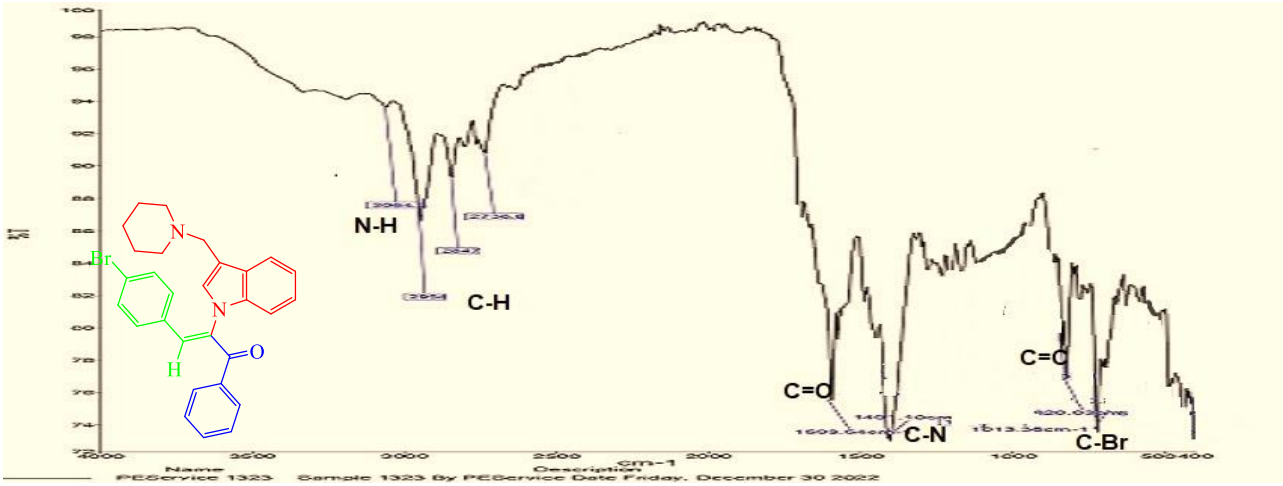


Figure 4.04 FTIR of (2Z)-2-(1-H-indole-yl)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one 4.006c

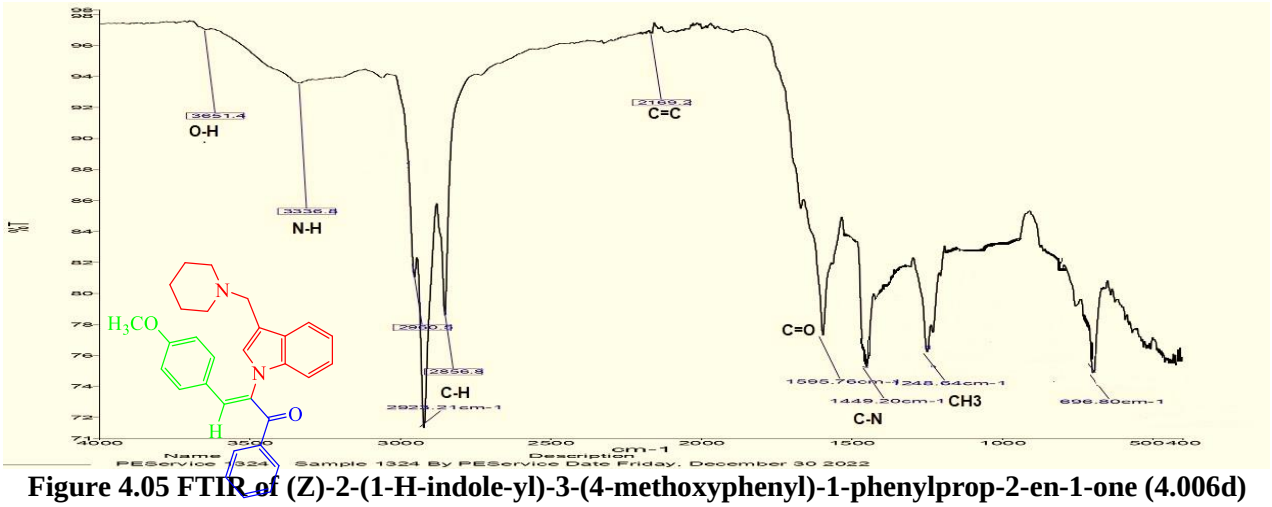


Figure 4.05 FTIR of (Z)-2-(1-H-indole-yl)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (4.006d)

^{1}H and ^{13}C Spectra of synthesized compounds (2Z)-2-(1-H-indole-yl)-3-(4-subsituted)-1-phenylprop-2-en-1-one (4.006 a-d)

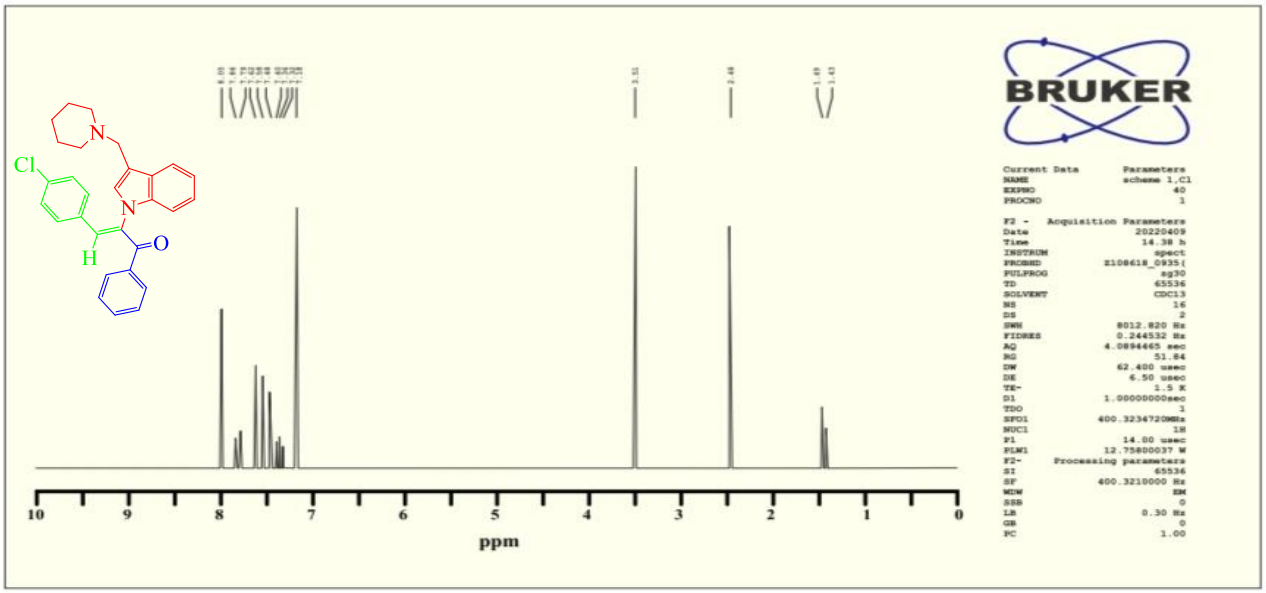


Figure 4.06 ^{1}H NMR of (2Z)-2-(1-H-indole-yl)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one 4.006a

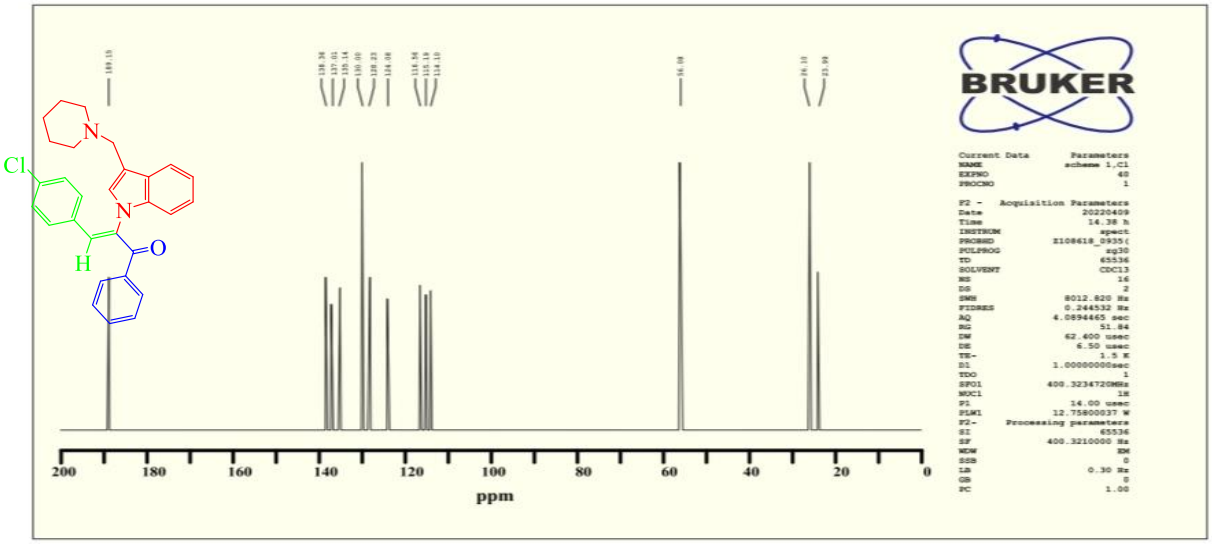


Figure 4.07 ^{13}C NMR of (2Z)-2-(1-H-indole-yl)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (4.006a)

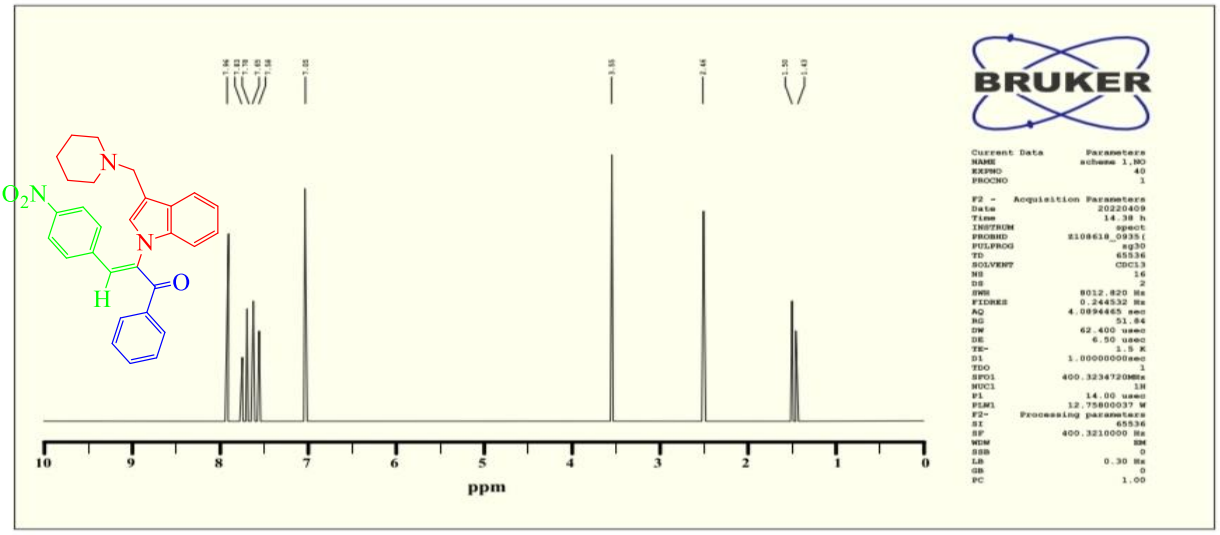


Figure 4.08 ^{1}H NMR of (2Z)-2-(1-H-indole-yl)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (4.006b)

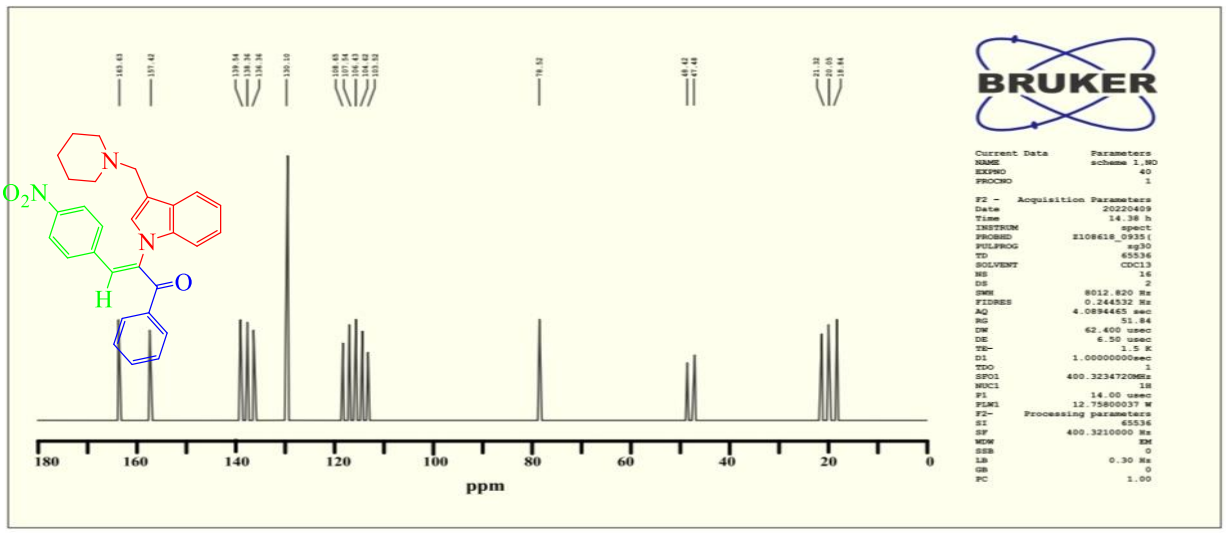


Figure 4.09 ^{13}C NMR of (2Z)-2-(1-H-indole-yl)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (4.006b)

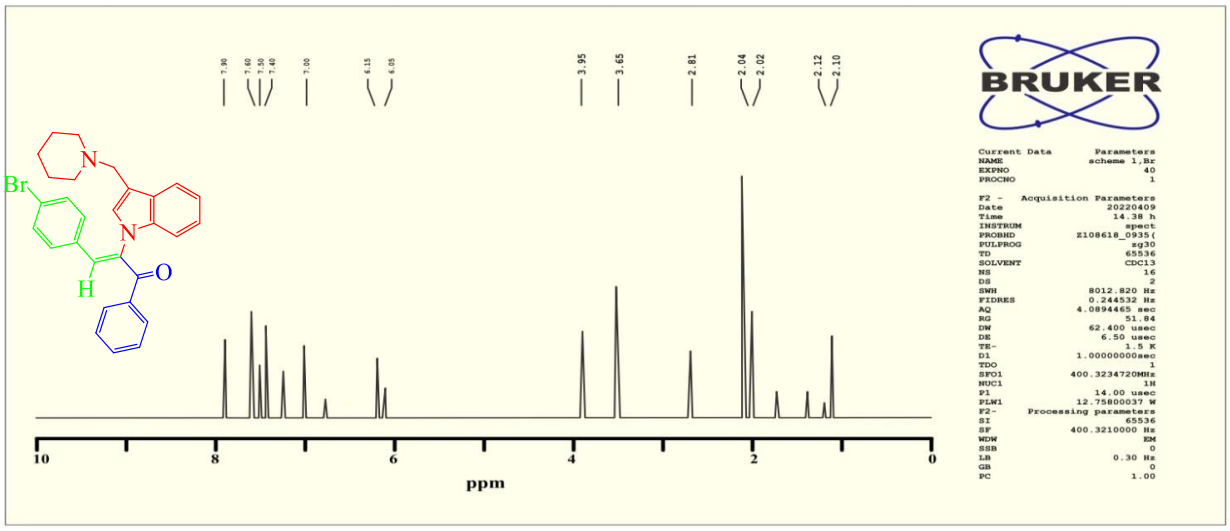


Figure 4.10 ^{1}H NMR of (2Z)-2-(1-H-indole-yl)-3-(4-bromophenyl)-1-phenylprop-2-en- 1-one (4.006c)

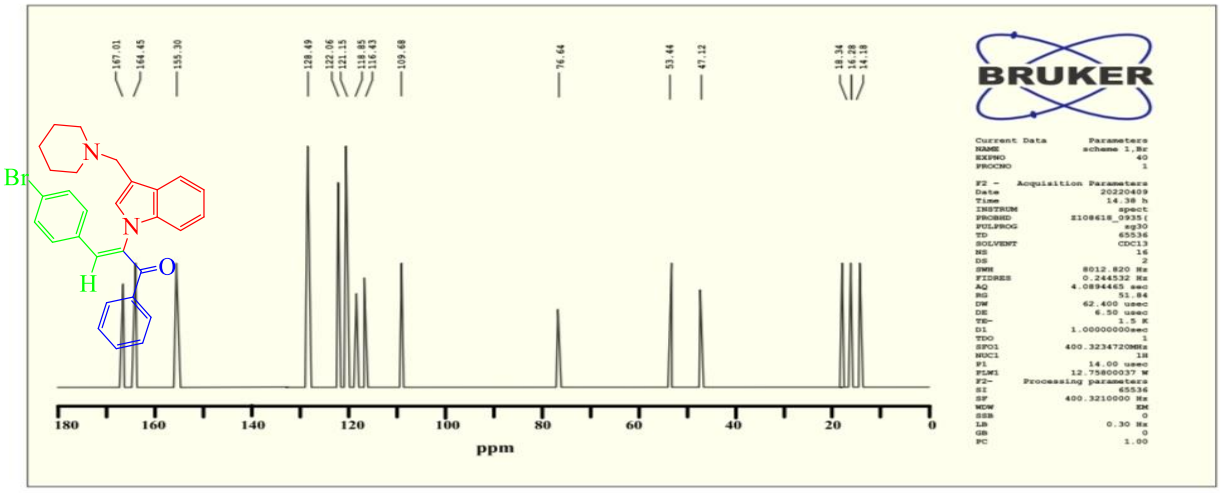


Figure 4.11 ^{13}C NMR of (2Z)-2-(1-H-indole-yl)-3-(4-bromophenyl)-1-phenylprop-2-en- 1-one (4.006c)

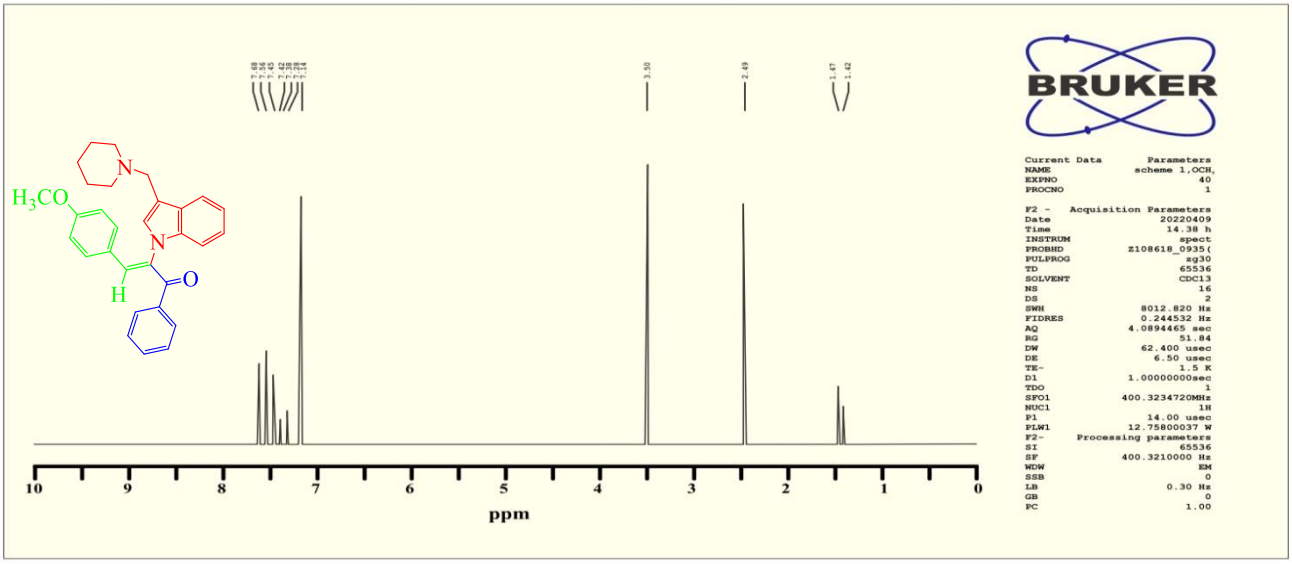


Figure 4.12 ^{1}H NMR of (Z)-2-(1-H-indole-yl)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (4.006d)

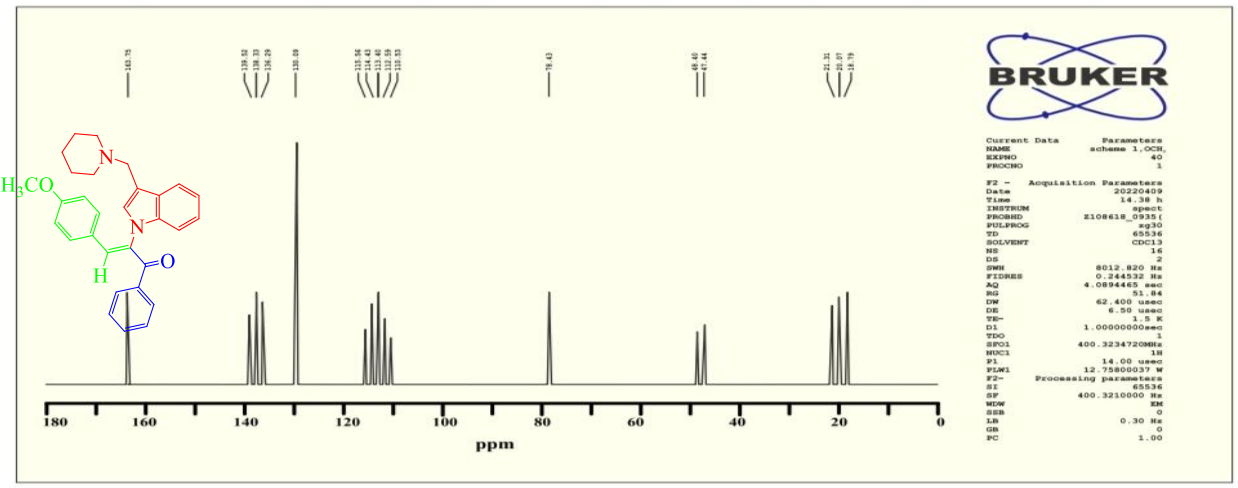


Figure 4.13 ^{13}C NMR of (Z)-2-(1-H-indole-yl)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (4.006d)

Mass Spectra of synthesized compounds (2Z)-2-(1-H-indole-yl)-3-(4-subsituted)-1-phenylprop-2-en-1-one (4.006 a-d)

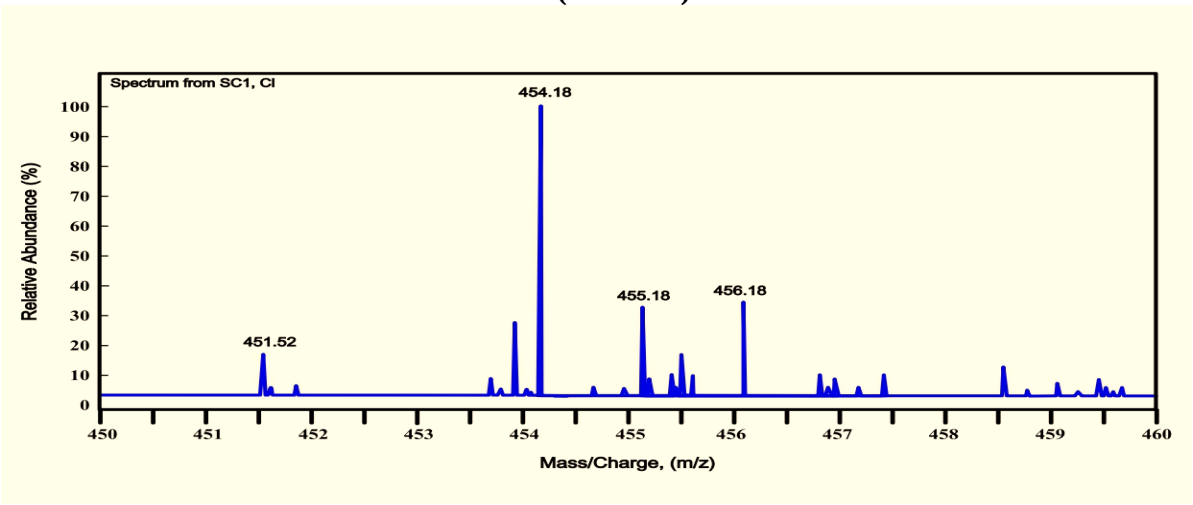


Figure 4.14 MASS Spectra of (2Z)-2-(1-H-indole-yl)-3-(4-chlorophenyl)-1-phenylprop- 2-en-1-one (4.006a)

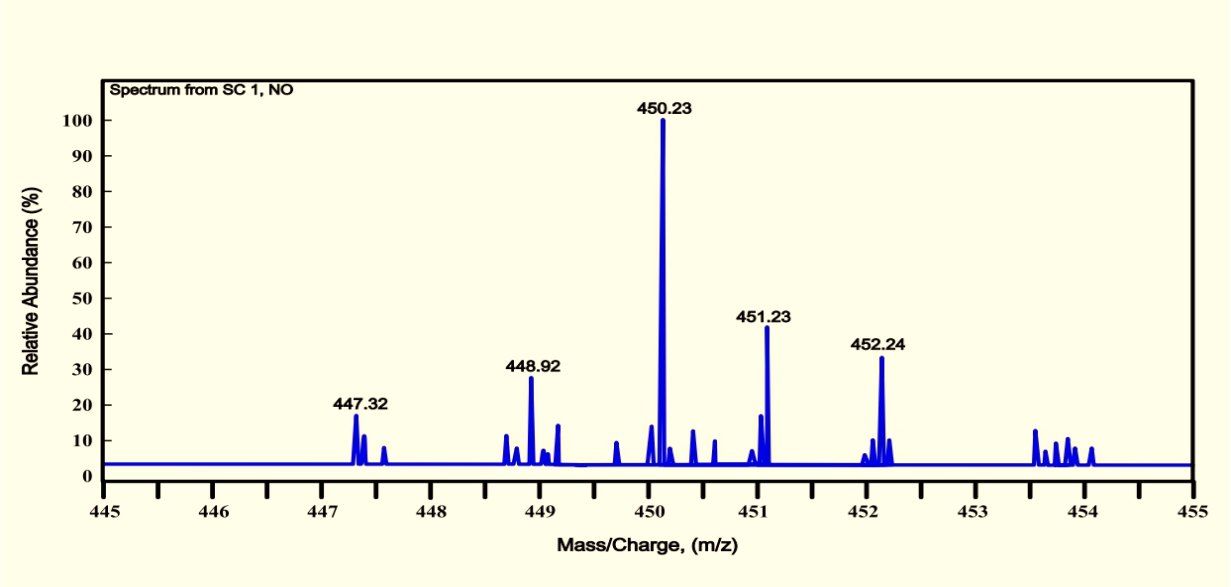


Figure 4.15 MASS Spectra of (2Z)-2-(1-H-indole-yl)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (4.006b)

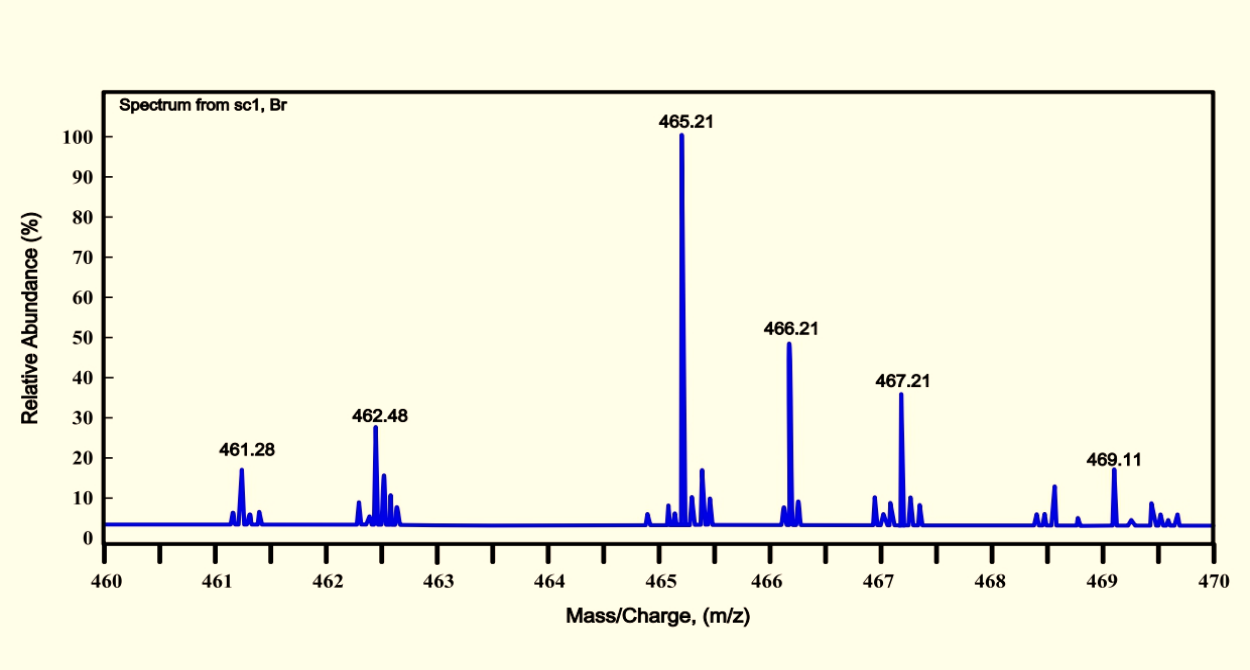


Figure 4.16 MASS Spectra of (2Z)-2-(1-H-indole-yl)-3-(4-bromophenyl)-1-phenylprop-2-en- 1-one (4.006c)

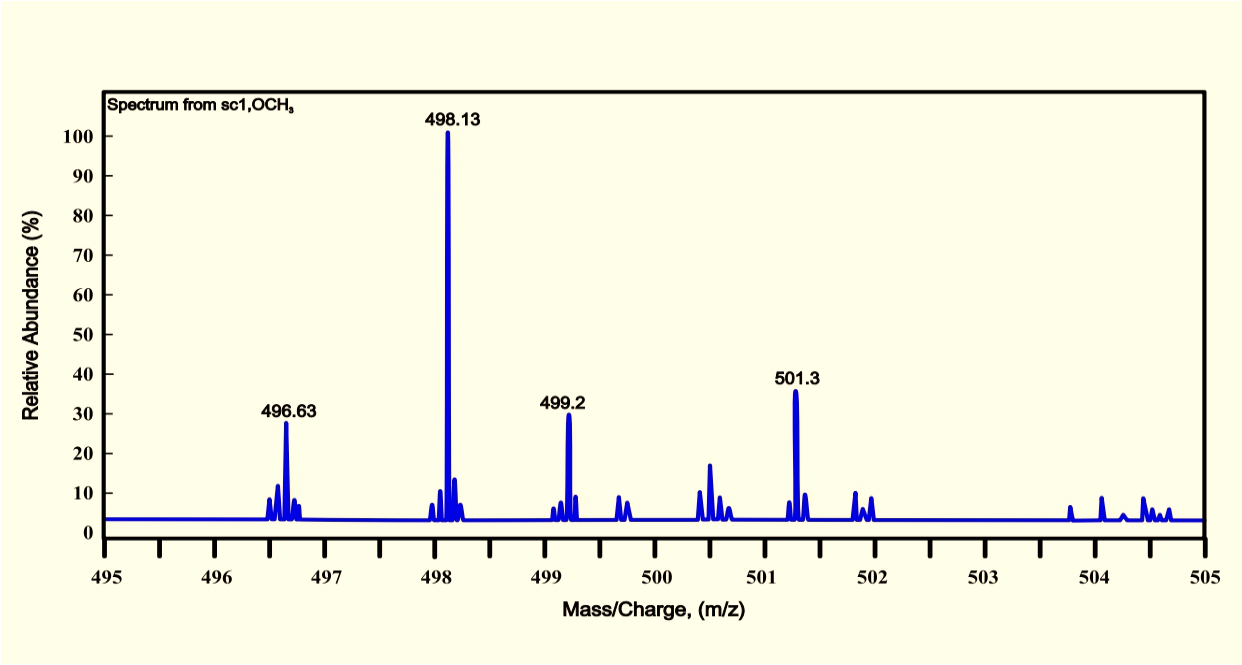


Figure 4.17 MASS Spectra of (Z)-2-(1-H-indole-yl)-3-(4-methoxyphenyl)-1-phenylprop-2- en-1-one (4.006d)

4.6 Electrokinetic study of synthesised compounds 4.004 and 4.006(a-d)

4.6.1 Electrokinetic Study for synthesis of 2(1H-indol-1-yl)-1-phenyl (4.004)

4.6.1.1 Effect of time in the synthesis of compound 4.004

Indole (4.001)	3-(piperidine-1-ylmethy)-3H-indole (4.002)	Chloroacetophenone (4.003)	Solvent	Potential applied (In Volt)	Time (Hrs)	pH	Yield of compound 4.004 (%)
0.2 M	0.1M	0.1 M	Ethanol	2.0	2.5	9	55
0.2 M	0.1M	0.1 M	Ethanol	2.0	3.0	9	83
0.2 M	0.1M	0.1 M	Ethanol	2.0	3.5	9	83
0.2 M	0.1M	0.1 M	Ethanol	2.0	4.0	9	83

4.6.1.2. Effect of pH in the synthesis of compound 4.004

Indole (4.001)	3-(piperidine-1-ylmethy)-3H-indole (4.002)	Chloroacetophenone (4.003)	Solvent	Potential applied (In Volt)	Time (Hrs)	pH	Yield of compound 4.004 (%)
0.2 M	0.1M	0.1 M	Ethanol	2.0	3.0	7	-
0.2 M	0.1M	0.1 M	Ethanol	2.0	3.0	8	58
0.2 M	0.1M	0.1 M	Ethanol	2.0	3.0	9	83
0.2 M	0.1M	0.1 M	Ethanol	2.0	3.0	10	83

4.6.1.3 Effect of applied potential in the synthesis of compound 4.004

Indole (4.001)	3-(piperidine-1-ylmethy)-3H-indole (4.002)	Chloroacetophenone (4.003)	Solvent	Potential applied (In Volt)	Time (Hrs)	pH	Yield of compound 4.004 (%)
0.2 M	0.1M	0.1 M	Ethanol	0.5	3.0	9	No response
0.2 M	0.1M	0.1 M	Ethanol	1.5	3.0	9	62
0.2 M	0.1M	0.1 M	Ethanol	2.0	3.0	9	83
0.2 M	0.1M	0.1 M	Ethanol	2.5	3.0	9	82.5

4.6.2 Electrokinetic study of *(2Z)-2-(1-H-indole-yl)-3-(4-subsituted)-1-phenylprop-2-en-1-one (4.006 a-d)*

4.6.2.1* Electrokinetic study of *(2Z)-2-(1-H-indole-yl)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (4.006 a)

4.6.2.1.1 Effect of time in the synthesis of compound 4.006 a

2(1H-indol-1-yl)-1-phenyl ethanone (4.004)	4-substituted benzaldehyde (4.005 a)	Solvent	Potential applied (In Volt)	Time (Hrs.)	pH	Yield of compound (4.006 a) (%)
0.1 M	0.2 M	Ethanol	2.5	2.0	8	51
0.1 M	0.2 M	Ethanol	2.5	2.5	8	63
0.1M	0.2 M	Ethanol	2.5	3.0	8	76
0.1 M	0.2 M	Ethanol	2.5	3.5	8	76

4.6.2.1.2 Effect of pH in the synthesis of compound 4.006 a

2(1H-indol-1-yl)-1-phenyl ethanone (4.004)	4-substituted benzaldehyde (4.005 a)	Solvent	Potential applied (In Volt)	Time (Hrs.)	pH	Yield of compound (4.006 a) (%)
0.1 M	0.2 M	Ethanol	2.5	3.0	7	48
0.1 M	0.2 M	Ethanol	2.5	3.0	8	76
0.1M	0.2 M	Ethanol	2.5	3.0	9	72
0.1 M	0.2 M	Ethanol	2.5	3.0	10	70

4.6.2.1.3 Effect of applied potential in the synthesis of compound 4.006 a

2(1H-indol-1-yl)-1-phenyl ethanone (4.004)	4-substituted benzaldehyde (4.005 a)	Solvent	Potential applied (In Volt)	Time (Hrs.)	pH	Yield of compound (4.006 a) (%)
0.1 M	0.2 M	Ethanol	1.5	3.0	8	No response
0.1 M	0.2 M	Ethanol	2.0	3.0	8	61
0.1M	0.2 M	Ethanol	2.5	3.0	8	76
0.1 M	0.2 M	Ethanol	3.0	3.0	8	76

4.6.2.2 Electrokinetic study of *(2Z)-2-(1-H-indole-yl)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (4.006 b)*

4.6.2.2.1 Effect of time in the synthesis of compound 4.006 b

2(1H-indol-1-yl)-1-phenyl ethanone (4.004)	4-substituted benzaldehyde (4.005 b)	Solvent	Potential applied (In Volt)	Time (Hrs.)	pH	Yield of compound (4.006 b) (%)
0.1 M	0.2 M	Ethanol	2.5	2.0	9	59
0.1 M	0.2 M	Ethanol	2.5	2.5	9	66
0.1M	0.2 M	Ethanol	2.5	3.0	9	73
0.1 M	0.2 M	Ethanol	2.5	3.5	9	73

4.6.2.2.2 Effect of pH in the synthesis of compound 4.006 b

2(1H-indol-1-yl)-1-phenyl ethanone (4.004)	4-substituted benzaldehyde (4.005 b)	Solvent	Potential applied (In Volt)	Time (Hrs.)	pH	Yield (%)
0.1 M	0.2 M	Ethanol	2.5	3.0	7	-
0.1 M	0.2 M	Ethanol	2.5	3.0	8	54
0.1M	0.2 M	Ethanol	2.5	3.0	9	73
0.1 M	0.2 M	Ethanol	2.5	3.0	10	73

4.6.2.2.3 Effect of applied potential in the synthesis of compound 4.006 b

2(1H-indol-1-yl)-1-phenyl ethanone (4.004)	4-substituted benzaldehyde (4.005 b)	Solvent	Potential applied (In Volt)	Time (Hrs.)	pH	Yield (%)
0.1 M	0.2 M	Ethanol	0.5	3.0	9	-
0.1 M	0.2 M	Ethanol	1.5	3.0	9	60
0.1M	0.2 M	Ethanol	2.5	3.0	9	73
0.1 M	0.2 M	Ethanol	3.0	3.0	9	73

4.6.2.3 Electrokinetic study of *(2Z)-2-(1-H-indole-yl)-3-(4-bromophenyl)-1-phenylprop-2-en-1-one (4.006c)*

4.6.2.3.1 Effect of time in the in the synthesis of compound 4.006 c

2(1H-indol-1-yl)-1-phenyl ethanone (4.004)	4-substituted benzaldehyde (4.005 b)	Solvent	Potential applied (In Volt)	Time (Hrs.)	pH	Yield (%)
0.1 M	0.2 M	Ethanol	2.5	2.5	9	-
0.1 M	0.2 M	Ethanol	2.5	3.0	9	48
0.1M	0.2 M	Ethanol	2.5	3.5	9	69
0.1 M	0.2 M	Ethanol	2.5	4.0	9	69

4.6.2.3.2 Effect of pH in the in the synthesis of compound 4.006 c

2(1H-indol-1-yl)-1-phenyl ethanone (4.004)	4-substituted benzaldehyde (4.005) (a-d)	Solvent	Potential applied (In Volt)	Time (Hrs.)	pH	Yield (%)
0.1 M	0.2 M	Ethanol	2.5	3.5	7	-
0.1 M	0.2 M	Ethanol	2.5	3.5	8	51
0.1M	0.2 M	Ethanol	2.5	3.5	9	69
0.1 M	0.2 M	Ethanol	2.5	3.5	10	69

4.6.2.3.2 Effect of potential in the in the synthesis of compound 4.006 c

2(1H-indol-1-yl)-1-phenyl ethanone (4.004)	4-substituted benzaldehyde (4.005) (a-d)	Solvent	Potential applied (In Volt)	Time (Hrs.)	pH	Yield (%)
0.1 M	0.2 M	Ethanol	0.5	3.5	9	-
0.1 M	0.2 M	Ethanol	1.5	3.5	9	39
0.1M	0.2 M	Ethanol	2.5	3.5	9	69
0.1 M	0.2 M	Ethanol	3.0	3.5	9	69

4.6.2.4 Electrokinetic study of *(Z)-2-(1-H-indole-yl)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (4.006d)*

4.6.2.4.1. Effect of Time in the in the synthesis of compound 4.006 d

2(1H-indol-1-yl)-1-phenyl ethanone (4.004)	4-substituted benzaldehyde (4.005) (a-d)	Solvent	Potential applied (In Volt)	Time (Hrs.)	pH	Yield (%)
0.1 M	0.2 M	Ethanol	2.5	2.0	8	-
0.1 M	0.2 M	Ethanol	2.5	2.5	8	-
0.1M	0.2 M	Ethanol	2.5	3.5	8	77
0.1 M	0.2 M	Ethanol	2.5	3.5	8	77

4.6.2.4.2 Effect of pH in the in the synthesis of compound 4.006 d

2(1H-indol-1-yl)-1-phenyl ethanone (4.004)	4-substituted benzaldehyde (4.005) (a-d)	Solvent	Potential applied (In Volt)	Time (Hrs.)	pH	Yield (%)
0.1 M	0.2 M	Ethanol	2.5	3.5	7	-
0.1 M	0.2 M	Ethanol	2.5	3.5	8	77
0.1M	0.2 M	Ethanol	2.5	3.5	9	77
0.1 M	0.2 M	Ethanol	2.5	3.5	10	77

4.6.2.4.3 Effect of potential in the in the synthesis of compound 4.006 d

2(1H-indol-1-yl)-1-phenyl ethanone (4.004)	4-substituted benzaldehyde (4.005) (a-d)	Solvent	Potential applied (In Volt)	Time (Hrs.)	pH	Yield (%)
0.1 M	0.2 M	Ethanol	1.5	3.5	8	-
0.1 M	0.2 M	Ethanol	2.0	3.5	8	58
0.1M	0.2 M	Ethanol	2.5	3.5	8	77
0.1 M	0.2 M	Ethanol	3.0	3.5	8	77

4.7 Result and discussion

In this chapter, we explore the synthesis of Indole derivatives of Mannich bases, highly valued for their ability to create natural compounds and agro-chemicals such as nucleotides, alkaloids, antibiotics, and plant growth regulators. Throughout history, the Mannich reaction has played a crucial role in the production of various medicinal compounds, as was previously discussed. The α-β-unsaturated carbonyl system found in chalcone gives it immense biological potential. Thus, we aimed to combine the Mannich base with chalcone in this chapter. The results were promising, as the addition of chalcone to the Mannich base scaffold resulted in highly effective antibacterial and antifungal compounds.

Different parameters such as reaction time, pH and applied potential that influenced the rate of electrochemical synthesis of Mannich bases were investigated. There are certain fix values of parameters, where optimum result was obtained.

Synthesis of compound 4.004 was carried out at different reaction time periods ranging 2.0 hrs to 3.5 hrs at various pH ranging from pH 7 to pH 10 and, at different applied potentials from 0.5V to 2.5V respectively. The maximum yield (83%) was obtained at pH 8 with applied voltage 3.0 V and 2.0 hrs of reaction time.

Synthesis of compound 4.006a was carried out at different reaction time periods ranging from 2hrs to 4 hrs and at various pH ranging from pH 7 to Ph 10 and at diffedrent applied potential from 1.5V to 3V respectively the maximum yield (76%) was obtained at pH 8 with applied voltage 2.5V and 3hrs of reaction time.

Synthesis of compound 4.006b was carried out at different reaction time periods from 2hrs to 3.5 hrs and at various pH ranging from pH 7 to pH 10 and at different applied potential from 0.5V to 3V respectively the maximum yield (73%) was obtained at pH 9 with applied voltage 2.5V and 3hrs of reaction time.

Synthesis of compound 4.006c was carried out at different reaction time periods from 2.5hrs to 4 hrs and at various pH ranging from pH 7 to pH 10 and at different applied potential from 0.5V to 3V respectively the maximum yield (69%) was obtained at pH 9 with applied voltage 2.5V and 3.5hrs of reaction time.

Synthesis of compound 4.006d was carried out at different reaction time periods from 2hrs to 3.5 hrs and at various pH ranging from pH 7 to pH 10 and at different applied potential from 0.5V to 3V respectively, the maximum yield (77%) was

obtained at pH 8 with applied voltage 2.5V and 3.5hrs of reaction time.

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