ONE POT SYNTHESIS ANDCHARACTERIZATION OF TWO NEW SPIRO HETEROCYCLES DERIVED FROM 1,2,3,4-TETRAHYDRO-β-CARBOLINE AND ISATINS

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CONTENTS

ABSTRACT

1,2,3,4-Tetrahydro- β-carboline (THβC) and isatin moieties are two important structural motifs of many biologically active natural products. This inspired us to synthesize novel spirooxindole-tetrahydro-β-carboline molecular hybrids which may have potential biological importance due to synergistic effects. Spiro fused heterocycles with four contiguous stereocentres were obtained via [3+2] cycloaddition reaction of chloro-substituted chalcone with an azomethine ylide generated in situ by the reaction of 1,2,3,4-tetrahydro-β-carboline and various isatins. All the spiro compounds were characterized by various spectroscopic techniques and the biological activities to be explored.

CHAPTER 1

INTRODUCTION

1.1. β-Carboline and derivatives

β-Carboline **1** constitute a group of natural and synthetic alkaloids comprising a tricyclic pyrido[3,4-b] indole ring structure. These heterocycles has been formed in plants and animals via Maillard reaction between amino acids and reducing sugars.[1] β-Carbolines and their derivatives have importance in medicinal chemistry due to their biological and pharmacological properties.[2] β-Carboline alkaloid, harmine, isolated from seeds of *Peganum harmala* is widely distributed in the plants, marine creatures, insects, mammalians and human tissues.[3] β-Carbolines have been detected in tobacco leaves, cigarettes, and cigarette smoke as well.

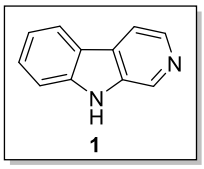


Figure 1: β-Carboline

1.2. 1,2,3,4-Tetrahydro-β-carboline

1,2,3,4-Tetrahydro-β-carboline (tryptoline) **2** is a natural organic derivative of β-carboline. These compounds possess a wide spectrum of biological activities and has many pharmacological applications. They are potential neuroactive alkaloids found in chocolate and drugs. Tryptoline also act as a tricyclic antidepressant which affects chemicals in brain that are unbalanced with depression.[4]

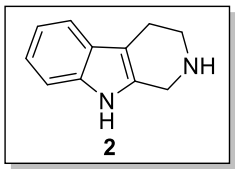


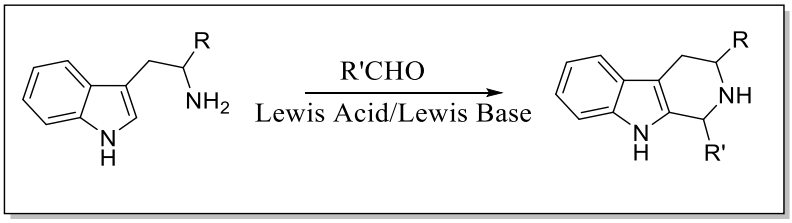
Figure 2: 1,2,3,4-tetrahydro- β-carboline

1.2.1. Synthesis of 1,2,3,4- tetrahydro–β-carboline

One of the most powerful methods to synthesize the 1,2,3,4-tetrahydro-β-carboline ring system is the Pictet–Spengler reaction.

a) Pictet–Spengler reaction

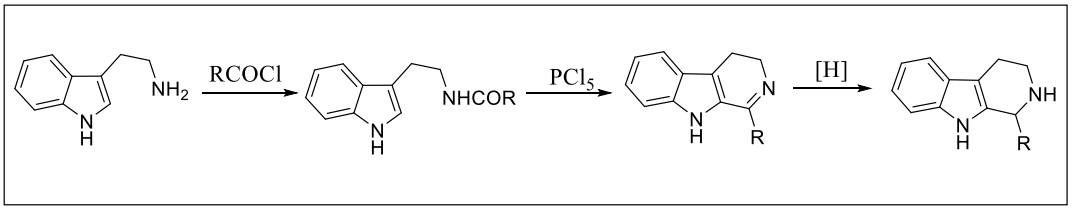
Tryptamine and aldehydes undergo condensation reaction as shown in Scheme 1 to generate corresponding imines followed by intramolecular cyclization catalyzed by Bronsted acids or Lewis acids.[5] A linear relationship was found between the rate of the cyclization and the acidity of the reaction media. For the construction of stereochemically and structurally complex alkaloids this method of synthesis has been proven convincingly.[6]



Scheme 1

b) Bischler- Napieralski reaction

It is the most easily conceivable classical reaction for the synthesis of tetrahydro-β-carboline from β-indolylamides (Scheme 2). This reaction involves the acylation of an exocyclic amine followed by dehydration of the corresponding amide. Commonly used dehydrating agents are PCl_5, $POCl_3$, $SOCl_2$, $ZnCl_2$ and BF_3.[7]



Scheme 2

1.2.2. Biological importance of 1,2,3,4- tetrahydro–β-carboline

Tetrahydro–β-carboline have many pharmacological and biological activities such as antimicrobial, antitumor, antiviral, and anticonvulsant activities, which has led to increased interest in the synthesis of many compounds.

a) Antiviral activity

Tetrahydro–β-carbolines have been recognized as antiviral compounds since 1984 when Rinehart et al. first studied eudistomins (a β-carboline derivative, Figure 3) against herpes simplex virus-1 (HSV-1).

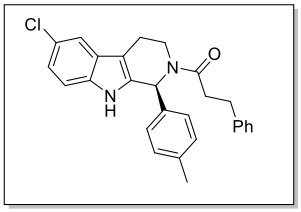


Figure 3: Antiviral agent with THBC motif

The antiviral activities of eudistomins have never been further studied or developed, but a different series of THβCs have been more recently studied against the human papilloma virus (HPV). In a study by Glaxo Smith Kline, a series of 1-substituted THβC derivatives were optimized and resulted in a compound possessing nanomolar activity against HPV.

b) Anticancer activity

Since the 1980s, THβC derivatives have been tested against cancer cell lines. The first reports on the cytotoxicity of compounds with THβC structure came in 1990 when the newly isolated eudistomins were studied for antileukemic properties. Eudistomin showed antitumor activity against leukemic cell lines L1210 and L5178Y (Figure 4).[8]

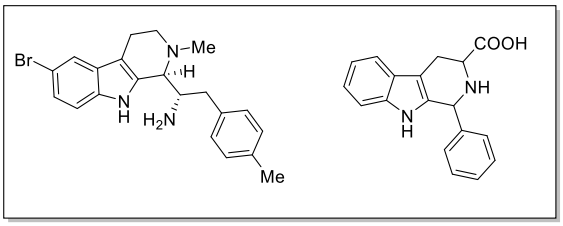


Figure 4: Anticancer agents with THBC motif

c) Antioxidant activity

When human body lacks antioxidants, reactive oxygen species (ROS) would be overproduced and damage the tissues and DNA which lead to various diseases.[9] Tetrahydro carbolines as shown in figure 5 are excellent scavengers of antioxidants and exhibit their activity in both humans and foodstuffs. The antioxidant effect of βCs is dependent on their structures.[10]

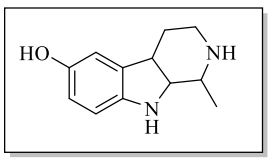


Figure 5: Antioxidant agent with THBC motif

1.3. Isatin

Isatin **3** (Figure 6) is a well-known natural product found in plants and was first isolated from the fruits of *Couroupita guianensis*. In humans, it is a metabolic derivative of adrenaline

and also a component of secretion from parotid gland of Bufo frogs.[11] It has anxiogenic, sedative, anticonvulsant activities and acts as a potent antagonist on atrial natriuretic peptide receptors in vitro.[12]

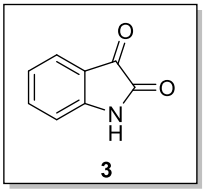


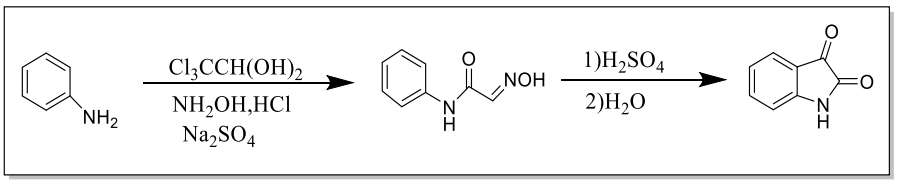
Figure 6: Isatin

1.3.1. Synthesis of isatin

Isatin was first synthesized by Erdman and Laurent in 1841, by oxidation of indigo using chromic and nitric acids. It can be synthesized in many different ways.

1) <u>Sandmayer's process</u>

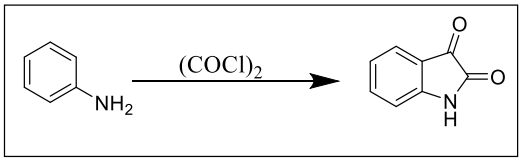
A primary aryl amine was treated with chloral hydrate and hydroxylamine in aqueous sodium sulphate to give α-isonitrosoacetanilide, which was isolated and treated with strong concentrated sulphuric acid to yield isatin (Scheme 3).



Scheme 3

2) <u>Stolle's method</u>

Aniline when treated with oxalyl chloride yields chlorooxalylanilide, which on cyclization in presence of Lewis acid ($AlCl_3$) yield isatin (Scheme 4). This method is also very useful to synthesize 1- Maryland polycyclic isatin from phenothiazine, phenoxazine, dibenzoazepine and indol.[13]



Scheme 4

1.3.2. Biological importance of isatin

Isatin and its derivatives show various biological activities like anti-cancer, anti-bacterial, anti-tubercular, anti-HIV and anti-oxidant.

a) Anticancer activity

Isatin is an important pharmacophore unit in two clinically approved anticancer drugs: sunitinib and toceranib phosphate (Figure 7). Isatin based conjugates with thiazolidine and pyrazoline moieties were synthesized and screened for antitumor activity.

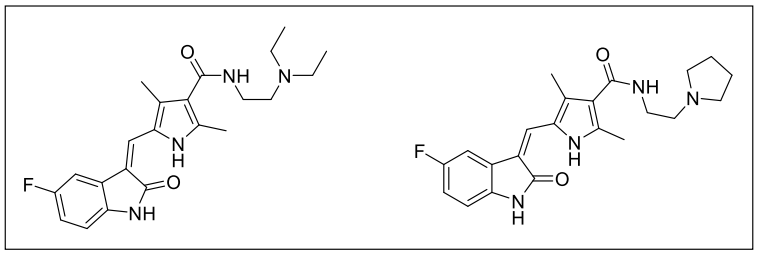


Figure 7: Anticancer agents with isatin motif

b) Antibacterial activity

Isatin derivatives display therapeutic potential against a variety of pathogenic microbes. In several studies, Schiff bases and Mannich bases of isatin and its derivatives were reported to possess significant anti-bacterial activity (Figure 8). In addition to the anti-bacterial activity, some of the isatin derivatives also shows significant anti-fungal activity comparable to the standard drug Clotrimazole.

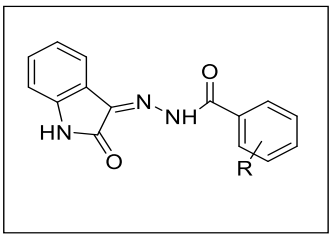


Figure 8: Antibacterial agent with isatin motif

c) Anti-viral activity

Isatin based molecular hybrids have been reported as dual inhibitors of HIV-Reverse transcriptase (Figure 9). HIV-RT plays a key role in the replication cycle of HIV-1 which is associated with important enzymatic activities, namely DNA/RNA dependent polymerase and ribonuclease H. In recent studies, isatin-thiazoline hybrids have been reported as dual inhibitors of HIV- Reverse Transcriptase.[14]

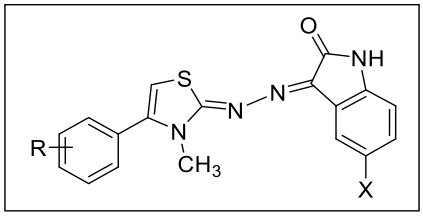


Figure 9: Antiviral agent with isatin motif

1.4 Azomethine ylides

Azomethine ylides are 1,3-dipoles having four π electrons spread over the three-atom C–N–C unit. They can be represented by four zwitterionic resonance forms shown in figure 10.

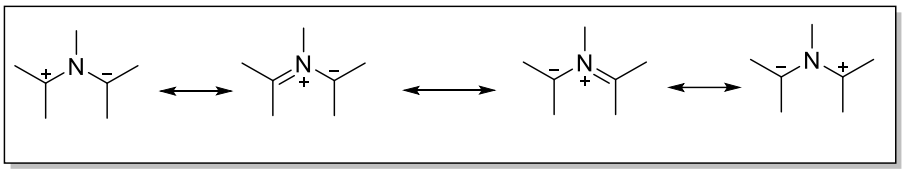
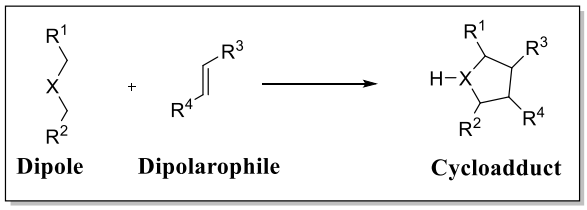


Figure 10: Zwitterionic resonance in azomethine ylide

Azomethine ylides participate as electron-rich dipoles in 1,3-dipolar cycloadditions for the synthesis of various five-membered heterocycles with potential biological activities. These reactions are highly stereo- and regioselective. In terms of frontier molecular orbitals, cycloaddition involves the dominant interaction between the highest occupied molecular orbital (HOMO) of the azomethine ylide and the lowest unoccupied molecular orbital (LUMO) of the dipolarophile (Scheme 5).[15]



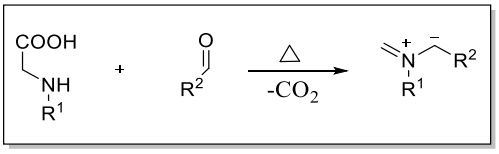
Scheme 5: 1,3-Dipolar cycloaddition

1.4.1 Generation of Azomethine ylides

Some of the common methods for the generation of azomethine ylides include decarboxylative condensation of glycine derivatives with aldehydes, photolytically or thermally induced aziridine ring opening and N-metallation– deprotonation of the aldimine sequence.[16]

1) <u>By decarboxylative route</u>

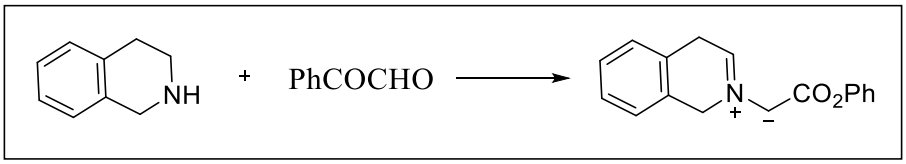
One of the easiest methods of forming azomethine ylides is by the decarboxylative condensation of an aldehyde with an amino acid (Scheme 6). Alternate method for synthesis of azomethine ylide is the condensation of an aldehyde with amine.[17]



Scheme 6

2) By iminium route

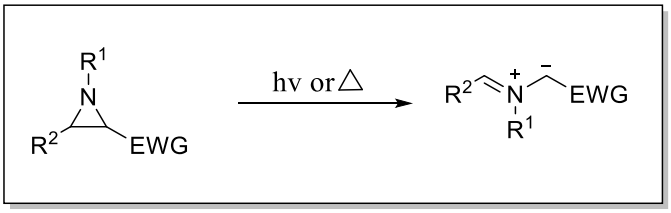
Generation of azomethine ylides through iminium route by 1,5-hydrogen shift in various secondary amines are reported. It can be illustrated as shown in Scheme 7.



Scheme 7

3) From aziridines

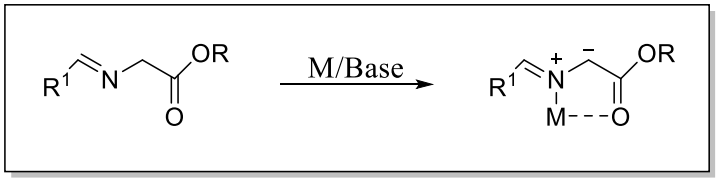
Azomethine ylides can be generated from ring opening of aziridines which can result in different 1,3-dipoles where C–N bond breaks. This reaction is a stereospecific process and follows Woodward-Hoffmann rules. The thermal ring opening reaction proceeds via *con* rotation while the photochemical ring opening proceeds via *dis* rotation (Scheme 8).[18]



Scheme 8

4) By N-metallation

In this method, the metal coordinates to the nitrogen in order to activate the substrate for deprotonation to generate azomethine ylide as shown in scheme 9.[19]



Scheme 9

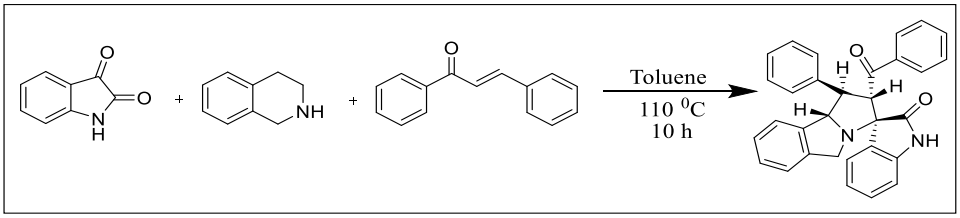
1.5 Objectives of the present study

- To explore the utilization of 1,2,3,4- tetrahydro-β-carboline as a source of 1,3-dipoles by reaction with isatins.
- To check the reactivity of the generated 1,3- dipoles with chloro-substituted chalcone as dipolarophile to synthesize potential bioactive spiro heterocycles.
- To characterize the synthesized spiro heterocycles by using FTIR, ^{1}H NMR, ^{13}C NMR and CHN analysis.

CHAPTER 2

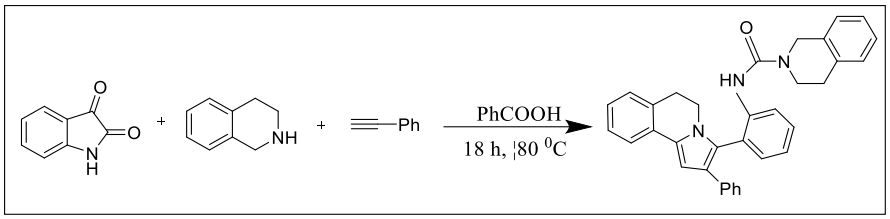
REVIEW OF LITERATURE

In 2022, D.J. Boruah *et al*. reported one-pot three-component method for the stereoselective synthesis of pyrrolo[2,1-a] isoquinolines from isatins, chalcones and 1,2,3,4-tetrahydroisoquinoline in toluene at 110 ^{0}C for 10h without using a metal catalyst or additive (Scheme 1). A series of pyrrolo[2,1a] isoquinolines were synthesised in excellent yields and a single diastereomer product was formed in all the cases. The synthesised compounds have better anti-tuberculosis properties compared to the standard drug Rifampicin.[20]



Scheme 1

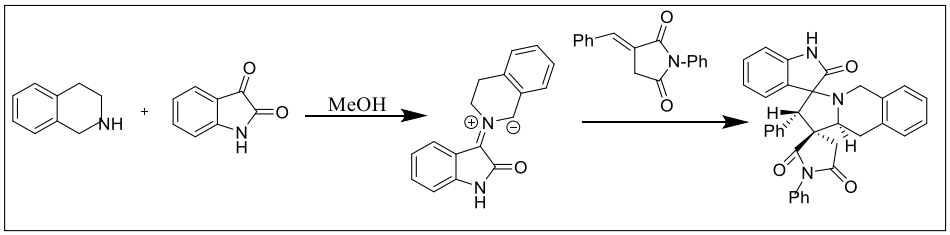
A multicomponent reaction between isatin, tetrahydroisoquinoline, and terminal alkyne in the presence of benzoic acid for the synthesis of 5,6-dihydropyrrolo[2,1-a] isoquinolines was reported by Aritra Ghosh *et al*. in 2019 (Scheme 2). This three-component reaction proceeds via sequential formation of spirooxindole.[21]



Scheme 2

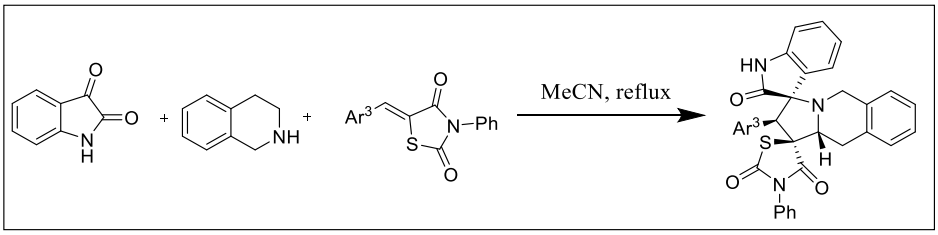
In 2019, Boudriga *et al*. conducted a highly diastereoselective multicomponent 1,3-dipolar cycloaddition reaction of tetrahydroisoquinolinium N-ylides, generated in situ from cyclic diketones and isoquinoline, and (E)-3-arylidene-1-phenyl-pyrrolidine-2,5-diones. An

unprecedented regioselectivity was observed in this cycloaddition leading to the construction of a dispirooxindole skeleton and the reaction afforded the kinetic product (Scheme 3).[22]



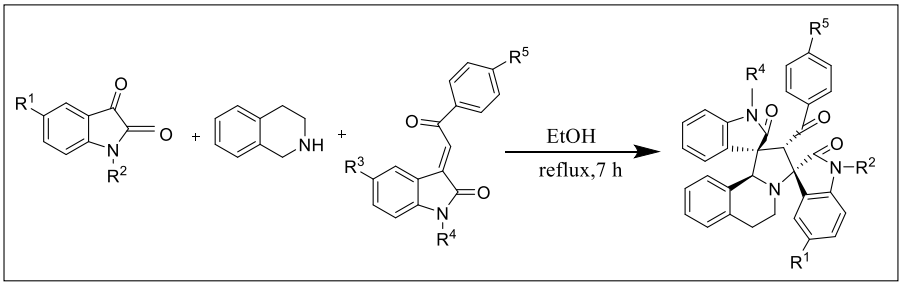
Scheme 3

Toum *et al*. developed an efficient diastereoselective route for the synthesis of spiropyrrolo[1,2-a] isoquinoline-oxindole skeleton by a one-pot three-component cycloaddition reaction of (Z)-5-arylidene-1,3-thiazolidine-2,4-diones, isatin derivatives, and 1,2,3,4-tetrahydroisoquinoline (THIQ). The regioselectivity of the reaction is both temperature- and solvent-dependent and the product was obtained in excellent yields (Scheme 4).[23]



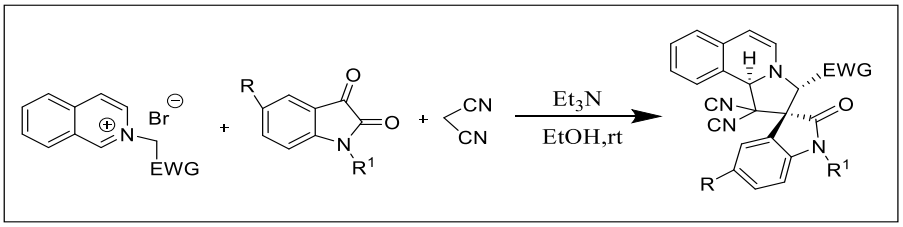
Scheme 4

Huang *et al.* reported the three-component reaction of 1,2,3,4-tetrahydroisoquinoline, isatins and 3-phenacylideneoxindoles for the diastereoselective synthesis of dispirooxindoles in ethanol. This reaction proceeds via [3+2] cycloaddition of in situ generated azomethine ylide with the exocyclic double bond of 3-phenacylideneoxindoles (Scheme 5). High regioselectivity and diastereoselectivity has been obtained by ^{1}H NMR spectra and single crystal structures.[24]



Scheme 5

In 2019, Sun *et al*. proposed a three-component reaction of N-(4-nitrobenzyl), N-ethoxycarbonylmethylisoquinolinium bromide, isatins and malononitrile in ethanol to form spiro[indoline3,2′-pyrrolo[2,1-a] isoquinolines]. This reaction promoted by trimethylamine has good yield and high diastereoselectivity (Scheme 6).[25]



Scheme 6

CHAPTER 3

MATERIALS AND METHODS

3.1. Chemicals Used

Isatin, methyl iodide, propyl iodide, 4-chlorobenzaldehyde and acetophenone were purchased from Spectrochem Pvt. Ltd. 1,2,3,4-Tetrahydro-β-carboline was purchased from Sigma- Aldrich. Sodium hydroxide and potassium carbonate were also used. All chemicals were used as such without further purification. Commercial grade solvents were used.

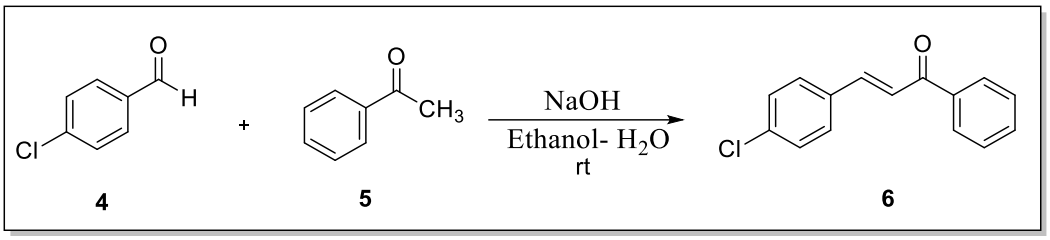
3.2. Materials required

Round bottom flask (50 ml), Funnel, Conical flask, Magnetic Stirrer, Condenser, TLC plate

3.3. Methods

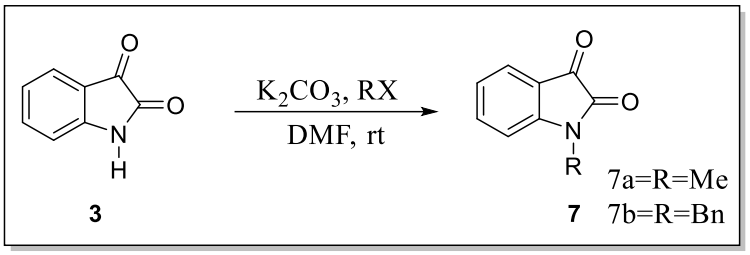
3.3.1. Synthesis of (E)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (Chloro Chalcone)

A mixture of 4-chlorobenzaldehyde (1.42 mmol) and acetophenone (1.42 mmol) were added to a solution of NaOH (7.1 mmol) in water and ethanol (1:1) and stirred for 15 minutes at room temperature. After completion of the reaction the crude product was filtered, washed with water and dried.



3.3.2. General procedure for the synthesis of 1-alkylindoline-2,3-dione

Isatin (1 mmol) and alkyl halide (1.2 mmol) were dissolved in DMF (20 ml) and anhydrous K_2CO_3 (3 mmol) was added. Mixture was stirred under room temperature for 1 h. The reaction mixture was worked up using brine solution and HCl (2N) to obtain the crude product.



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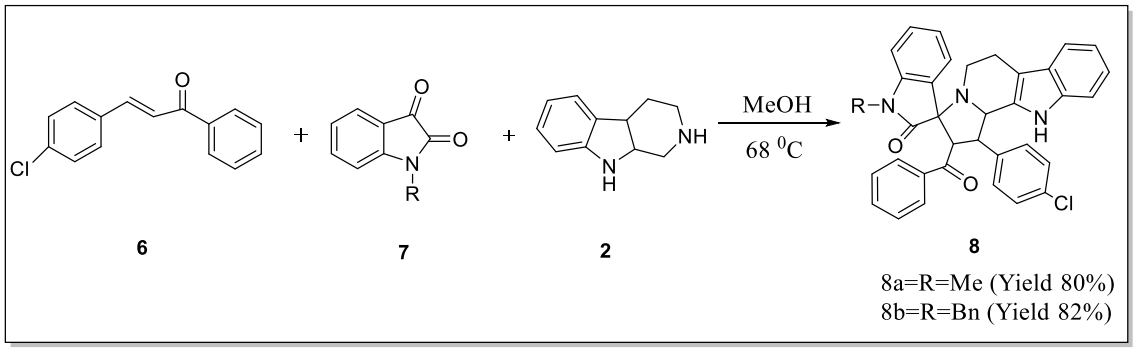
3.3.3. General Synthesis of 2'-benzoyl-1'-(4-chlorophenyl)-1-alkyl-1',2',5',6',11',11b'- hexahydrospiro[indoline-3,3'-indolizino[8,7-b] indol]-2-one

Chloro-substituted chalcone (1 mmol), alkyl isatin (1 mmol) and tetrahydro-β-carboline (1 mmol) were taken in a 50 ml RB flask. It was dissolved in methanol and stirred at 68 ^{0}C for 12 h. The reaction was monitored using thin layer chromatography. A precipitate was obtained, which was filtered, washed with methanol and dried.



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3.4. Laboratory tools and techniques

3.4.1. Thin Layer Chromatography

Thin layer chromatography (TLC) is an analytical technique used to verify the identity and purity of a compound. It is also used to monitor the progress of a reaction. It is based on the distribution of the compounds in a mixture between a fixed (or a stationary) and a moving (or a mobile) phase. In TLC, the stationary phase is a thin layer of adsorbent coated on a glass plate or an aluminium foil. Silica gel, cellulose, or alumina are the commonly used adsorbents in TLC. A suitable solvent system is used as the mobile phase. A small quantity of a mixture of compounds is placed at the end of the TLC plate by means of a capillary tube and the TLC plate is placed in a solvent chamber. The solvent travels upward by capillarity and the separation of components takes place. The component that is held less tightly to the stationary phase rises easily along with the solvent than those held more tightly. When the solvent reaches the top of the plate, the plate is taken out of the solvent chamber and dried. Each component is

observed at different positions on the plate. If the components are colourless, they are visualised either under UV radiation of short waves (254 nm) or by using iodine vapours.

3.4.2. Rotary Evaporator

The rotary evaporator consists of a heating water bath in which a round bottom (RB) flask is made to rotate under vacuum. When vacuum is applied the boiling point of the liquid decreases which facilitates the rapid evaporation of the liquid. When the RB flask rotates steadily, a film of the solution is constantly being pulled up on the upper inside wall and a relatively large heated surface is thereby furnished for vaporization. Rotavapor is used for the distillation of solvents, concentration of solutions and suspensions, solvent extraction, recycling of solvents, drying of powders and granules, etc.

3.4.3. Infrared Spectroscopy

Infrared (IR) spectroscopy is a powerful tool for elucidating the structure of compounds. It is associated with the absorption of IR radiation and subsequent increase in the amplitude of molecular vibrations. When the energy of vibration matches with the energy of radiation, absorption occurs. Since vibrational energy is dependent of reduced mass of two atoms connected by a bond and the force constant (strength) of the bond, each bond has a unique vibrational energy and it can absorb only the radiation with exactly the same energy as the vibrational energy. This property is exploited in IR spectroscopy for the detection of functional groups in a compound.

3.4.4. Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy deals with the study of radio wave induced transition between magnetic energy levels of nucleus. Nucleus with non-zero spin (called an NMR active nucleus) has inherent magnetic moment and this magnetic moment can interact with an external magnetic field. When an NMR active nucleus is placed in an external magnetic field, nuclear magnetic energy levels become non-degenerate. The nuclear magnetic 12 resonance phenomenon occurs when nuclei aligned with an applied field are induced to absorb energy and change their spin orientation with respect to the applied field. When an external magnetic field is applied, the nucleus begins to precess about its own spin axis with an angular frequency called the Larmor frequency. This precession generates an oscillating electromagnetic field of same frequency. When radio wave of this frequency is supplied to nucleus energy can be absorbed leading to a nuclear transition. In a molecule, not all the nuclei

are in identical chemical environments. Slight changes in local environment causes changes in the frequency of radio wave absorbed. That is, nuclei in dissimilar chemical environments give different NMR signals. This feature of NMR can be utilized for the structure determination of compounds.

3.5. Characterization of Compounds

NMR spectra were recorded on a 400MHz Bruker Avance FTNMR spectrometer. Chemical shifts were reported relative to TMS as the internal standard. IR spectra were recorded on an Agilent Cary 630 FTIR spectrometer. Analytical thin layer chromatography was performed on silica gel coated on aluminium sheets and was visualized using UV light of 254 nm. CHN data was recorded using Perkin Elmer 2400 Series II CHNS/O analyser.

CHAPTER 4

RESULTS AND DISCUSSION

4.1. Characterization of 2'-benzoyl-1'-(4-chlorophenyl)-1-methyl-1',2',5',6',11',11b'-hexahydrospiro[indoline-3,3'-indolizino[8,7-b] indol]-2-one (8a)

The structure of the compound **8a** was characterized by IR, ^{1}H NMR, ^{13}C NMR and CHN analysis (Figures 1-3). In the IR spectrum, the carbonyl group stretching was observed at 1672 cm^{-1} and amide carbonyl stretching was observed at 1609 cm^{-1}. A broad peak at 3304 cm^{-1} corresponds to NH stretching. In the ^{1}H NMR spectrum, the multiplets ranging from δ 6.67-8.07 ppm corresponds to 17 aromatic protons and one NH proton. Three hydrogens attached to the stereocenters were observed as doublet (δ 5.90-5.93), triplet (δ 5.14-5.19) and doublet (δ 4.45 - 4.47) respectively. Four methylene protons of the THBC moiety were observed as a multiplet from δ 2.59-2.88 and 2.92-2.94 ppm. A singlet at δ 2.89 ppm corresponds to methyl protons. In the ^{13}C NMR spectrum, aromatic carbons were observed between δ 108-144 ppm. Chalcone carbonyl and the amide carbonyl were observed at δ 199 ppm and δ 176 ppm respectively. The spiro center observed at δ 75 ppm. The stereocenters were observed at δ 59, 57 and 51 ppm respectively. The peaks at δ 43 and δ 25 ppm were attributed to two methylene carbons. Methyl carbon attached to nitrogen was observed at δ 25 ppm. Table 1 gives the CHN analysis of the compound **8a.**

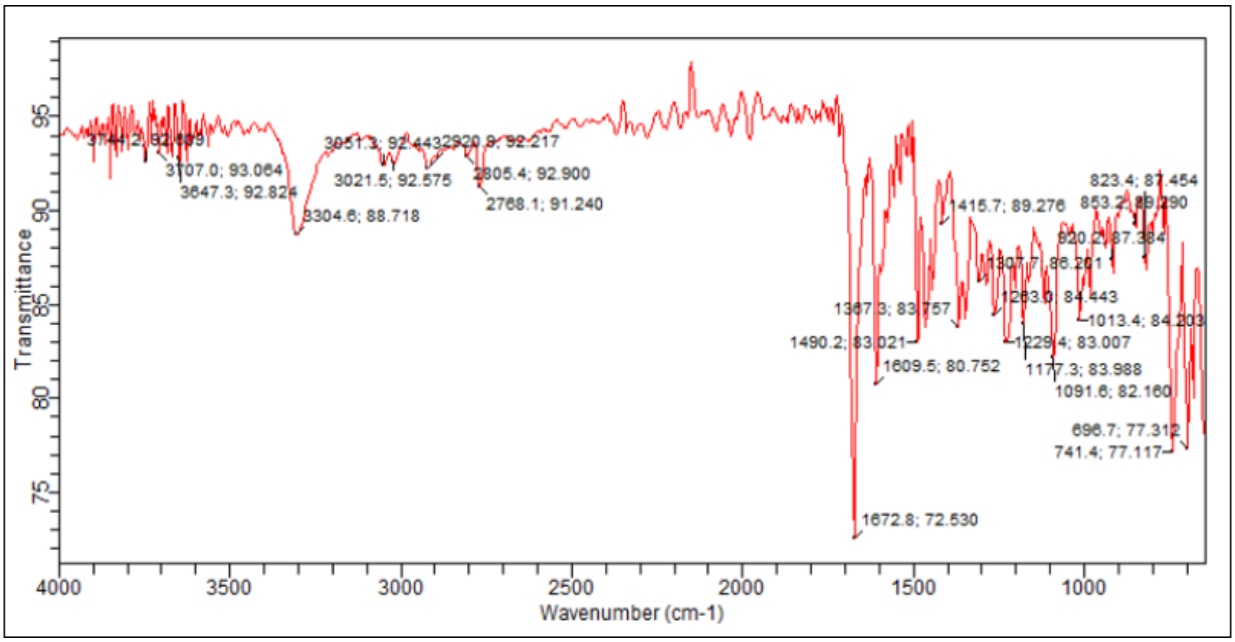


Figure 1: IR spectrum of compound 8a

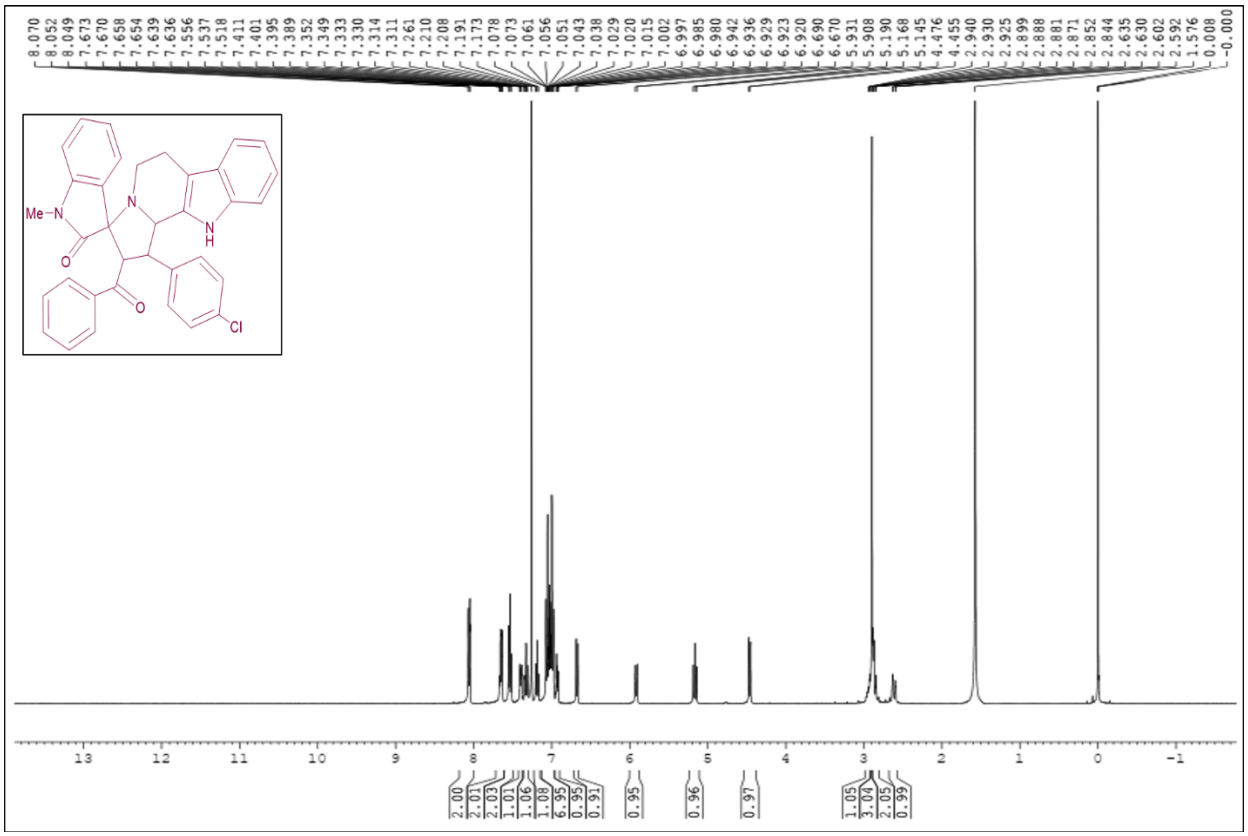


Figure 2: ^{1}H NMR of compound 8a

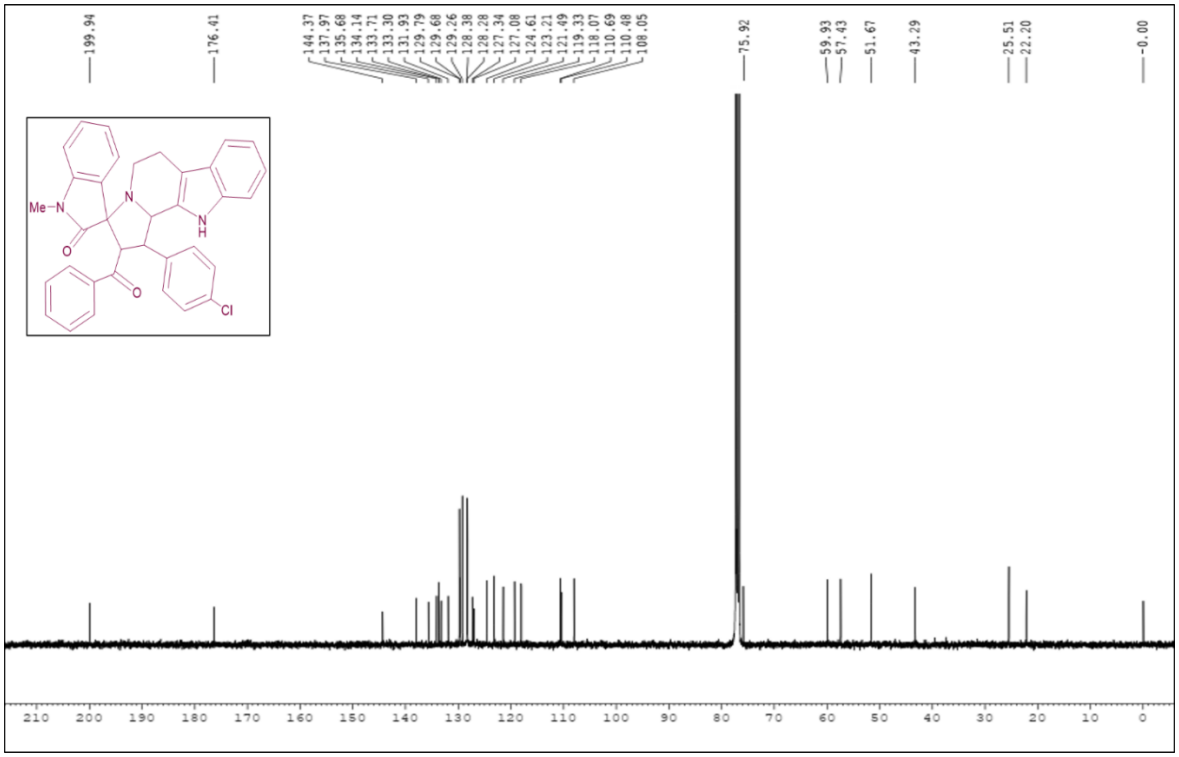


Figure 3: ^{13}C NMR of compound 8a

Table 1: CHN Analysis Data of compound 8a

Element	Analytically calculated %	Experimentally observed %
C	75.33	75.35
H	5.06	5.05
N	7.53	7.52

Properties and Spectral details of Compound 8a

- **Appearance:** White solid (Yield 80%)
- **Molecular formula:** $C_{35}H_{28}ClN_3O_2$
- **Molecular weight:** 558.08
- **Melting point:** 240-242 ℃
- **Solubility:** Soluble in $CHCl_3$, DCM, and DMSO
- **IR (cm^{-1}):** 3304, 3051, 2920, 2768, 1672, 1609, 1490
- **^{1}H NMR (δ ppm, 400 MHz, $CDCl_3$):** 6.67-8.07 (18H, m, 17 Ar-H & 1 NH), 5.90-5.93 (1H, d, J = 9.2 Hz, CH), 5.14-5.19 (1H, t, J = 9.2 Hz, CH), 4.45-4.47 (1H, d, J = 8.4 Hz, CH), 2.59-2.88, 2.92-2.94 (4H, m, CH_2), 2.99 (3H, s, CH_3)
- **^{13}C NMR (δ ppm, 100 MHz, $CDCl_3$):** 199.9, 176.4, 144.3, 137.9, 135.6, 134.1, 133.7, 133.3, 129.7, 129.6, 129.2, 128.3, 128.2, 127.3, 127.0, 124.6, 123.2, 121.4, 119.3, 118.0, 110.6, 110.4,108.0, 75.9, 59.9, 57.4, 51.6, 43.2, 25.5, 22.2
- **Elemental Analysis:** Analytically calculated %: C, 75.33; H, 5.06; N, 7.53. Found %: C, 75.35; H, 5.05; N, 7.52.

4.2. Characterization of 2'-benzoyl-1'-(4-chlorophenyl)-1-benzyl-1',2',5',6',11',11b'-hexahydrospiro[indoline-3,3'-indolizino[8,7-b] indol]-2-one (8b)

The structure of the compound **8b** was characterized by IR, ^{1}H NMR, ^{13}C NMR and CHN analysis (Figures 4-6). In the IR spectrum, the carbonyl group stretching was observed at 1691 cm^{-1} and amide carbonyl stretching was observed at 1609 cm^{-1}. A broad peak at 3375 cm^{-1} corresponds to NH stretching. In the ^{1}H NMR spectrum, twenty-two aromatic protons and one NH proton were observed as multiplets ranging from δ 6.46-8.08 ppm. Three hydrogens attached to the stereocenters were observed as doublet (δ 5.94-5.96), triplet (δ 5.21-5.25) and

doublet (δ 4.54-4.56) respectively. Four methylene protons of the THBC moiety were observed as a multiplet and a doublet between δ 2.61-2.93 ppm. Methylene protons of the benzyl carbon were observed as two doublets between δ 4.29-4.33 ppm and δ 5.04-5.08 ppm. In the ^{13}C NMR spectrum, aromatic carbons were observed between δ 108-144 ppm. Chalcone carbonyl and the amide carbonyl were observed at δ 199 ppm and δ 176 ppm respectively. The spiro center was observed at δ 75 ppm. The stereocenters were observed at δ 59, 57 and 51 ppm. The peaks at δ 43.2 and δ 25 ppm were attributed to two methylene carbons. Methylene carbon attached to aromatic ring was observed at δ 43.2 ppm. Table 1 gives the CHN analysis of the compound **8b.**

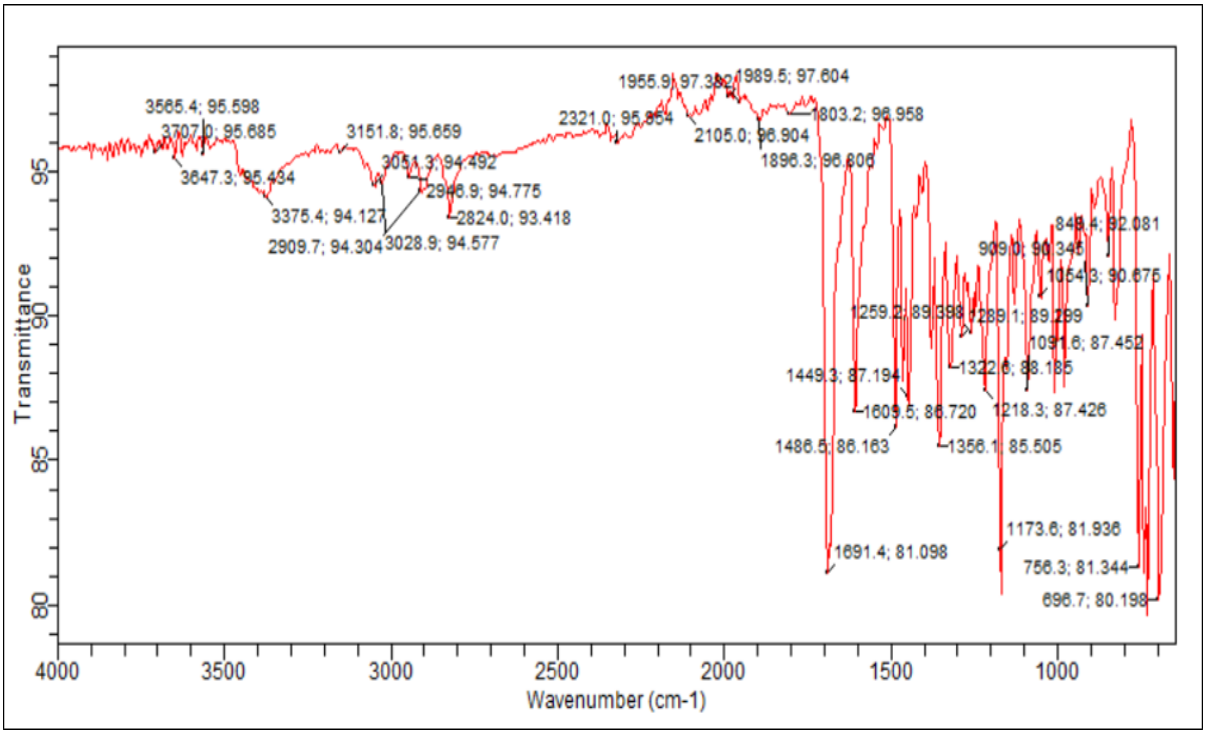


Figure 4: IR spectrum of compound 8b

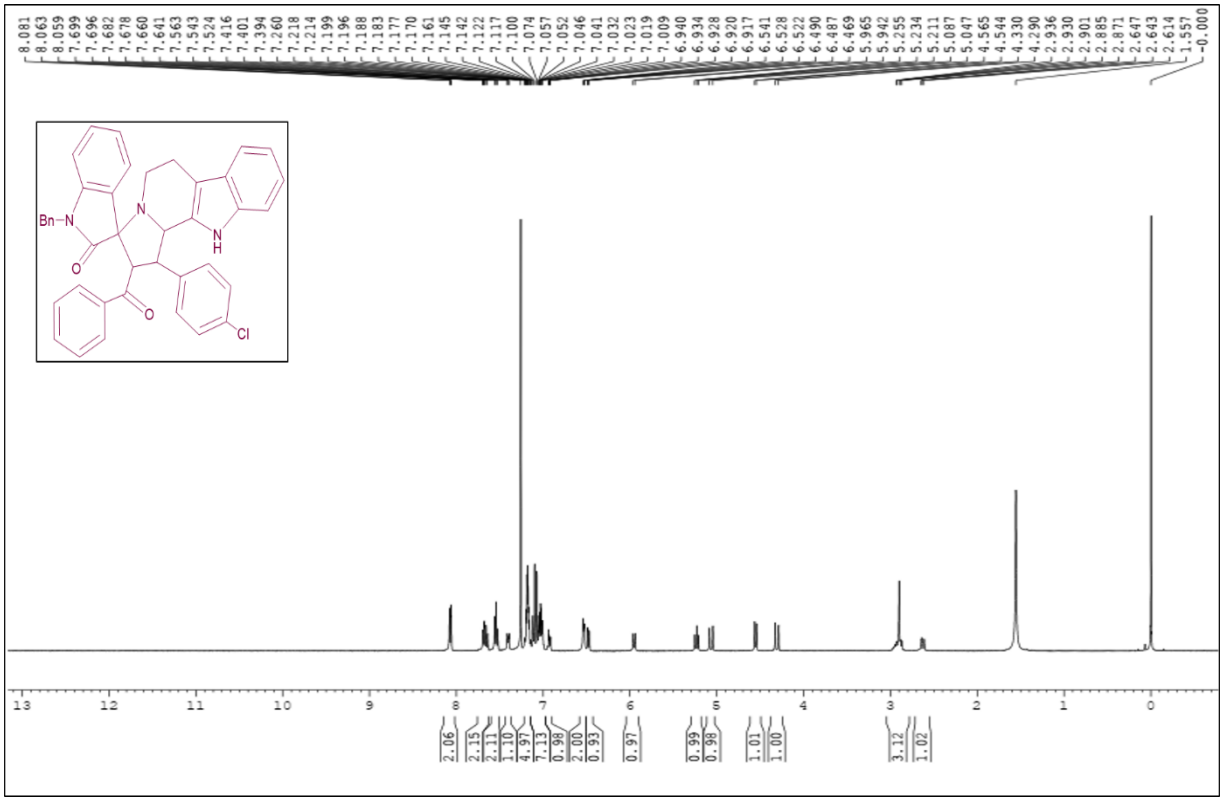


Figure 5: ^{1}H NMR of compound 8b

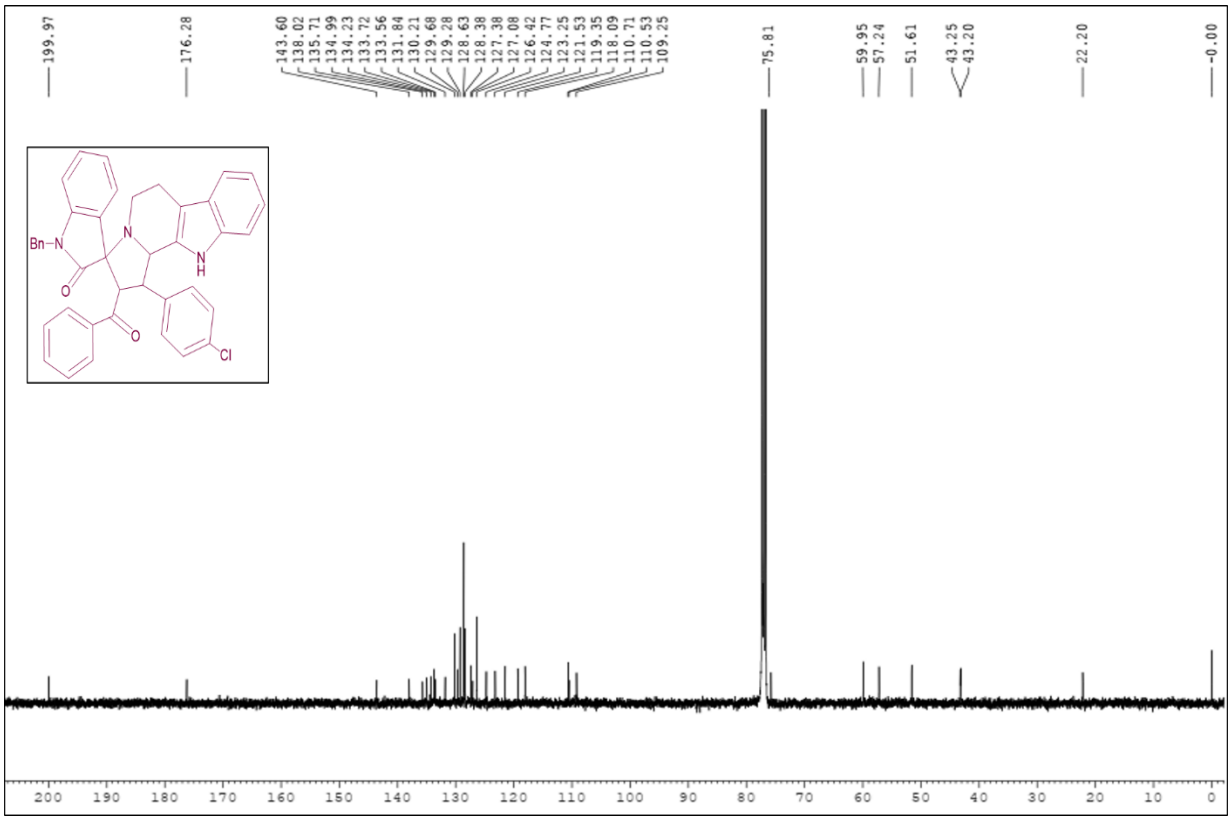


Figure 6: ^{13}C NMR of compound 8b

Table 2: CHN Analysis Data of compound 8b

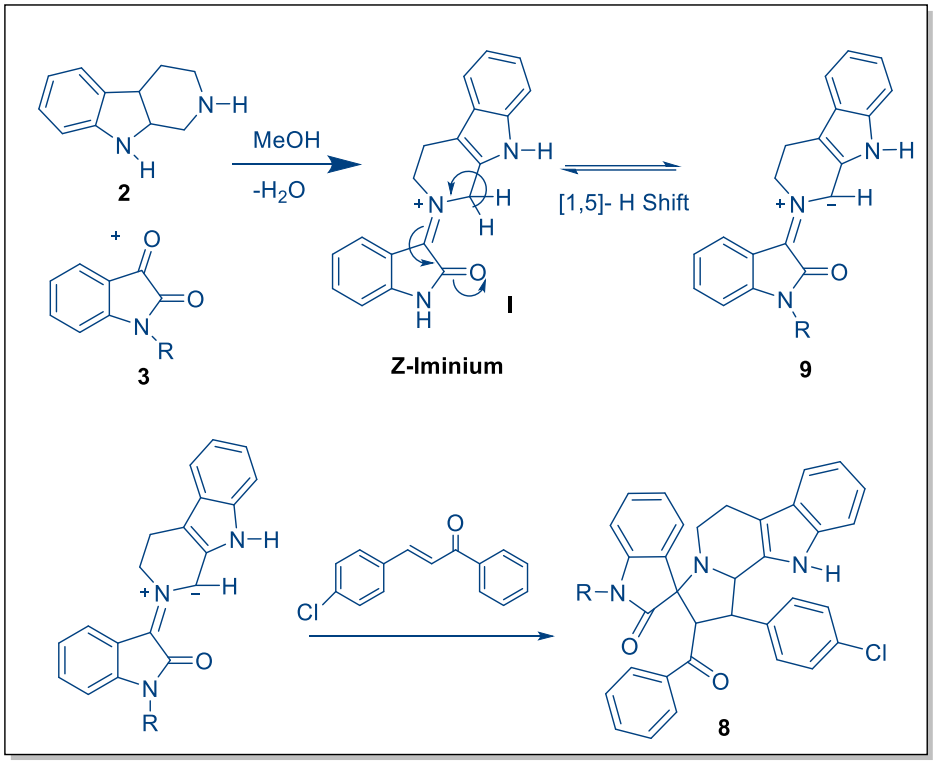
Element	Analytically calculated %	Experimentally observed %
C	77.65	77.64
H	5.09	5.09
N	6.63	6.64

Properties and Spectral details of Compound 8b

- **Appearance:** White solid (Yield 82%)
- **Molecular formula:** $C_{41}H_{32}ClN_3O_2$
- **Molecular weight:** 634.18
- **Melting point:** 246-248 ℃
- **Solubility:** Soluble in $CHCl_3$, DCM, and DMSO
- **IR (cm^{-1}):** 3375, 3054, 2946, 2824, 1691, 1609, 1486
- **^{1}H NMR (δ ppm, 400 MHz, $CDCl_3$):** 6.46-8.08 (23H, m, 22 Ar-H & 1 NH), 5.94-5.96 (1H, d, J = 9.2 Hz, CH), 5.21-5.25 (1H, t, J = 9.2 Hz, CH), 4.54-4.56 (1H, d, J= 8.4 Hz, CH), 4.29-4.33(1H, d, J=16 Hz, CH_2-Bn), 5.04-5.08 (1H, d, J=16Hz, CH_2-Bn), 2.61-2.93 (4H, m, CH_2)
- **^{13}C NMR (δ ppm, 100 MHz, $CDCl_3$):** 199.9, 176.7, 143.6, 138.0, 137.6, 134.9, 134.2, 133.7, 133.5, 131.8, 130.2, 129.6, 129.2, 128.6, 128.3, 127.3, 127.0, 126.4, 124.7, 123.2, 121.5, 119.3, 118.0, 110.7, 110.5, 109.2, 75.8, 59.9, 57.2, 51.6, 43.25, 43.2, 22.2
- **Elemental Analysis:** Analytically calculated %: C, 77.65; H, 5.09; N, 6.63. Found %: C, 77.64; H, 5.09; N, 6.64.

4.3. Mechanistic Rationale

The reaction probably takes place by the generation of azomethine ylide **9** from Z-iminium intermediate **I** by a [1,5]-H shift followed by deprotonation. The generated ylide undergo [3+2] cycloaddition to yield a spiro heterocycle **8** with four contiguous stereocentres.



The exact structure with stereochemistry at spirocenters can be ascertained only after NOE analysis and after obtaining single crystal X-Ray data.

CHAPTER 5

CONCLUSION

We have generated an azomethine ylides from N-alkyl isatins and 1,2,3,4-tetrahydro-β-carboline and explored their reactivity using chloro-substituted chalcone as dipolarophile to yield spiro fused heterocycles with four contiguous stereocentres via [3+2] cycloaddition. Two compounds were synthesized and isolated by chromatography-free method. Characterization of the synthesized compounds were done by FTIR, ^{1}H NMR, ^{13}C NMR and CHN analysis.

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