A New Avenue for the Synthesis of Some Biologically Active Isatin Derivatives

THESIS SUBMITTED IN PARTIAL FULFILLMENT FOR THE AWARD OF DEGREE

DOCTOR OF PHILOSOPHY

By

SURESH KUMAR MAURY

Department of Chemistry
Indian Institute of Technology
(Banaras Hindu University)
Varanasi-221005

Roll No: 17051008 **Year of Submission: 2022**

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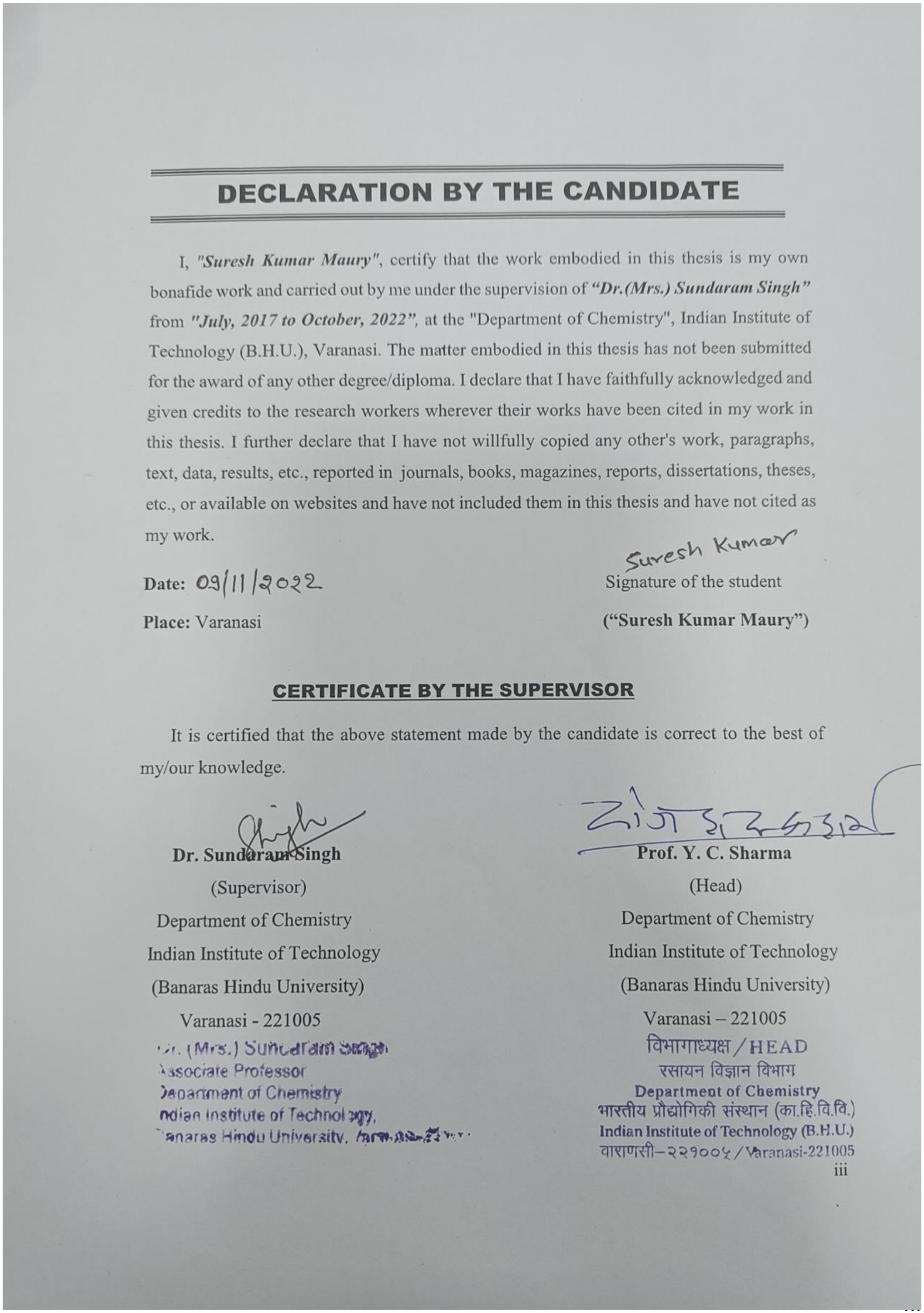
It is further certified that the student has fulfilled all the requirements of Comprehensive Examination, Candidacy, and SOTA for the award of Ph.D. Degree.

Dr. Sundaram Singh
(Supervisor)
Department of Chemistry
Indian Institute of Technology
(Banaras Hindu University)
Varanasi - 221005

Dr. (Mrs.) Sundaram Singh
Associate Professor
Department of Chemistry
Indian Institute of Technology,
Banaras Hindu University, Varanasi - [illegible]



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Place: Varanasi
("Suresh Kumar Maury")

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Dr. Sundaram Singh
(Supervisor)
Department of Chemistry
Indian Institute of Technology
(Banaras Hindu University)
Varanasi - 221005

(Mrs.) Sundaram Singh
ssociate Professor
epartment of Chemistry
ndian Institute of Technology,
anaras Hindu University, [illegible]

Prof. Y. C. Sharma
(Head)
Department of Chemistry
Indian Institute of Technology
(Banaras Hindu University)
Varanasi – 221005

विभागाध्यक्ष / HEAD
रसायन विज्ञान विभाग
Department of Chemistry
भारतीय प्रौद्योगिकी संस्थान (का.हि.वि.वि.)
Indian Institute of Technology (B.H.U.)
वाराणसी–२२१००५ / Varanasi-221005

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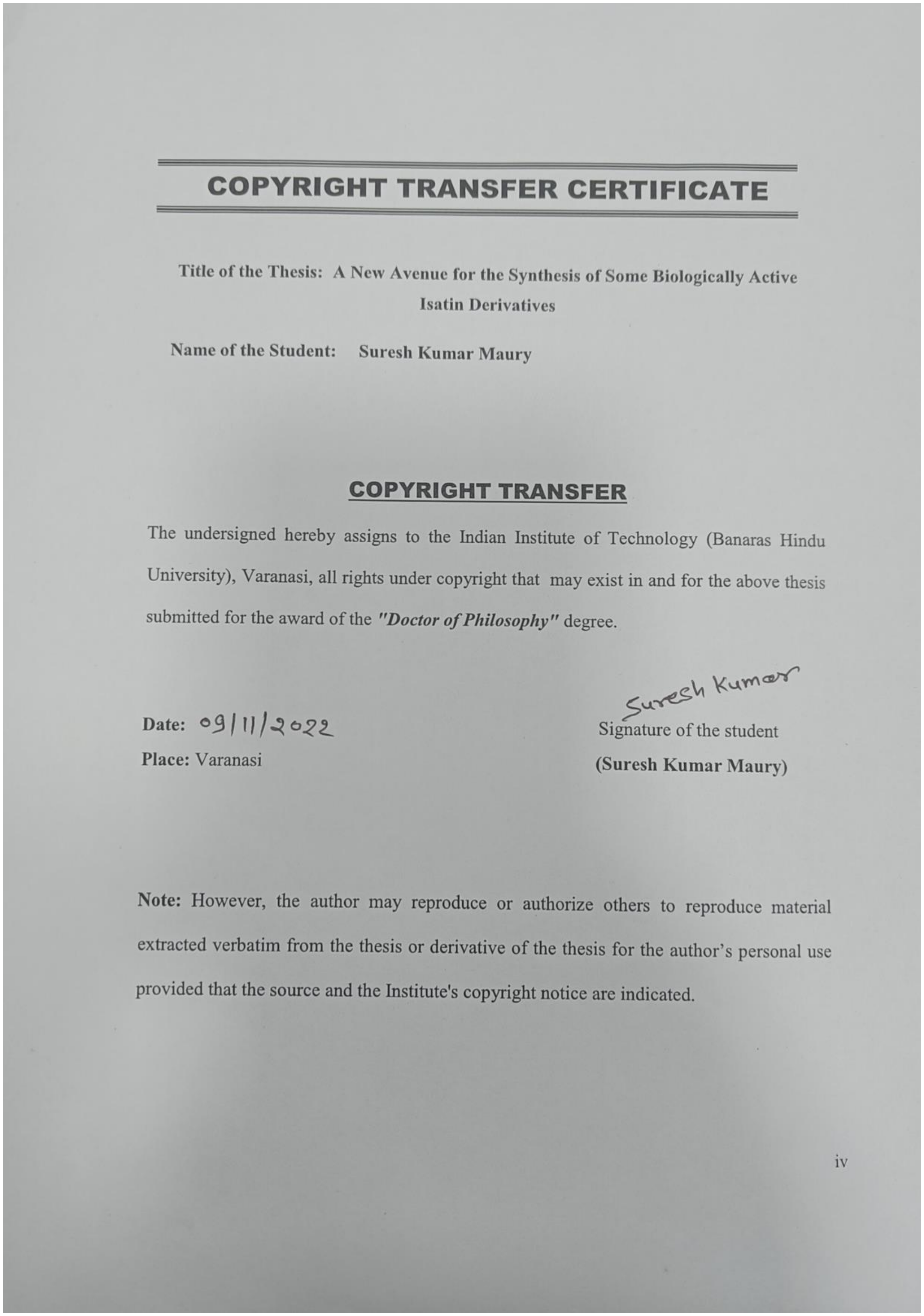

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Suresh Kumar

Date: 09/11/2022 **Suresh Kumar Maury**

Research scholar

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List of Notations, Symbols and Abbreviations

Notations	**Abbreviations**
%	Percentage
<	Less than
>	More than
°	Degree
Å	Angstrom
Ac	Acetyl
Ac_2O	Acetic anhydride
AcOH	Acetic acid
brs	Broad singlet
Obser.	Observed
Calc.	Calculated
©	Copyright
$CHCl_3$	Chloroform
$CDCl_3$	Deuterated chloroform
cm	Centimeter
J	Coupling constant
DMF	Dimethylformamide
DMSO-d^6	Deuterated dimethyl sulfoxide
D_2O	Deuterated water
ºC	Degree Celsius
d	Doublet
DMAP	4-Dimethylaminopyridine
DCE	Dichloroethane
DCM	Dichloromethane
CH_3CN	Acetonitrile
K_2CO_3	Potassium carbonate
dd	Doublet of doublet
ddd	Doublet of doublet of doublet
ddt	Doublet of doublet of triplet

DMSO	Dimethyl sulfoxide
dq	Doublet of quartet
dt	Doublet of triplet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DABCO	1,4-Diazabicyclo[2.2.2]octane
equiv.	Equivalent
EtOH	Ethanol
EtOAc	Ethyl acetate
equiv.	Equivalent
g	Gram; Gravitational force
h	Hour
Hz	Hertz
IR	Infra-Red
m	Multiplet
MeOH	Methanol
mg	Milligram
MHz	Megahertz
min	Minute
mL	Milliliter
mm	Millimeter
mmol	Millimole
µm	Micrometer
M.p.	Melting point
nm	Nanometer
NMR	Nuclear Magnetic Resonance
n-BuLi	*n*-Butyllithium
KOH	Potassium hydroxide
pH	Potential of hydrogen
ppm	Parts per million
RT	Room temperature
s	Singlet
NMP	N-Methyl-2-pyrrolidone
t-Bu	Tertiary butyl
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography
TMS	Tetramethylsilane

TFA	Trifluoroacetic acid
UV	Ultraviolet
XRD	X-ray Diffraction
HRMS	High-resolution mass spectrometry
MWI	Microwave irradiation
MCR	Multicomponent reactions
NMR	Nuclear magnetic resonance
α	Alpha
β	Beta
γ	Gamma
δ	Chemical shift
[ox]	Oxidation
R_f	Refractive Index
o	Ortho
m	Meta
p	Para
H_2O_2	Hydrogen peroxide
H_2SO_4	Sulfuric acid
Et_3N	Triethylamine
$Sc(OTf)_3$	Scandium triflate
$Cu(OTf)_2$	Copper (II) trifluoromethanesulfonate
$Yb(OTf)_3$	Ytterbium (III) trifluoromethanesulfonate
TBHP	*tert*–Butylhydroperoxide
BHT	Butylatedhydroxytoluene
$LiAIH_4$	Lithium aluminium hydride
$ZnCl_2$	Zinc chloride
$KMnO_4$	Potassium permanganate
$K_2S_2O_8$	Potassium persulfate
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxidanyl
ZnO	Zinc oxide
CH_3COOH	Acetic acid
p-TSA	*p*-Toluenesulfonic acid
NH_2SO_3H	Sulfamic acid

TiO_2	Titanium dioxide
CuCl	Copper (I) chloride
$AlCl_3$	Aluminium chloride
$NaBH_4$	Sodium borohydride
DTBP	Di-*tert*-butyl peroxide
et al.	et alia, Latin for “and others”
i.e.	that is
e.g.	Example
equiv.	Equivalents

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General Experimental Considerations

All the chemicals were procured from Aldrich, USA and E. Merck, Germany and were used as received. The solvents were purchased from Merck, India and Ranbaxy, India and were purified before its use. The preparation and particulars of the substrates employed for the work undertaken are given in their respective chapters. **Melting points** were measured using Stuart Melting point apparatus SPM10 in open capillary tubes and are uncorrected. **Infrared (IR)** spectra were recorded on Perkin-Elmer FT-IR-5300 spectrophotometer (ν_{max} expressed in cm^{-1}). The **^{1}H** (500 MHz) and **^{13}C** (126 MHz) **NMR** spectra were run on a Bruker Advance 500 MHz FT-NMR at 500 MHz spectrometers. Chemical shifts are given in δ ppm, using tetramethylsilane (TMS) as an internal standard. **HRMS** (m/z) were recorded in an electron ionization or electrospray ionization (ESI) mode on Water-Q-TOF premier-HAB213 and Sciex X500RQTOF instruments. The **elemental microanalyses** were performed on Exeter Analytical Inc Model, CE-440 elemental analyzer.

Thin-layer Chromatography (TLC) was performed on glass plates (7.5 × 2.5 and 7.5 × 5.0 cm) coated with Merck silica gel GF 254 using various combinations of ethyl acetate and n-hexane as an eluent. Visualization of spots was accomplished either in iodine chamber or by exposure to UV light. Merck silica gel (100-200 mesh) was used for column chromatography (approximately 15-20 g per 1 g of the crude product).

Preface

A central objective in synthetic organic chemistry has been to develop a greener and more economically competitive processes for the efficient synthesis of biologically active compounds with potential application in the pharmaceutical and related industries.

Isatin and its derivatives represent an important class of ‘privileged structures’ capable of serving as ligands for a wide range of biological targets. Due to this reason, in past few decades, isatin and its derivatives have been used extensively as key intermediate in organic synthesis.

The content of the thesis have been divided into five chapters.

Chapter 1 gives an overview of the chemistry of isatin, it starts from short introduction followed by methods of synthesis and after that chemical reactivity of isatin. In this section, reduction, oxidation, electrophilic aromatic substitution, N-substitution and reactivity of the carbonyl group of isatin are briefly covered. After that, synthesis of isatin based spiro-fused heterocyclic scaffolds and at least, recent application of isatin in organic synthesis have been briefly included. The actual investigation and findings are presented in the subsequent four chapters.

Chapter 2 deals with a facile and efficient multicomponent synthesis of benzodiazepine ring via the reaction of isatin, diphenylamine, and 1,3-diketone under ultrasound irradiation in water. **Chapter 3** gives an account for a grinding induced catalyst-free, multicomponent synthesis of indoloindole pyrimidine from isatin, barbituric acid and enaminone under ethanol as a solvent at room temperature.

Chapter 4 investigates of a facile and ecologically friendly one-pot multicomponent synthesis of biologically active spiro [indoline-3, 4'-quinoline] derivatives via oxidative coupling of indole with enaminone and malononitrile under EtOH: H_2O (4:1) as a solvent. **Chapter 5** describes a facile, efficient and environment friendly , easy work, short reaction time approach for the synthesis of Spiro[Indoline-3,4'-Quinoline] via one pot, four component reaction of amine, dimedone, isatin , and malononitrile using DABCO in the presence of ethanol at 80^{o}C.

CHAPTER 1

OVERVIEW OF ISATIN DERIVATIVES

Chapter 1

Overview of Isatin Derivatives

1.1 Brief Introduction

As a simple natural product produced by the metabolism of adrenaline, isatin is also known as 1H-indole-2, 3-dione (1H-indole-2, 3-dione) **(Figure 1.1)**, is present in people and plants of the genus Isatis in the species Couroupita guianensis [1-6]. Indole quinone and indenedione are other names for isatin. Indole is the source of isatin, a significant class of heterocyclic chemicals [7]. Erdmann and Lauren first discovered it in the early 19th century as an indigo oxidation product, and Kekule hypothesized its current structure [8]. Isatin and its derivatives have an extensive range of pharmacological and biological characteristics [9]. Isatin contains an aromatic ring, a lactam moiety, and a ketone, giving it the rare ability to serve as both an electrophile and a nucleophile. Numerous reactions are carried out on it, including ring expansions, N-substitutions, spiro-annulations, electrophilic aromatic substitutions at positions C-7 and C-5 of the phenyl ring, and nucleophilic additions to the C-3 carbonyl group, nucleophilic additions, and chemoselective reductions. It can be employed as a beginning material for synthesizing heterocyclic compounds and as a raw material for forming pharmaceuticals due to its specific reactivity **(Figure 1.2)** [10-12].

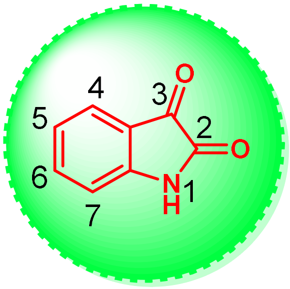


Figure 1.1 Structure of isatin

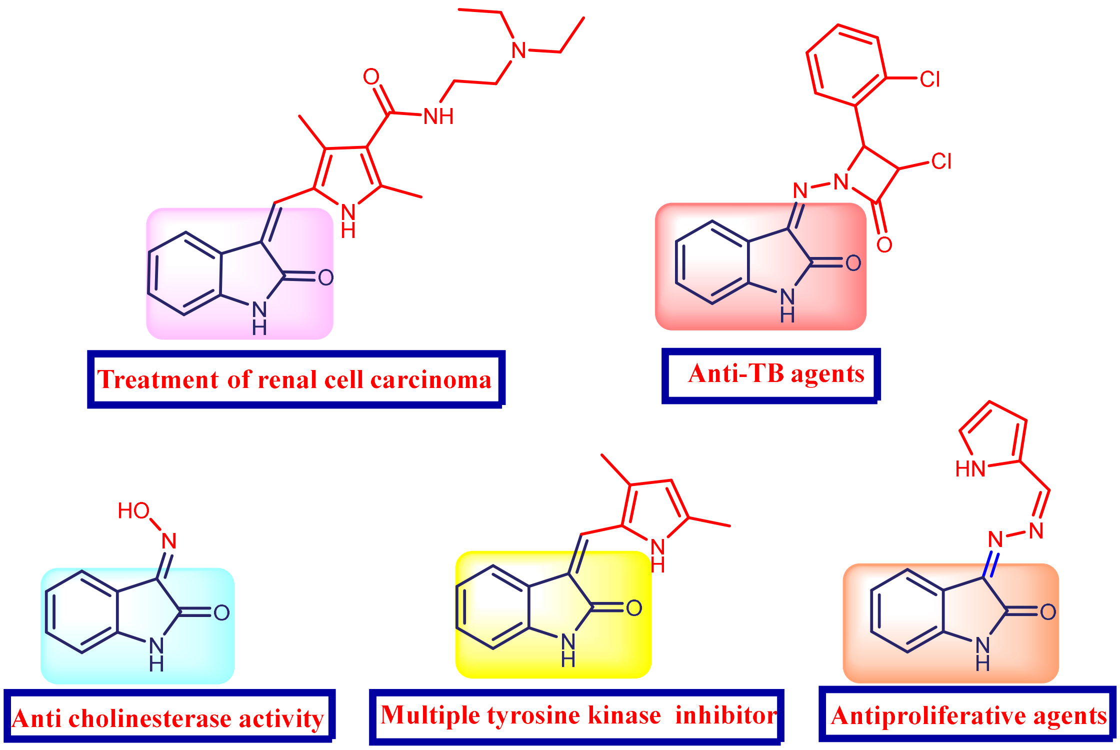


Figure 1.2 Biologically Active compounds with isatin Moieties

Before, the study of isatin derivatives was associated with creating dyes. However, more recently, it has been discovered that these heterocycles possess anti-cancer [13], anti-bacterial [14], antifungal [15], anti-diabetic [16], anti-convulsant[17], anti-tubercular [18], anti-HIV [19], anti-oxidant [20], anti-glycation [20], anti-malarial [21], anti-inflammatory [22], analgesic [23], and anti-anxiety [24] participate in metabolism, acetylcholinesterase inhibitors [25] and to encourage plant growth. Some medications include the isatin skeleton used to treat various ailments like epilepsy [26] and tuberculosis **(Figure 1.3)** [27]. Therefore, a medicinal chemist's current focus is on the requirement to develop innovative isatin derivatives for emerging therapeutic targets.

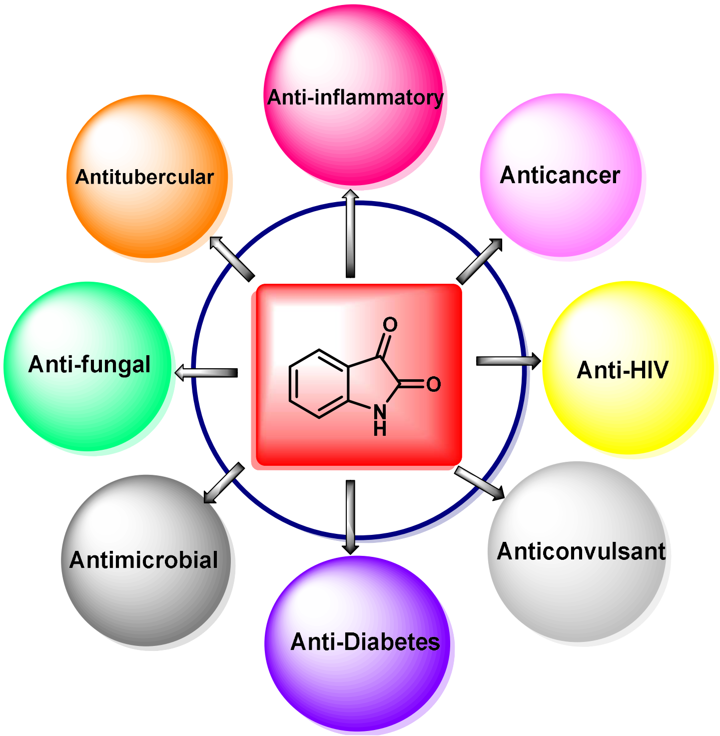
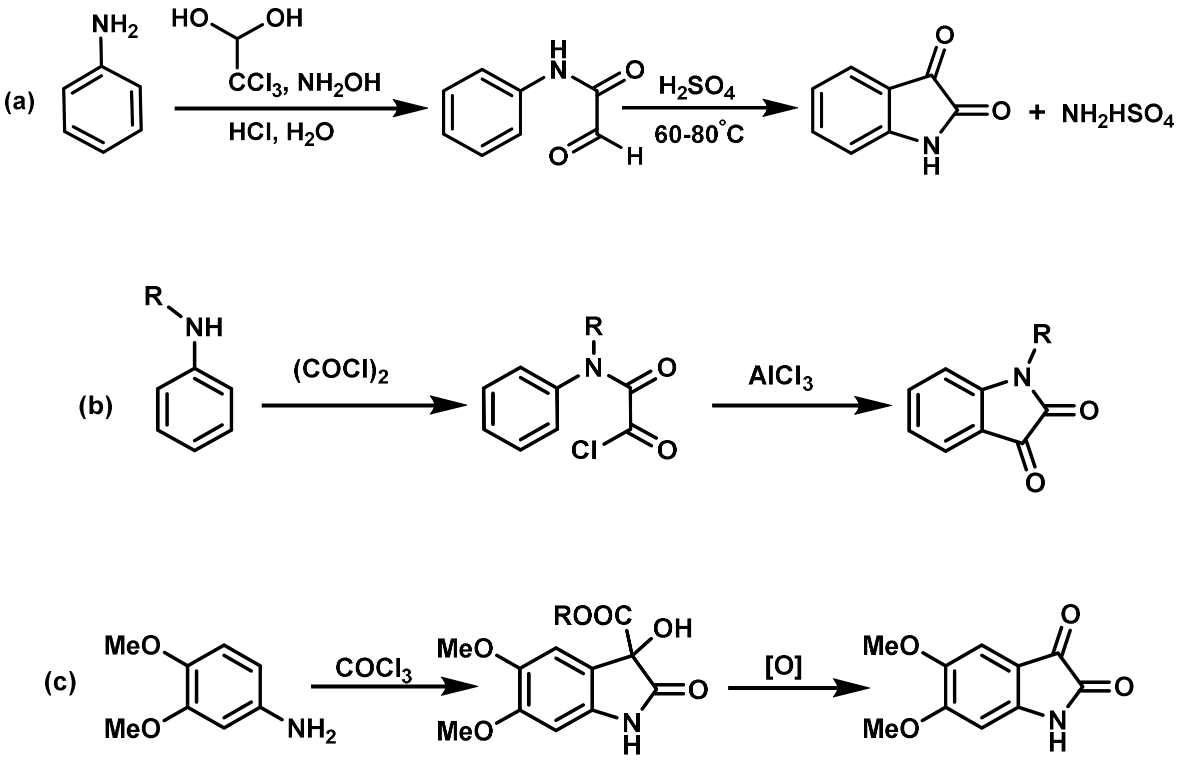


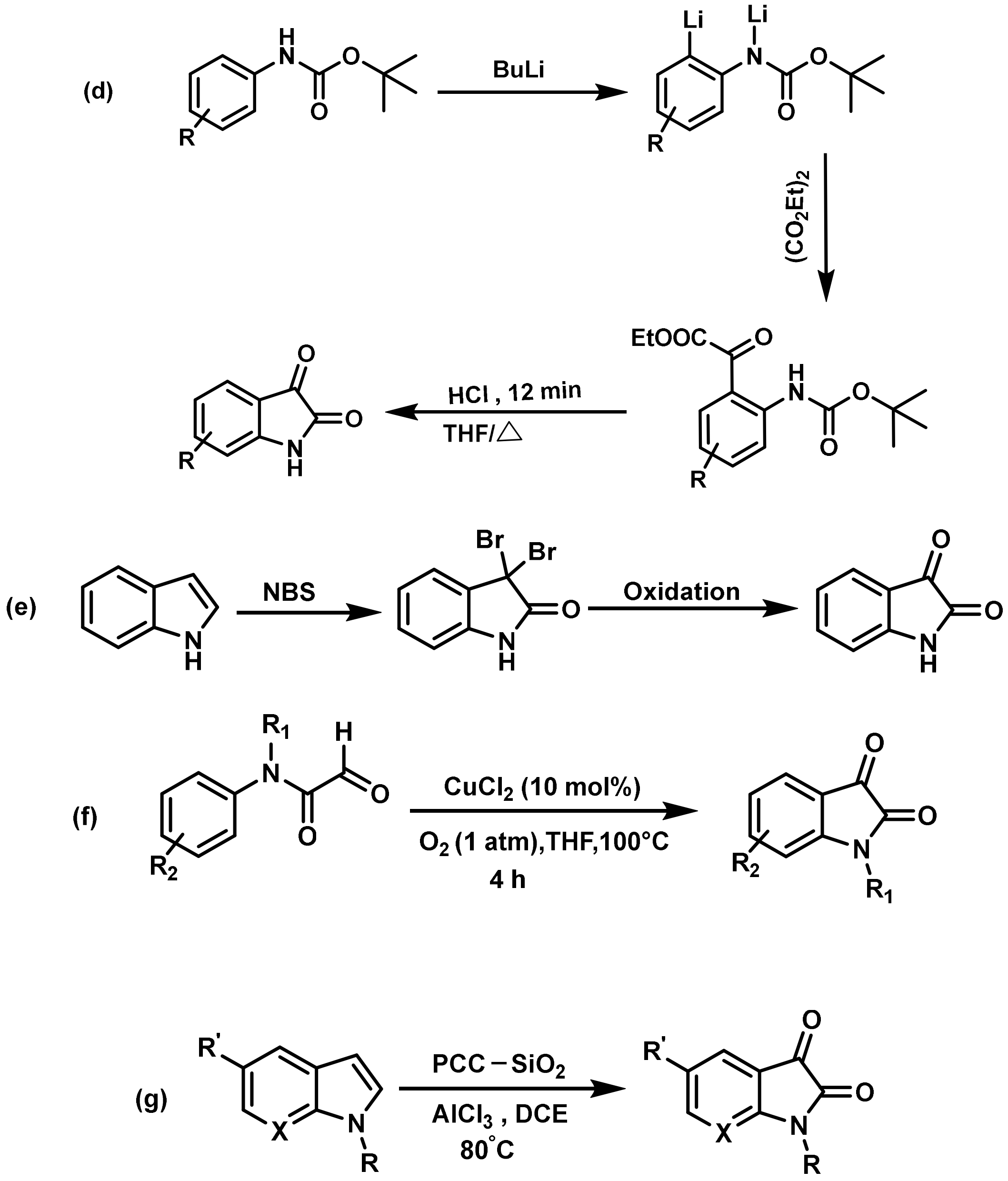
Figure 1.3 Biological importance of isatin derivatives

1.2 Synthetic approaches of Isatin

The most primitive approach for making isatin was created by Sandmeyer [28-30], who used a reaction between substituted aniline derivatives, chloral hydrate, and hydroxylamine hydrochloride in aqueous sodium sulfite to produce the intermediate isonitrosoacetanilide. By further cyclizing intermediate isonitrosoacetanilide with strong sulfuric acid, substituted isatin derivatives are formed **(Scheme 1.1a)**. This method suffers from some limitations, such as harsh reaction conditions. It fails if the isonitrosoacetanilides bear electron-donating groups, the formation of a mixture of regioisomers, and generally moderate yields. Though, yield can be enhanced using microwave conditions. Using Sandmeyer's technique, Kurkin [31] created isatins from optically active anilines. Additionally, they increased the aniline's solubility by using ethanol as a solvent. The Stolle approach is a suitable substitute for the Sandmeyer method. This method lets N-substituted anilines interact with oxalyl chloride to create an intermediate chlorooxalylanilide that can be cycled in Lewis acids **(Scheme 1.1b)** [32, 33]. This process has been utilized to develop 1-arylisatin [34] and polycyclic isatins made from dibenzoazepine, indoline, phenoxazine, and phenothiazine [35, 36]. Raj et al. [37] revealed some improvements to this process. This methodology shows that H-zeolite is a superior Lewis acid catalyst compared to homogeneous Lewis acid catalysts like $SnCl_4$ and $BF_3.Et_2O$. The technique only needs to filter the catalyst and evaporate the solvent to produce good yields of isatins. Klein [33] used Stole's method for isatin synthesis, but in a different way. In this method, "(E)-2-((benzyloxy) imino) acetyl chloride" was first synthesized by treating benzyloximinoacetic acid with oxalyl chloride, which on reaction with aniline and bases such as triethylamine or diisopropylethylamine in common organic solvent provide isatin. Another way to make isatins, according to Gassman [38, 39], involves converting substituted anilines into 3-methylthiooxindoles, which are then oxidized to produce the equivalent substituted isatins. An aromatic substituted amine reacts with either an oxomalonate ester or its hydrate in the presence of an acid to produce a 3-(3-hydroxy-2-oxindole) carboxylic acid derivative, which upon oxidative decarboxylation, results in the appropriate isatin derivative, according to the Martinet [40] method for the synthesis of isatins **(Scheme 1.1c)**. Hewawasam and Meanwell [42] recently created a new technique for the synthesis of isatins [41] that is unaffected by the electronic properties of substituents attached to the aromatic ring and characterized by expected regiochemical control. This technique produced dianions by excess use of a number of different butyllithium reagents in THF at -78°C with N-pivaloylanilines or N-(tert-butoxycarbonyl) anilines. The resultant dianions were then subjected to ethyl oxalate treatment, and the intermediate α-ketoesters were cyclized and deprotected using HCl to produce the isatin derivatives. When a metalation directing group, such as an amino-protected group, is used as a replacement, this approach has the benefit of being regioselective for synthesizing 4-substituted isatins from meta-substituted anilines **(Scheme 1.1d)**. Using N-bromosuccinimide, Parrick and colleagues [43] devised a technique for generating isatins from indoles by promoting their oxidation to generate 3, 3-dibromooxindoles, which were subsequently hydrolyzed to the necessary isatin

(Scheme 1.1e). Tang, Bo-Xiao, et al. have reported a new intramolecular C-H oxidation/ acylation procedure with O_2 as the terminal oxidant and two C-H bonds as the reaction partners in the presence of copper-catalyst (**Scheme 1.1f**) [44]. Recent studies have described a quick and efficient method for converting 7-azaindoles and indoles into 7-azaisatins and isatins utilizing pyridinium chlorochromate-silica gel (PCC-SiO_2) and $AlCl_3$ in dichloroethane **(Scheme 1.1g)** [44].





Scheme 1.1 Most common synthetic approaches for the preparation of isatin

Besides these well-known methods, other approaches are also reported for synthesizing isatin [45, 46].

1.3 Study of the reactivity of isatin

Isatin will primarily react at three separate sites: C-3 for carbonyl reactions, C-5 for aromatic substitution, and N-alkylation **(Figure 1.4)**. Illustrates what might happen if the such compound contains electron-withdrawing groups in the benzene or at the nitrogen attack at C-2.

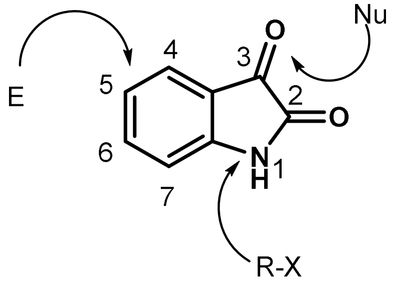
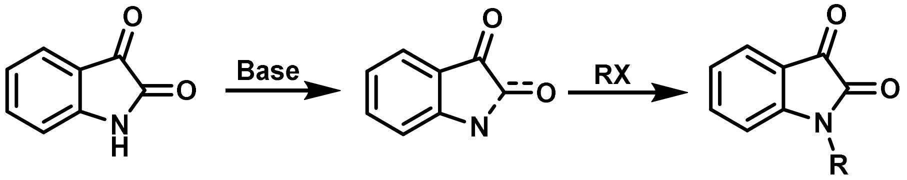


Figure 1.4 Study of reactivity of isatin

1.3.1 N- substitution at isatin

Several approaches have been developed for preparing *N*-alkyl isatins from the sodium salt of isatin. This can be accomplished under basic circumstances, using alkyl chlorides, bromides, and iodides; as well as reactive allyl-, benzyl-, and propargyl halides or sulfates. Conventional heating is often employed to produce the *N*-substituted isatins under reflux. The N-alkylation of isatin typically begins with the reaction of the isatin substrate with any number of bases, such as Na_2CO_3, K_2CO_3, Cs_2CO_3, LiH, NaH, CaH_2, TEA, LiOH, and solvent (DMF, DMA, HMPT, MeCN, DMSO, NMP, EtOH, MeOH, Me_2CO) [47-50], to produce the salt of the isatin, which is then reacted with an alkyl halide to give a N-alkylated isatin **(Scheme 1.2)**. By reacting with $Ph_3Bi(OAc)_2$ and Cu (0) in an inert environment [51] or with aryl bromides and cupric oxide [52], isatin produced N-arylisatin in quantifiable amounts.



Scheme 1.2 Synthesis of N- substituted isatin derivatives

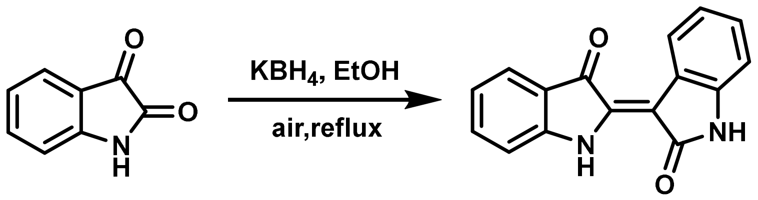
It is simple to use the Mannich reaction with isatins. The N-aminomethylisatins (Mannich bases) produced by this reaction can even be made by the reaction of N-hydroxymethyl derivatives and an amine [51] or acetyl chloride to generate N-chloromethylisatin. It can be processed with potassium phthalimide or alcohol to produce the corresponding N-phthalimidomethyl or N-alkoxymethyl isatins [53]. Isatin derivatives like isatin-3-hydrazones [54] and isatin-3-thiosemicarbazones [55] can also be used in the Mannich process.

The formation of *N*-acylisatins has been reported in various conditions under reflux with anhydrides or acyl chlorides. The reaction was carried out in the absence of additives [56] or by the use of perchloric acid in benzene, triethylamine in benzene [57], pyridine in benzene [58], or catalyst triethylamine in chloroform; or by converting isatin to sodium isatide in toluene under reflux using NaH and successive reaction with acyl chlorides [59].

By using the same techniques for producing 1-acylisatins, isatin and sulfonyl chlorides react to produce N-Sulfonylisatins. For instance, the yield of 1-tosylisatin from the reaction of tosyl chloride and isatin in the presence of Et_3N or with the sodium salt of isatin was 71 - 74% [57]. Isatin is converted to 1-chloroisatin, and indoles to 3-chloroindoles [60] using an efficient and mild oxidizing agent, sodium hypochlorite, with acetic acid, without the generation of byproducts [61]. The reaction of the sodium salt of isatin and phenyliodine (III) *bis*-trifluoroacetate provided *N*-[phenyliodine (III)] *bis*-isatin in excellent yield.

1.3.2 Reactivity due to the carbonyl group of isatin

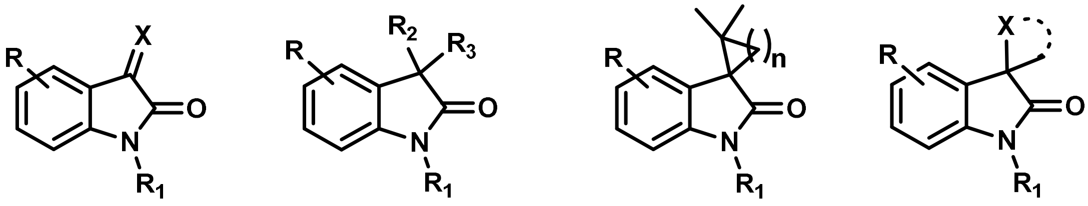
The C-2 and C-3 positions of isatin and isatin derivatives are more prone to nucleophilic reactions. The type of nucleophile, the substituents linked to the isatin nucleus, particularly those bonded to the nitrogen atom, and the solvent and temperature utilized all affect how chemoselective these reactions are. The initial compounds obtained may go through further reaction in the presence of a second nucleophilic group to yield cyclization products. Indurabins were formed by dimerizing isatins (1 equivalent) with KBH_4 (0.5 equivalent) in ethanol or methanol **(Scheme 1.3)** [62].



Scheme 1.3 Synthesis of Indurabins

1.3.3 Reactivity due to C-3 carbonyl group of isatin

The most attractive application of isatins in chemical synthesis is undoubtedly due to the extremely reactive C-3 carbonyl group, which also functions as a prochiral center. The C-3 carbonyl group of isatins is subjected to reactions that generally involve nucleophilic additions or spiroannulation and produce derivatives of the 2-oxindole (**Figure 1.5**).



X=NR, CR_2
2-Oxindoles with
sp^2-hybridized C-3

2-Oxindoles with
sp^3-hybridized C-3

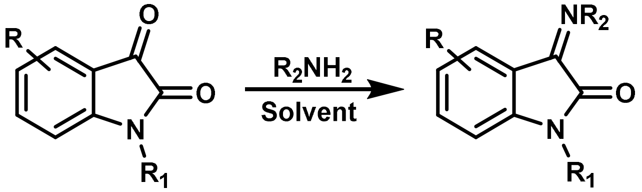
n=1-6

X= N, O, S

Figure 1.5 Reactivity due to C-3 carbonyl group of isatin

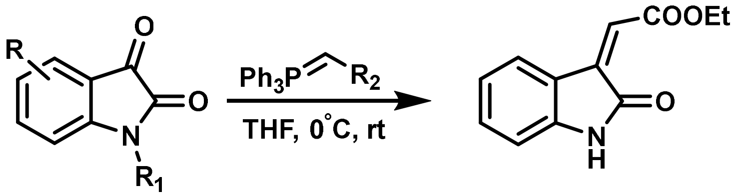
Due to their presence in numerous natural products like spirotryprostatins, gelsemine, horsfiline, gelseverine, rhynchophylline, and elacomine, among others, 2-oxindoles, especially those that are spiro-fused to other cyclic frameworks (**Figure 1.5**), have piqued the interest of researchers in the fields of synthetic organic chemistry and medicinal chemistry worldwide. They have reportedly been shown to exhibit a range of bioactivities [63], including MDM2 inhibitors [64], progesterone receptor modulators [65], anti-cancer [66], anti-HIV [67], anti-tubercular [68], and anti-malarial [69-70].

The attempts to synthesize C-3 functionalized 2-oxindoles from isatins take advantage of the reactivity of the isatins' C-3 carbonyl group with nucleophiles **(Scheme 1.4)** [71].



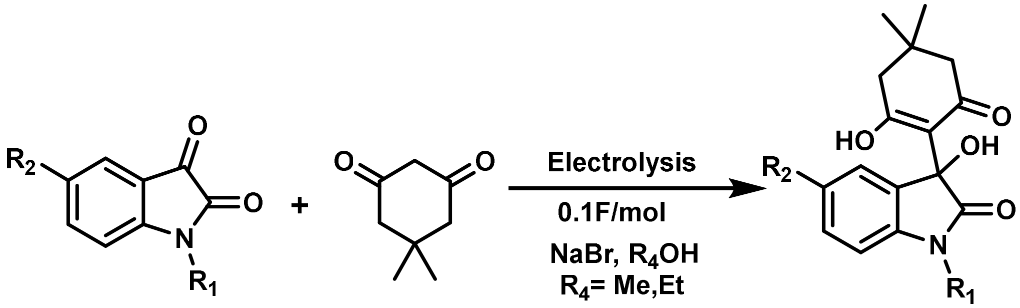
Scheme 1.4 Synthesise C-3 functionalized 2-oxindoles

The ketone carbonyl group has been known to react with nucleophiles containing nitrogen atoms like amines, hydrazines, semicarbazides, and thiosemicarbazides to generate imines [72, 73], hydrazones [74], semicarbazones [26], and thiosemicarbazones [75], respectively. These nucleophiles frequently interact with isatins at room temperature or after a brief period of heating without a catalyst. The formation of quaternary 3-aminooxindoles in aqueous media by propargylation and allylation in zinc and indium catalysts, respectively, is described using isatin-3-imines and isatin-3-hydrazones [76]. Alkynes are added to N-*tert*-butylsulfinylimine of isatin using dialkylzinc [77]. It has been discovered that the Mannich reaction of N-protected isatin-3-imines with hydroxyacetone results in forming 3- amino-2-oxindoles in the presence of chiral primary amino acid as a catalyst [78]. The 3-alkylidene-2-oxindoles, frequently used in synthesizing spiro-fused cyclic frameworks, are produced directly through the reaction of isatins with the proper Wittig reagent and with active methylene compounds **(Scheme 1.5)** [79].



Scheme 1.5 Synthesis of 3-alkylidene-2-oxindoles

The 3-substituted 3-hydroxy-2-oxindoles produced by isatin's aldol reactions serve as crucial synthesis intermediates for various physiologically active alkaloids [80, 81]. In an undivided cell, 3-substituted 3-hydroxy-2-oxindoles are produced in good yields by an electrochemical aldol reaction between isatins and cyclic 1, 3-diketones of alcohol **(Scheme 1.6)** [82].

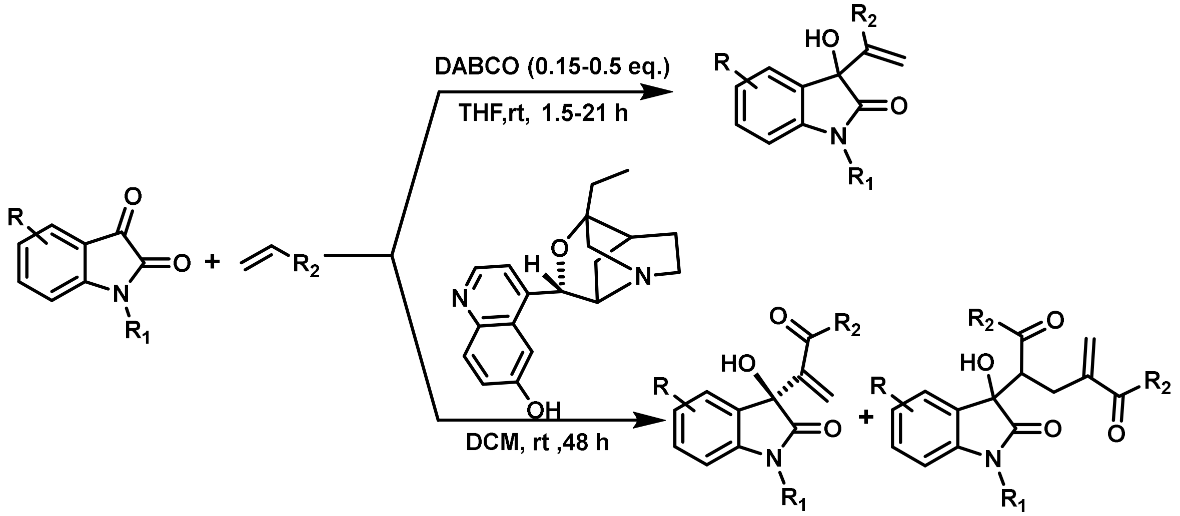


Scheme 1.6 Synthesis of 3-substituted 3-hydroxy-2-oxindoles

It has been attempted to perform the method enantioselectively since the aldol reactions of isatins convert the C-3 carbonyl carbon into a chiral center and have stereochemical repercussions. There are numerous instances of isatins reacting with inactivated carbonyl compounds in an enantioselective organocatalytic aldol fashion [83-85].

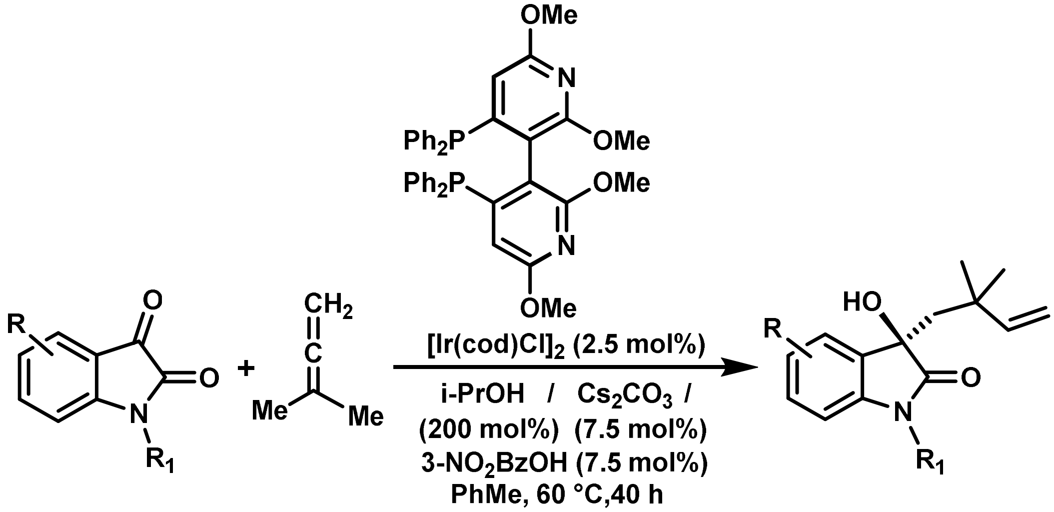
Isatins can also be converted to 3-hydroxy-3-nitromethyl-2-oxindoles by the nitro-aldol process with nitromethane, sometimes referred to as the Henry reaction, which uses diethylamine as a catalyst [86]. These nitromethyl-adducts are privileged compounds that have been used as building blocks in the total synthesis of natural products and their analogs since the nitro functionality can be directly transformed into a wide range of functional groups, such as ketone, amine, nitrile oxide, carboxylic acid, and so on.

Isatins have also been utilized in the Morita-Baylis-Hillman reaction as electrophilic components [87]. Activated alkenes react with isatin, as well as N-substituted isatins, in the presence of 1, 4-diazabicyclo[2.2.2]octane (DABCO) to produce an adduct (**Scheme 1.7**) [88].



Scheme 1.7 Synthesis of Morita-Baylis-Hillman adducts of isatin

Palladium-catalysed asymmetric allylation of isatins has been described with allyl alcohols in the presence of a new phosphorimidite ligand [89]. It is reported that allyl acetate reagents or 1,1-dimethylallene are used as precursors for transitory allyl-metal intermediates in an Ir-catalyzed transfer hydrogenation method for the allylation, crotylation, and reverse prenylation reactions of isatins [90]. Isatins were reverse prenylated with 1,1-dimethylallene to produce enantioselective compounds with good yields **(Scheme 1.8)**. While certain intricate additive combinations are needed, stoichiometric amounts of allyl metal reagents are not always necessary for this procedure.

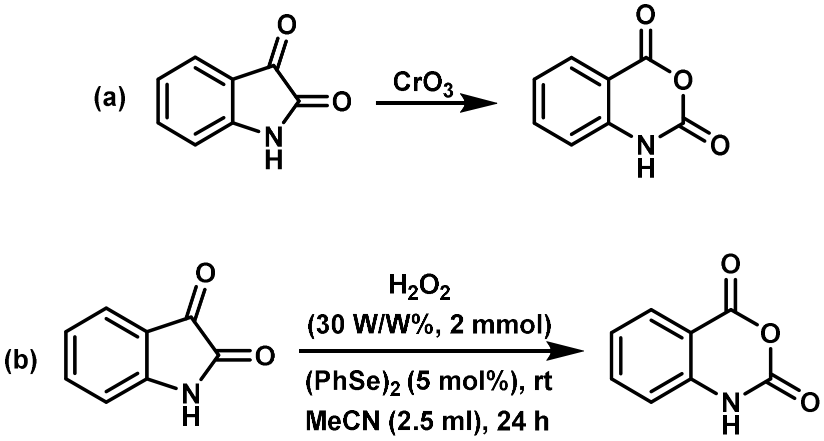


Scheme 1.8 Synthesis of enantioselective isatin derivatives

1.3.4 Oxidation

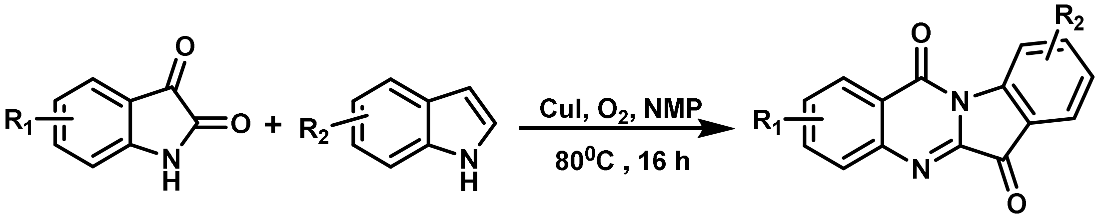
When oxidizing isatin to isatoic anhydride, the oxidizing agent of choice should be able to introduce an oxygen atom between the two nearby carbonyl groups without significantly destroying the ring structure. In the oxidation of isatins, many reagents, primarily peracids, have been successfully utilized in addition to chromium trioxide **(Scheme 1.9a)** [91].

The Oxidative transformation of isatin to isatoic anhydride was developed by Yu et al. using the selective organoselenium catalyst in the presence of H_2O_2 under mild and neutral conditions **(Scheme 1.9b)** [92].



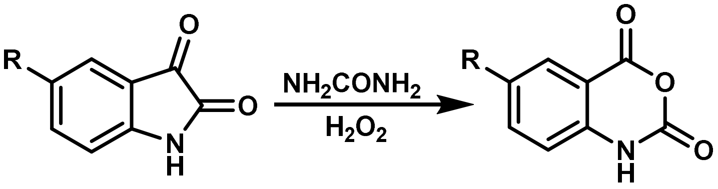
Scheme 1.9 Synthesis of isatoic anhydride

According to Moskovkina et al., the oxidation of isatin and its 5-substituted analogues with potassium permanganate in anhydrous acetonitrile produced the physiologically active molecule tryptanthrin [93]. Another study used CuI to catalyze the oxidative condensation of isatins and indoles to produce tryptanthrin and its derivatives **(Scheme 1.10)** [94].



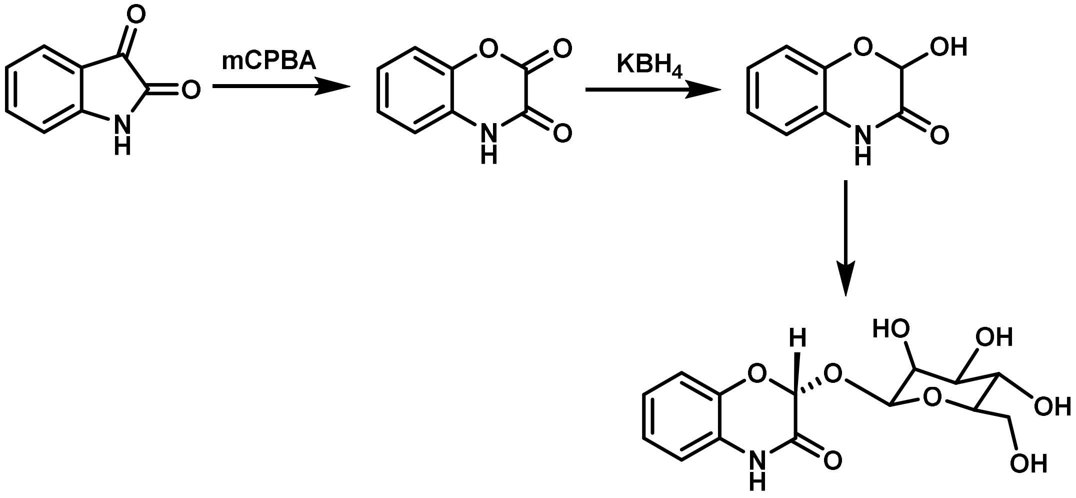
Scheme 1.10 Synthesis of tryptanthrin and its derivatives

A new, cheap, and eco-friendly oxidation of isatin was developed by Deligeorgiev et al. [95], by using the urea–hydrogen peroxide complex [92] (percarbamide, H_2NCONH_2. H_2O_2). After 24 hours, the oxidation produced yields in the range of 44-97% using either formic acid and sulfuric acid or a mixture of acetic anhydride and acetic acid as the catalyst. Additionally, the reactions produced highly pure isatoic anhydrides while operating at ambient temperature. The reaction time was reduced to 20 – 135 min after the mixture was exposed to ultrasound **(Scheme 1.11)**.



Scheme 1.11 Synthesis of derivative of isatoic anhydride

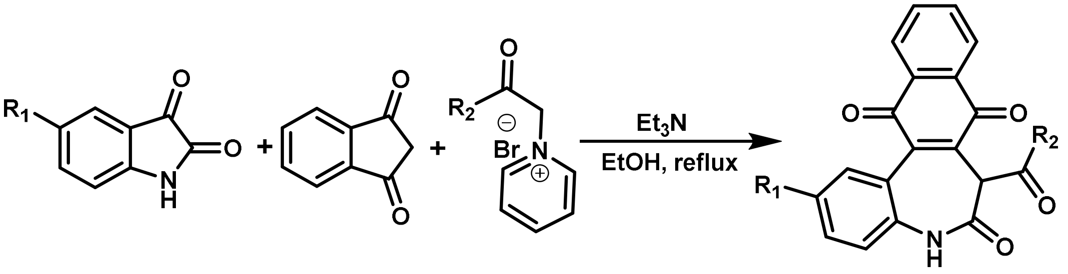
1,4-Benzoxazine-2,3(4H)-dione is produced via the oxidation of isatin with metachloroperbenzoic acid and was subsequently transformed into blepharin (glycoside obtained from Blepharis edulis Pers)**(Scheme 1.12)** [96].



Scheme 1.12 Synthesis of 1,4-Benzoxazine-2, 3(4H)-dione

1.3.5 Ring expansion reactions

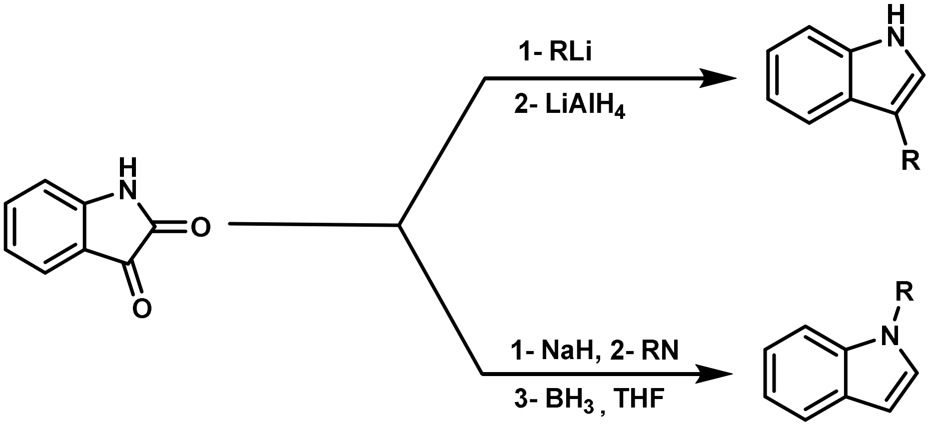
It has been claimed that the isatin ring was expanded by a particular two-carbon method to create the functionalized dibenzo [b,d]azepin-6-one scaffold **(Scheme 1.13)** [97]. N-substituted pyridinium bromide and indene-1,3-dione provide the two carbon atoms needed for the ring expansion.



Scheme 1.13 Synthesis of dibenzo [b,d]azepin-6-one scaffold

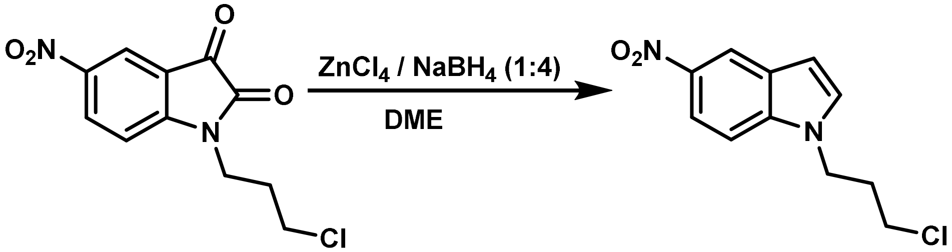
1.3.5 Reduction

Indoles were produced in moderate yields by reducing isatins with the help of lithium aluminum hydride in pyridine. However, in an inert environment, higher yields were made using solvent THF, and this approach was used to create substituted ellipticine derivatives. The Chemoselective alkylation of isatins occurs at sites N-1 or C-3; according to Menicagli et al., 1- or 3-alkyl indoles are produced when these compounds are subsequently reduced with metal hydrides (**Scheme 1.14)** [98].



Scheme 1.14 Synthesis of derivatves of indole

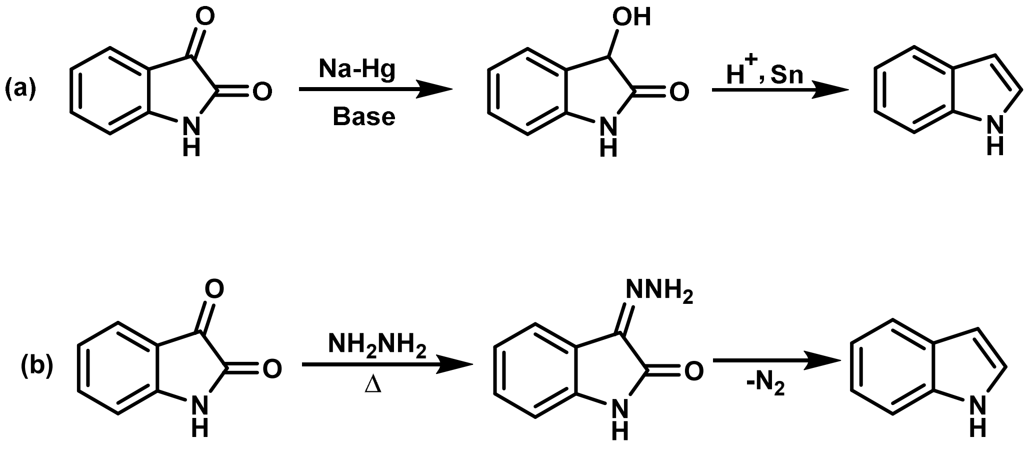
The reduction of *N*-acetylisatins [99] to *N*-alkylindoles was described by Pinto et al. [56] in 1994 using mild reaction conditions. Additionally, indoles have been successfully synthesized from N-substituted-5-nitroisatin utilizing the $ZnCl_4/NaBH_4$ combination in DME at ambient temperature **(Scheme 1.15)**. However, only 30% of the 5-nitro-direct isatin's reduction resulted in the desired 5-nitroindole [100].



Scheme 1.15 Synthesis of *N*-alkylindoles

Isatin, dioxindole, and oxindole's partial reduction products have been extensively used in chemical synthesis, particularly for creating new medications. Dioxindoles are produced by reducing isatin or adding carbanion to the C-3 ketone activity. Numerous methods can achieve this reduction, such as electrochemical and photochemical reductions [101], Fe/HCl in aqueous ethanol, and Zn/$HgCl_2$ in refluxing benzene [29]. By reacting with potassium tetracarbonylhydridoferrate [$KHFe(CO)_4$] [102], N-Methylisatin can be converted to the equivalent dioxindole in a quantifiable yield. Either dioxindoles or isatins are reduced to provide oxindoles. Greater yields of the required product have been obtained from reductions carried out by red phosphorous and iodic acid [29], H_2S in a co-solvent mixture/pyridine or the Wolf-Kishner reaction [103], in the presence of ethanol or isopropanol. Baeyer described the first known preparation of oxindole, which involved the reduction of isatin in two steps with sodium amalgam and base first to produce an intermediate 3-hydroxy-indolinone [104]. The oxindole was subsequently produced by further reducing this hydroxyl indolinone in the presence of tin using acidic conditions **(Scheme 1.16a)**. Crestini [105] developed a one-pot

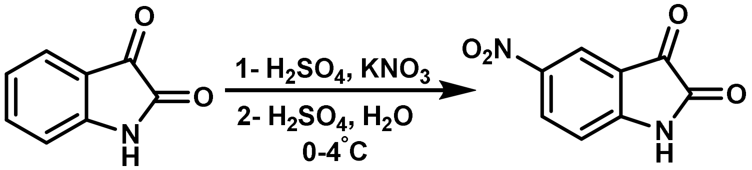
Wolff-Kishner reduction of isatins by refluxing the isatins in 98% hydrazine hydrate for 15 to 30 minutes without isolating the intermediate hydrazones after seeing that the hydrazones of α-dicarbonyl compounds may decompose under relatively mild circumstances **(Scheme 1.16b)**.



Scheme 1.16 Synthesis of indole

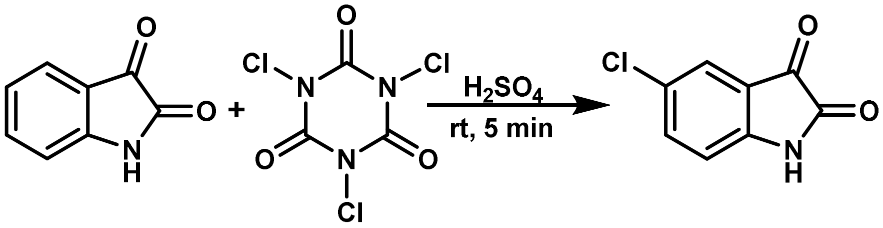
1.3.7 Electrophilic Aromatic Substitution of Isatin

The nitration at the C-5 position of isatin was reported by Calvery using fuming nitric acid in conc. sulfuric acid in 1925 [106]. However, a more practical method to produce 5-nitroisatin is to add dropwise a solution of isatin in sulfuric acid to a solution of potassium nitrate saturated in concentrated sulfuric acid at 0-4 ºC **(Scheme 1.17)**. The resultant isatin, whose melting point is 252-254 ºC, was isolated as crystals of a bright yellow or orange colour [107].



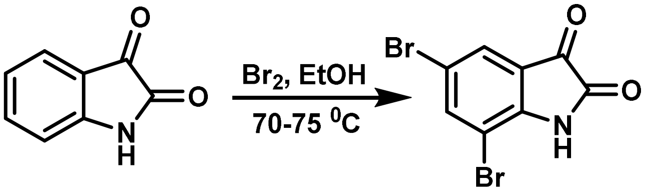
Scheme 1.17 Synthesis of 5-nitroisatin

N-Chloroamides, N-Chloroimides, and N-Chlorosaccharides have all been used to explain the chlorination of isatin at the C-5 position in a heterogeneous media (SiO_2/CH_2Cl_2) [108]. Moreover, a comparatively cheap path for chlorinating isatin at 5-position was reported by G. F. Mendoca using stable reagent trichloroisocyanuric acid (TICA) within 5 minutes without chlorination at N-position of isatin **(Scheme 1.18)** [109]. Isomeric 7-chloroisatin [11] was spotted in the reaction product through HRGC (high-resolution gas chromatography).



Scheme 1.18 Synthesis of 5-chloroisatin

Vine et al. described one approach for synthesizing various substituted bromo derivatives such as 5, 7-dibromoisatin, 5, 6-dibromoisatin, and 5, 6, 7-tribromoisatin under different bromination conditions **(Scheme 1.19)** [107]. Krishnegowda and colleagues continued this study to provide N-bromo derivatives from the starting material, 5, 7-dibromoisatin [110].



Scheme 1.19 Synthesis of 5, 7-dibromoisatin

1.3.8 Synthesis of isatin-based spiro-fused heterocyclic scaffolds

Spiro-cyclic framework construction has been difficult for synthetic chemists since it frequently demands a synthetic design based on specific techniques. Owing to steric strain, the existence of a spiro carbon atom triggers specific rearrangements, which can lead to various ring compounds. Isatins may be the only class of heterocyclic compounds that have been utilized so frequently in the design and synthesis of diverse spiro-cyclic frameworks, both carbocyclic and heterocyclic, either directly or through 3-substituted 2-oxindoles in such a complex scenario **(Figure 1.6)**.

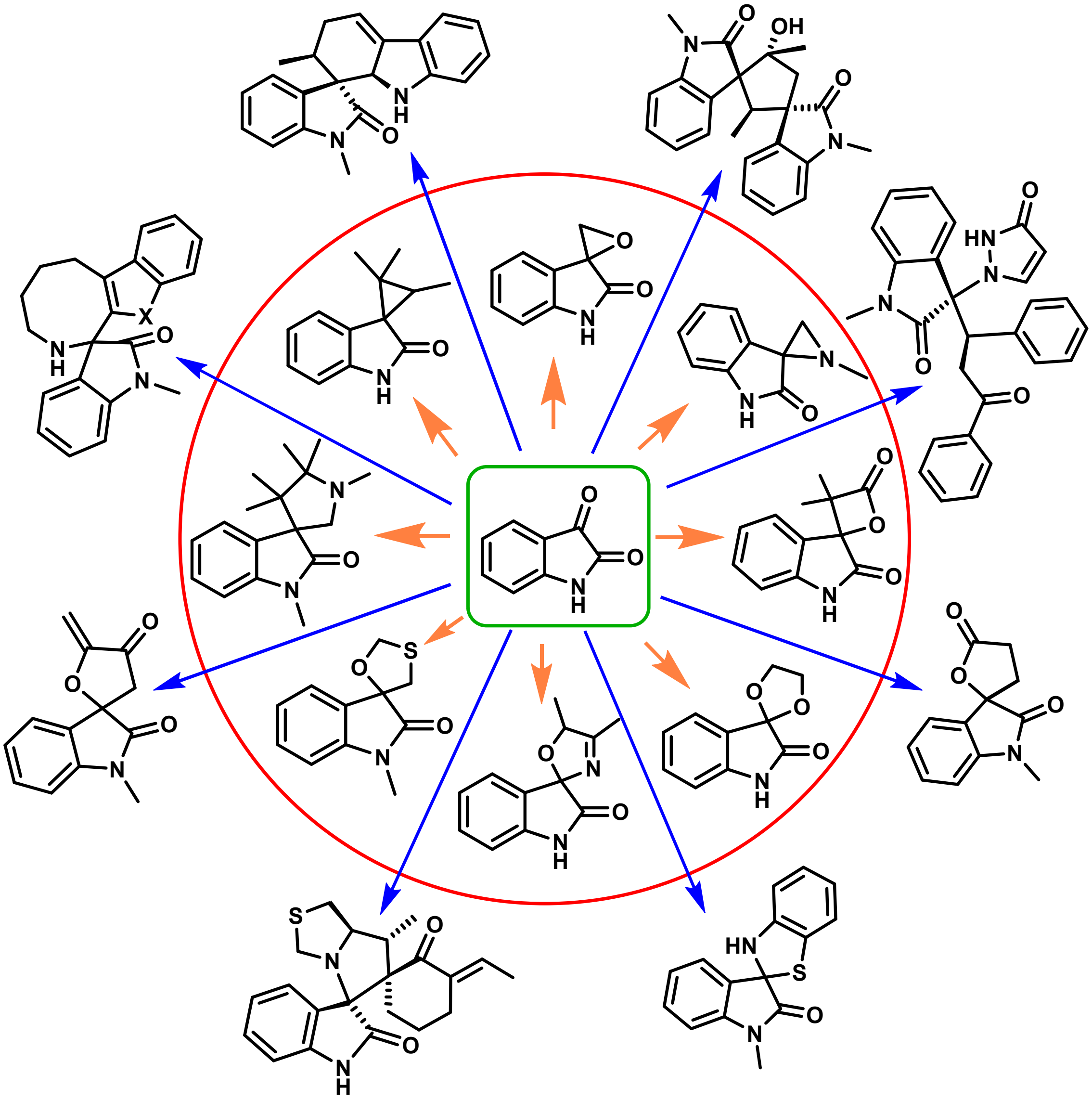
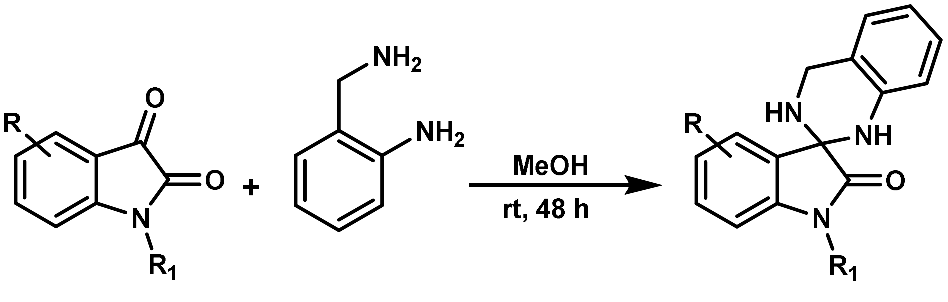


Figure 1.6 Structure of spiro-heterocyclic compound

Different spiro-heterocyclic moieties containing 2-oxindoles have been synthesized using isatins and their C-3 derivatives [111]. Such compounds are frequently formed from cyclocondensation or cycloaddition reactions of isatins with other reagents. Spiro-heterocyclic frameworks can now be easily and quickly synthesized in a single pot using multicomponent cascade reactions of isatins [112]. But in many cases, a straightforward C-3 isatin derivative, such as alkylideneisatins, isatin hydrazones, isatin imines, aldol-adducts of isatins, Baylis-Hillman adducts of isatins, etc., is sufficient to synthesize the desired spiro-heterocycle [113]. New asymmetric syntheses that produce complex compounds in an enantioselective way have been devised employing chiral metal complexes, chiral auxiliaries, and chiral organocatalysts.

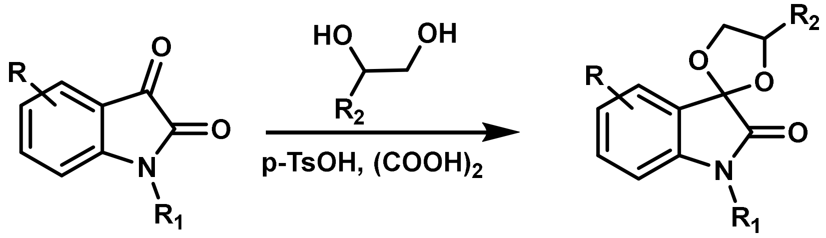
The formation of spiro-fused 2-oxindoles and 5- or 6-membered spiro-azaheterocycles has been described by the reactions of isatins with 1, 2-diamines, 1, 3-diamines, and ammonia (Bergman) [114, 115]. The synthesis of 2-oxindole spiro-fused to a 1, 2-dihydroquinazoline ring was developed by Cornforth in 1976 from a 1:2 molar reaction of isatin and ammonia [116]. The spiro-*N, N*-dimethylimidazolidine-oxindole was formed from the reaction of *N, N*-dimethylethylenediamine with isatin in the presence of water [117] and the spiro-tetrahydroquinazoline-oxindoles [118, 119] products were formed from the reaction of 2-aminobenzylamine with isatins in methanol solvent at room temperature (**Scheme 1.20**).



Scheme 1.20 Synthesis of spiro-*N, N*-dimethylimidazolidine-oxindole

However, a spiro-fused 2-oxindole was produced from a 1: 2 molar interaction between 2-aminobenzylamine and isatins in acetic acid [120, 121]. The condensation reaction of *o*-phenylenediamine with isatin in refluxing methanol has provided only a trace amount of the spiro-fused product [122]. While the reactions of *o*-phenylenediamine and 2,3-diaminopyridine with *N*-acylisatins in ethanol and acetic acid provide spiro-dihydroimidazole-oxindoles [51]. The spiro-1, 2, 5-oxadiazolo- imidazolidine-oxindole was synthesized from the cyclocondensation of a heterocyclic 1, 2-diamine, 3, 4-diaminofurazane with isatin in acetonitrile [123]. It has been claimed that isatins and 2-nitrobenzamides react with tin (II) chloride to produce spiroquinazolinone-oxindoles [124]. Together with the oxidized tin (IV), the tin (II) acts as an activator for the C-3 keto group of isatin and also a reducing reagent for changing the nitro group to the amino group of amides. It is important to note that the previous reports on the formation of these compounds involved a one-pot three-component reaction including isatins, amines, and isatoic anhydride [125].

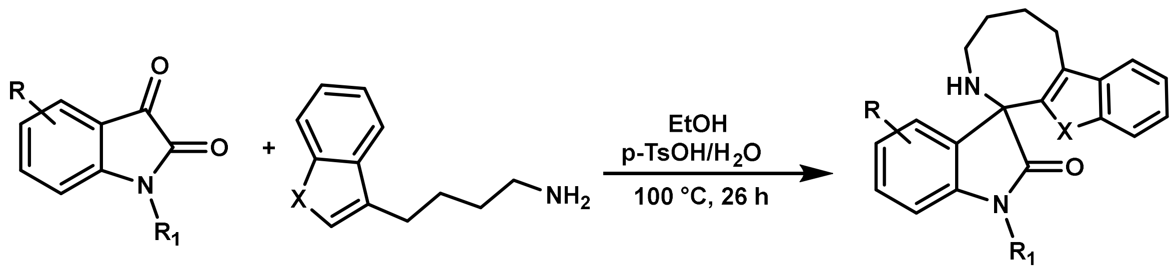
The reaction of ethylene glycols with isatin has been described to produce the spiro-dioxolane-oxindoles [126-128] under heterogeneous and homogeneous **(Scheme 1.21)** catalysis using the very acidic resin Dowex 50X-X2 [126-128]. This reaction is similar to the reaction of 1, 2-diamines with isatins.



Scheme 1.21 Synthesis of spiro-dioxolane-oxindoles derivatives

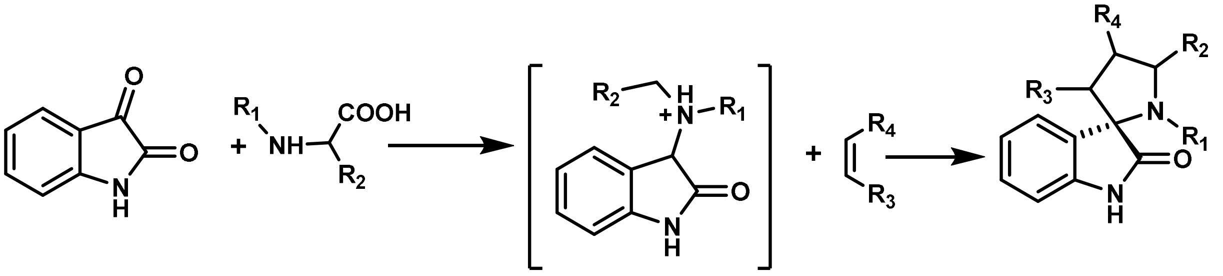
However, a heterogeneous catalyst is favored since it allows for a more environmentally friendly transformation without using more solvent [129]. The Keggin's heteropolyacids, specifically heteropolyphosphotungstic acid (HPW), Cs_2.2HPW, and HPW/SiO_2, are used to produce high yields of spiro-dioxolaneoxindoles without the need for solvents from isatin and 5-chloroisatin [130]. Isatin reacts with 2-aminothiophenol to provide spiro-benzothazoline-oxindoles in variable yields based on reaction conditions and the substituent present at the N-atom of isatin moiety [131].

However, when isatins are used as the ketone component in the Pictet-Spengler reaction [132, 133], the cyclization of isatins is switched to the carbonyl C-3 position, resulting in spiro molecules like spiro-tetrahydrocarboline-oxindoles. The access to seven- and eight-membered spiroazaheterocycles, such as spiro-tetrahydroazepine-oxindoles and spiro-hexahydroazocene-oxindoles, in lower yields is also made possible by an increase in the length of the amine chain. For instance, the reaction of 4-indol-(3- yl)-1-butanamine with 5-chloroisatin results in an 8% yield of spiro-hexahydroazoceneoxindole **(Scheme 1.22)**.



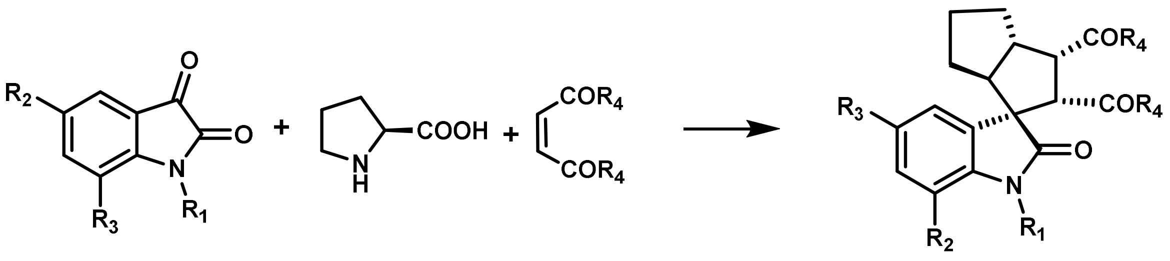
Scheme 1.22 Synthesis of spiro-hexahydroazoceneoxindole derivatives

Rehn et al. produced azomethine ylides by condensing isatin and α-amino acid derivatives in methanol and water, followed by adding the dipolarophiles by 1, 3-dipolar addition to forming pyrrolidine-2-spiro-3-(2-oxindole) **(Scheme 1.23)** [134-137].



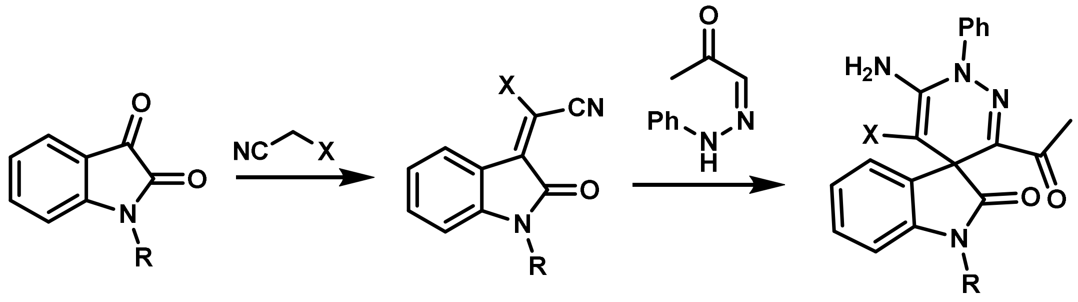
Scheme 1.23 Synthesis of pyrrolidine-2-spiro-3-(2-oxindole) derivatives

Maleates or maleamides have been used as dipolarophiles to generate two amide groups or two ester groups containing spiropyrrolizidine oxindoles **(Scheme 1.24)** [138].



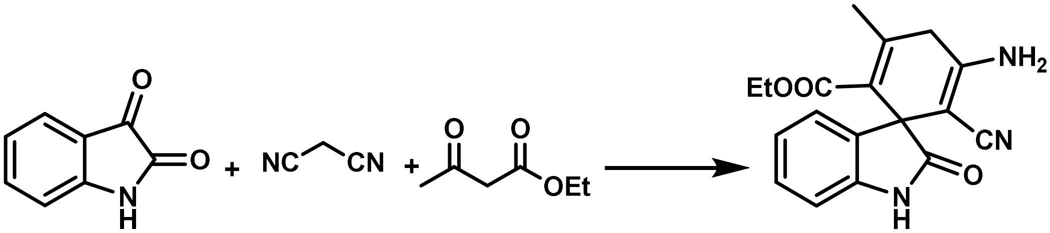
Scheme 1.24 Synthesis of spiropyrrolizidine oxindole derivatives

Using DBU as a catalyst, the Knoevenagel condensation reaction between isatin derivatives and active methylene reagents yielded 3-cyanomethylidene oxindole derivatives in excellent to good yields [139]. Then, these compounds underwent a Michael addition reaction with azaenamine that was enhanced by DBU to create spiro cyclic 2-oxindole derivatives **(Scheme 1.25)** [140-142].



Scheme 1.25 Synthesis of spiro cyclic 2-oxindole derivatives

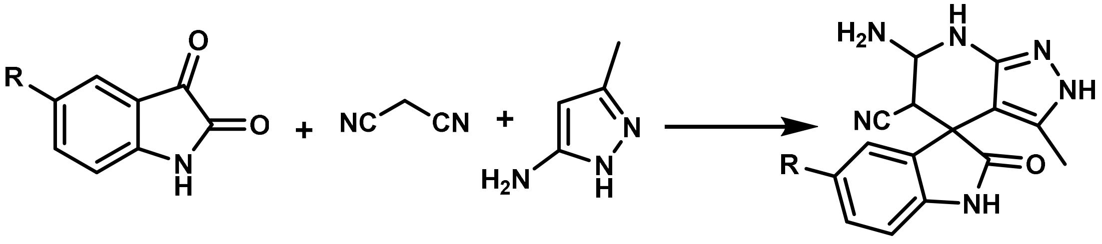
Multicomponent reactions (MCR) of isatin, ethyl cyano-acetate or malononitrile, and 1, 3-dicarbonyl compounds were utilized to synthesize fused spiro[4*H* pyran- oxindole] heterocycles [143, 144]. At the same time, Moghadam et al. produced an identical spiro product using an ionic liquid catalyst such as [BMIm]BF_4 [145]. This technique extensively uses diversity-oriented synthesis, drug discovery, and combinatorial chemistry **(Scheme 1.26)**.



Scheme 1.26 Synthesis of fused spiro[4*H* pyran- oxindole] heterocycles

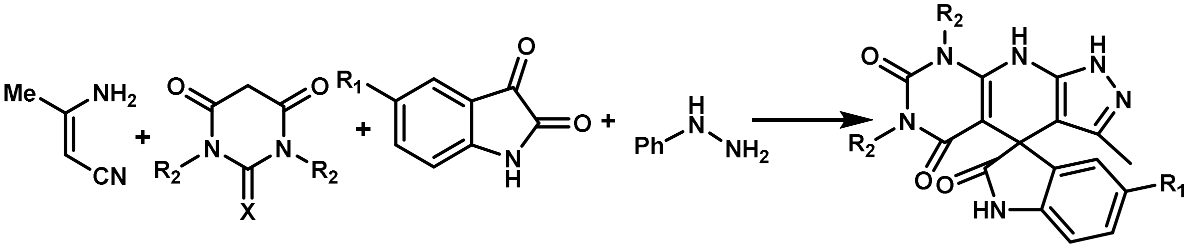
Jain et al. used 1-(6-bromohexyl)-1H-indol-2, 3-diones to create several unique unsymmetrical bis-indol-2, 3-diones in a contemporary synthesis. Through the application of previously unknown bis Schiff bases, these compounds have also been used to synthesize novel bis-spiroindoles [146].

Utilizing water as a green reaction media and sodium chloride as a green catalyst, a novel regio- and diastereoselective three-component synthesis of isatin, a-cyanoacetic ester, or malononitrile, and 5-amino-3-methylpyrazole was created to produce therapeutically beneficial pyrazolopyridinyl spirooxindoles **(Scheme 1.27)** [147, 148].



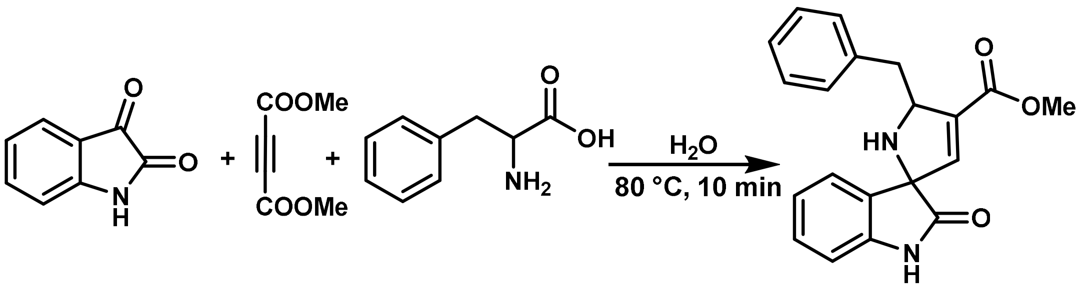
Scheme 1.27 Synthesis of pyrazolopyridinyl spirooxindole derivatives

A new four-component domino reaction of isatin/acenaphthylene-1,2-dione, 3-aminocrotononitrile, phenylhydrazine, and cyclic 1, 3-dicarbonyl compounds was reported by Balamurugan et al. [149] to produce spiro[indoline-3,4'-pyrazolo[3,4-b]pyridines in good to excellent yield using cellulose sulfuric acid (CSA) in the aqueous medium **(Scheme 1.28)** [150-152].



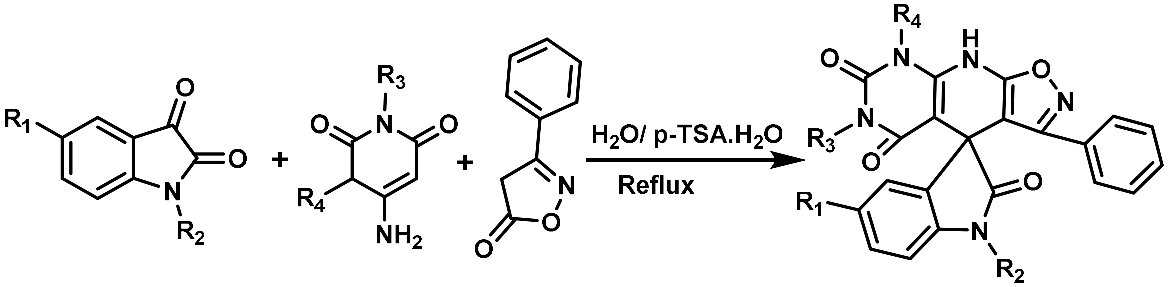
Scheme 1.28 Synthesis of spiro[indoline-3,4'-pyrazolo[3,4-b]pyridine derivatives

A catalyst and the base-free three-component reaction of isatin, but-2-ynedioates, and amino acid, was developed by Meshram et al. to provide spirooxindole compound containing isatin moiety using microwave irradiation (150W power) in the presence of aqueous medium **(Scheme 1.29)** [153-155].



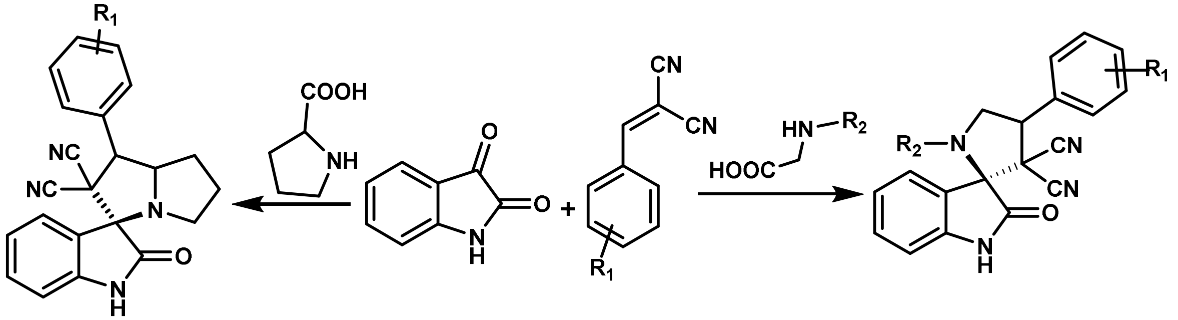
Scheme 1.29 Synthesis of spirooxindole compound containing isatin moiety

A new, single-pot multicomponent reaction of isatins, isooxazolones, and aminouracils has been reported to form a diverse spirooxindole-based framework regioselectively [156]. This synthesis was discovered preferably when N-alkyl/aryl/benzyl-substituted isatins were used; however, the side product isoxazoloquinolines were mainly produced **(Scheme 1.30)** [157, 158].



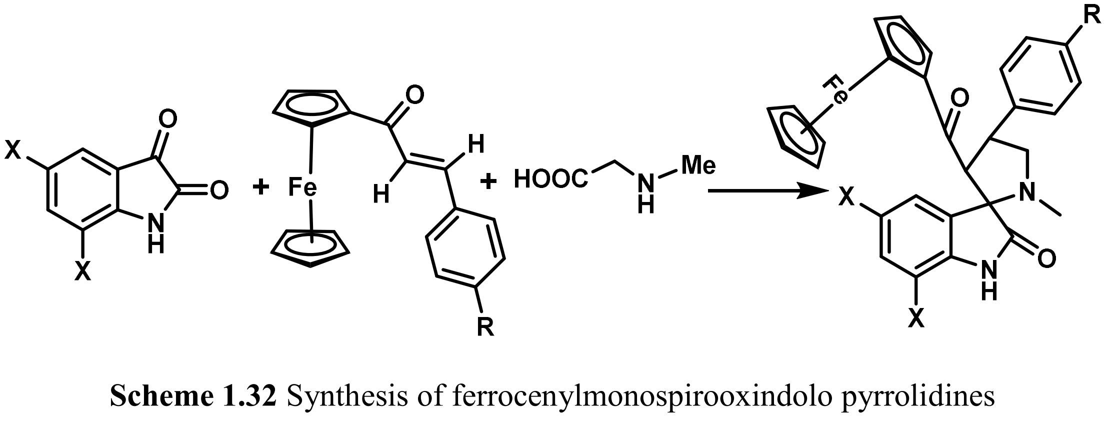
Scheme 1.30 Synthesis of regioselective spirooxindole-based framework

According to Companyo et al. [159], a stereoselective reaction combining oxindole, aldehyde, and benzoic acid using a modified proline catalyst produced the final spiro product with exceptional stereoselectivity in excellent yields. In a recent study, Chen and coworkers investigated the 1, 3-dipolar cycloaddition reactions of isatin, α-amino acids, and (E)-b-nitro-styrene, which demonstrated varied regioselectivity [160].Various arylidenemalononitrile were subjected to ordinary heating and ultrasonic irradiation conditions to react with nonstabilized azomethine ylides made from isatin and α-amino acids to form novel dicyano-functionalized spiropyrrolidine and spiropyrrolizidine [161] **(Scheme 1.31)**.



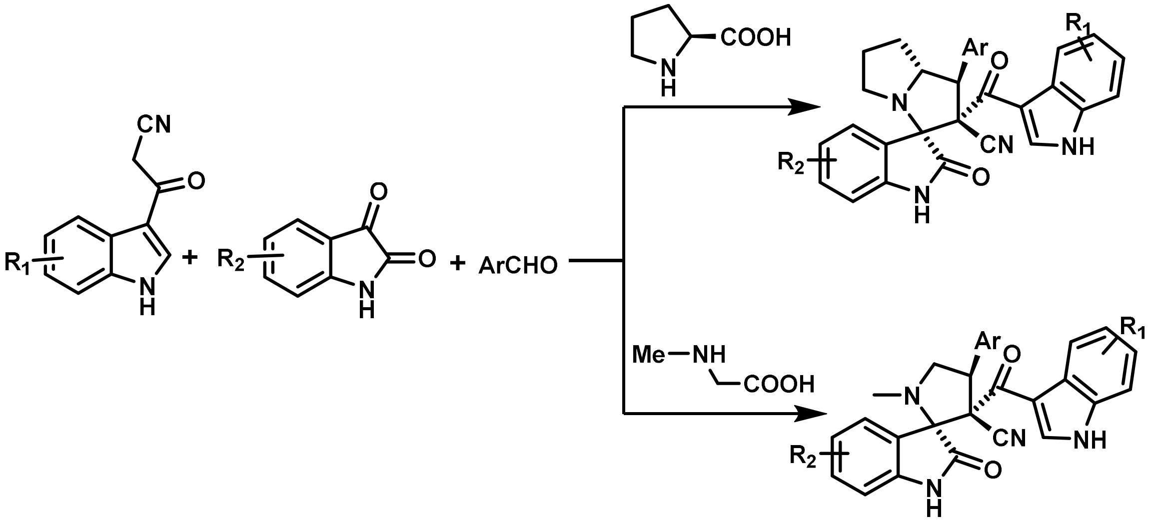
Scheme 1.31 Synthesis of dicyano-functionalized spiropyrrolidine and spiropyrrolizidine

Multicomponent reaction (MCR) of substituted isatins, 2-thioxo-4-thiazolidinone and active methylene reagent has been reported to provide novel spiro[indoline-3,4'-pyrano [2,3-c]thiazole]carbonitriles and condensed thiazole [5'',4'':5',6']pyrano[4',3':3,4]furo[2,3-b]indole derivatives through both conventional heating and microwave irradiation using NIO as a nanoparticle catalyst [162]. The formation of new ferrocenylmonospirooxindolo pyrrolidines in good yield was achieved by the [3+2]-cycloaddition reaction of different azomethine ylides of α-amino acids (proline, sarcosine) and isatins with several uncommon dipolarophilic partners such as ferrocene derivatives **(Scheme 1.32)** [163, 164].



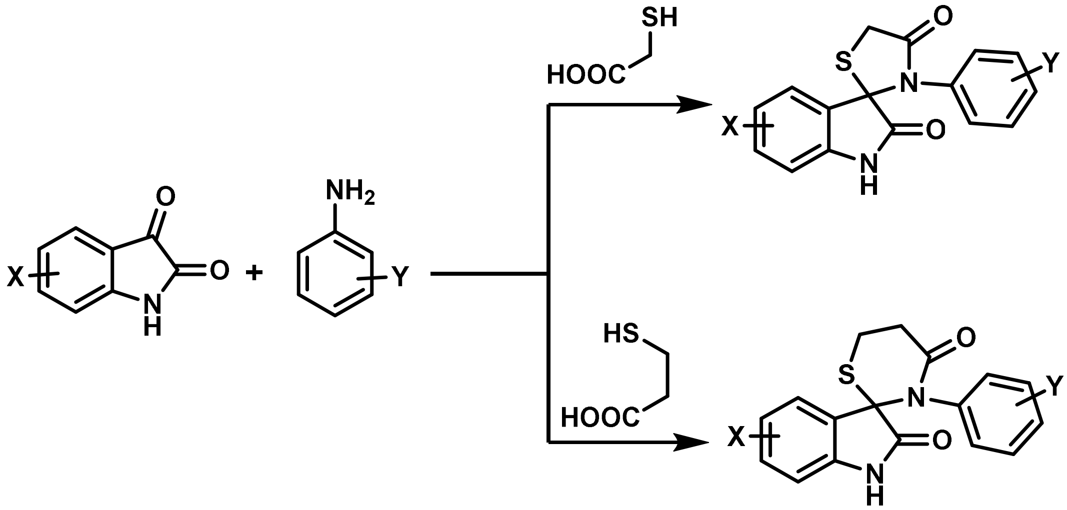
Scheme 1.32 Synthesis of ferrocenylmonospirooxindolo pyrrolidines

Ji and coworkers described a multicomponent reaction ([3+2] cycloaddition reaction) of 3-cyano-acetylindoles amino acids, aldehydes, and isatin **(Scheme 1.33)** [165].



Scheme 1.33 Multicomponent reaction ([3+2] cycloaddition reaction) of 3-cyano-acetylindoles amino acids aldehydes and isatin

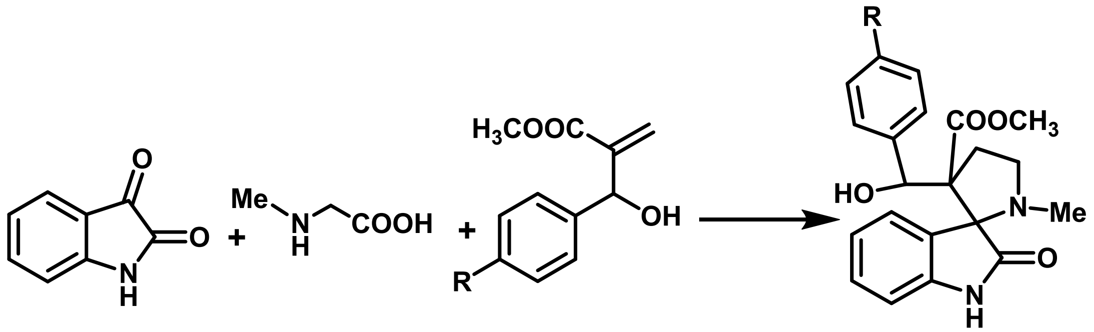
The synthesis of fluorinated spiro[3*H*-indole-3,2'-thiazolidine]- 2,4' (1*H*)-diones and fluorinated spiro[3*H*-indole-3,2'-tetrahydro-1,3-thiazine]-2,4' (1*H*)-diones was developed in good yield by Arya et al. using Bronsted acidic ionic liquid such as 1-methylimidazolium and 1-butyl-3-methylimidazolium and inorganic anions such as BF_4, PF_6, and p-TSA as catalysts via microwave irradiation [166]. Zeolite-supported Bronsted acid-catalyzed synthesis of Spiro[3*H*-indole-3,2'-[4*H*]pyrido[3,2-e]-1,3-thiazine]-2,4' (1*H*)diones was developed by reaction of 2-mercaptonicotinic acid with in situ–generated 3-indolylimine derivatives under ultrasonication. Instead of using conventional or microwave (MW) methods, ultrasonication is preferable (**Scheme 1.34**) [167].



Scheme 1.34 Synthesis of Spiro[3*H*-indole-3,2'-[4*H*]pyrido[3,2-e]-1,3-thiazine]-2,4'(1*H*)diones

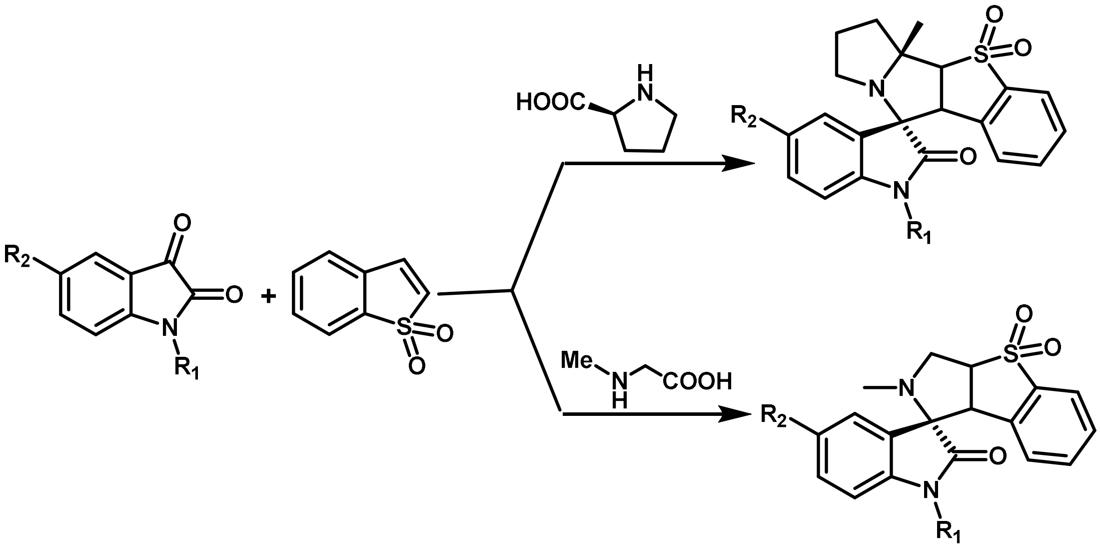
The formation of spiro[indoline-3,4'-pyrazolo[3,4-e][1,4]thiazepine]diones has been developed from the reaction of 5-amino-3-methyl-1-phenyl pyrazole, isatin, and 2-mercaptoaceticacid with bioglycerol-based sulfonic acid–functionalized carbon as a recyclable catalyst in MeCN [168]. Chen and Shi formed a similar spiro compound in the absence of a catalyst [169]. An efficient, simple, and green approach for synthesizing indole derivative-based spiro compound was developed from the reaction of *o*-amino thiophenol with indole-2,3-diones under aqueous micellar media using tetrabutylammonium bromide (TBAB) (15 mol%) as a surfactant [170]. The cycloaddition reaction of the olefinic bond of

Baylis–Hillman adducts with azomethine ylides was reported by Jayashankaran and coworkers to provide consistent cycloadducts as only regioisomers **(Scheme 1.35)** [171].



Scheme 1.35 Synthesis of spiropyrrolidines derivatives

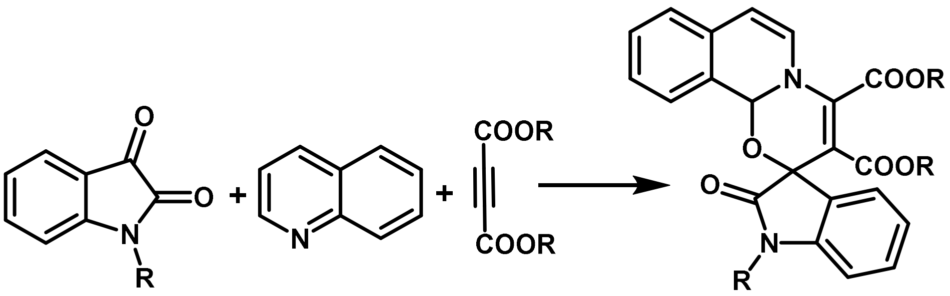
Using a 1, 3-dipolar cycloaddition reaction with isatin 1, 1-benzothiophene 1, 1-dioxide, sarcosine, or L-proline, a series of spirooxindoles including tri- and tetracyclic fused pyrrolo-benzothiophene 1, 1-dioxide derivatives were created **(Scheme 1.36)** [172].



Scheme 1.36 Synthesis of pyrrolo-benzothiophene 1, 1-dioxide derivatives

The 1, 3-dipolar cycloaddition reaction of isatin derivatives with the nitrile oxide generated in situ from 4-methoxybenzaldoxime, and sodium hypochlorite was developed to provide novel spiro [1, 4, 2-dioxazole-5, 3’-indolin]-2’-one derivatives [173].

A new spiro dioxa-bridged indole derivative was formed as a mixture of diastereomers from α-diazo ketones and isatin using $Rh_2(OAc)_4$ [174]. Isatin produced the necessary spiro systems with three heterocyclic moieties: indole, indazole, and thiazolidine, combined with 5-aminoindazole and mercaptoacetic acid [175]. The formation of spiro[1,3] oxazino [2,3-a] *N*-heterocyclic derivatives has been developed yields by Yavari et al. [176] from dialkyl acetylenedicarboxylates (DMAD) and *N*-heterocycles (isoquinoline, quinolone, orpyridine) in excellent yield using of *N*-alkylisatins or ninhydrin. The functionalized spiro compounds discussed in this paper could be considered valuable synthetic intermediates because they include atoms in multiple oxidation states (**Scheme 1.37)** [177].

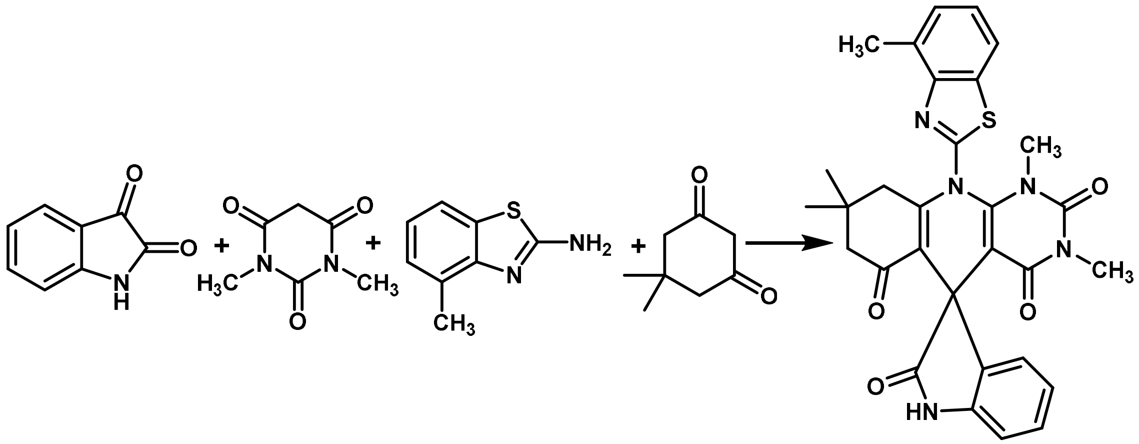


Scheme 1.37 Synthesis of spiro[1,3] oxazino [2,3-a] *N*-heterocyclic derivatives

The synthesis of spirooxindoles was reported via a single-pot, three-component reaction of isatin, barbituric acid, and isoxazole, in water using *p*-toluene sulfonic acid as a catalyst in good yield at 70 ^{0}C [178].

A one-pot, pseudomulticomponent approach for synthesizing spiro[diindenopyridine-indoline]triones and spiro[acenaphthylene-diindenopyridine]triones was developed by Ghahremanzadeh and coworkers from the reaction of 1, 3-indandione, isatin or acenaphthylene-1, 2-dione and aromatic amines, using a "grindstone chemistry" method [179]. Sun et al. observed a comparable reaction for a synthetic spiro molecule with acetone as an alternative of 1, 3- indandione [180].

The synthesis of structurally different spiroheterocycles with fused heterostructures utilizing an effective and environmentally friendly method was described by Kumar et al. employing a halogen-free -SO_3H functionalized ionic liquid/water as a recyclable medium **(Scheme 1.38)** [181].

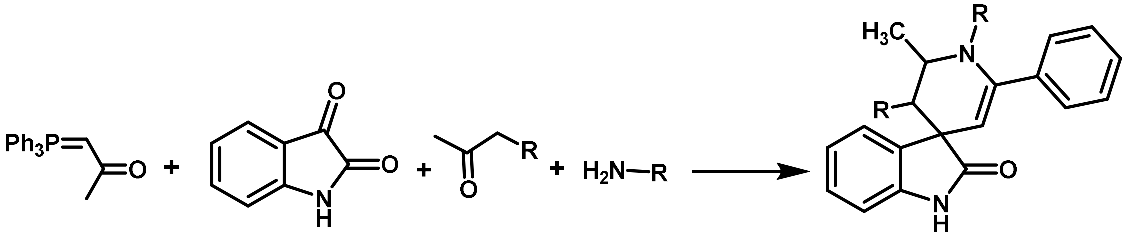


Scheme 1.38 Synthesis of spiroheterocycles in SO_3H-functionalized ionic liquid/water system

The formation of novel spironaphthopyrano[2,3-d]pyrimidine-5,3’-indolines and spiro[dibenzo[a,i]-xanthene-14,3’-indoline]-2',8,13-triones was described by Yang and coworkers through a single-pot, three-component reaction with [Hmim][HSO_4] as an effective and recyclable catalyst [182]. The multicomponent reaction of isatin, barbituric acid, and cyclohexane-1, 3-dione derivatives was developed to provide spiro[chromeno[2,3d]pyrimidine-5, 3’-indoline]-tetraones in the presence of ionic liquid media using K-10 as a catalyst for 30 min [183]. In a comparable investigation, Jadidi et al. carry out the same reactions using *p*-TSA as a catalyst in the presence of water [184].

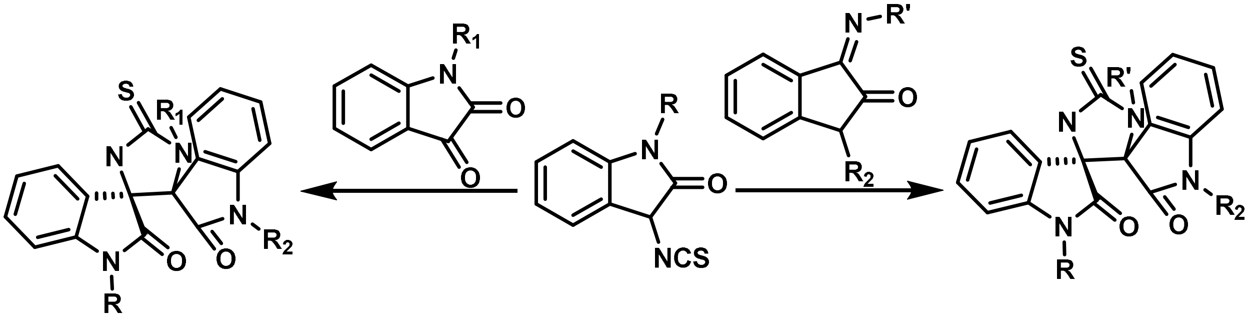
Dodecyl benzene sulfonic acid functionalized silica-coated magnetic nanoparticles were synthesized by Deng et al., which is used for the multicomponent reaction of isatin, barbituric acids, and cyclohexane 1,3-diones to provide various spirooxindole-pyrimidine derivatives [185].

An efficient and simple formation of spiro[indolinepyrido[2,3-d:6,5-d']dipyrimidine] and spiro[pyrimido[4,5-b]quinoline-5,5,-pyrrolo[2,3-d]pyrimidine] derivatives have been described by Jadidi et al. via a cyclocondensation reaction of isatin and 2, 6-diaminopyrimidin-4(3*H*)-one under refluxing ethanol [186]. The synthesis of spiro[indoline-3, 4’-pyridine]-3’-carboxylate derivatives was developed cleanly and efficiently using easily accessible starting materials **(Scheme 1.39)** [187].



Scheme 1.39 Synthesis of spiro[indoline-3,4′-pyridine]-3′-carboxylate derivatives

Dispiro[oxazolidine-2-thione]bisoxindoles and dispiro[imidazolidine-2-thione]bisoxindoles with structurally different properties have been produced using a very effective and diastereoselective reaction between 3-isothiocyanato oxindoles and isatins/isatinimines. Bisoxindoles produce excellent results under benign circumstances **(Scheme 1.40)** [188].



Scheme 1.40 Synthesis of dispiro[oxazolidine-2-thione]bisoxindoles and dispiro[imidazolidine-2-thione]bisoxindoles

Due to the significance of isatin derivatives, we are interested in knowing more about the chemistry of the benzodiazepine ring, indoloindole pyrimidine, and spiro[indoline-3,4'-quinoline. The following **chapters, 2–5,** cover the studies in detail.

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CHAPTER 2

A FACILE AND EFFICIENT MULTICOMPONENT ULTRASOUND-ASSISTED "ON WATER" SYNTHESIS OF BENZODIAZEPINE RING

A facile and efficient multicomponent ultrasound-assisted “on water” synthesis of benzodiazepine ring

2.1 Introduction

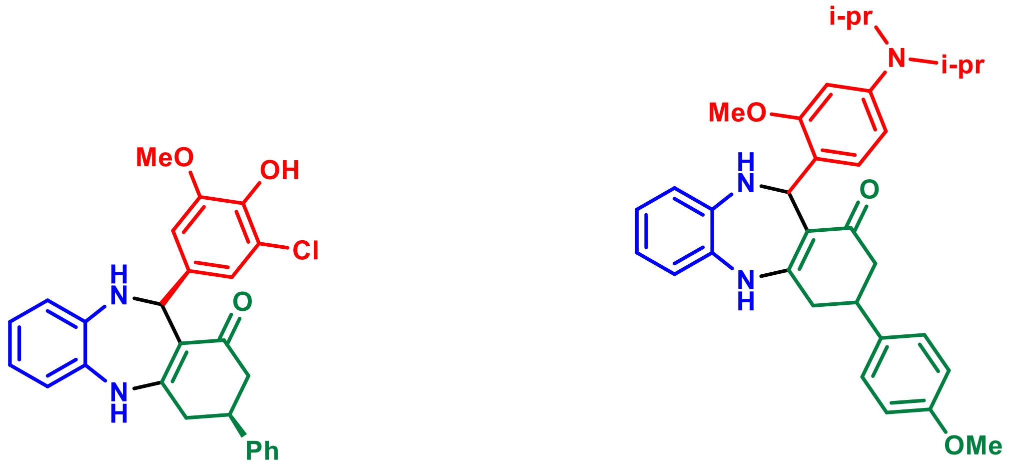
Recently, ultrasound irradiation has emerged as a clean and green method to speed up organic synthetic transformations [1-3]. The prominent advantages of ultrasound-assisted synthesis are high reaction rates, short reaction time, high yield, and mild reaction conditions. Actually, ultrasound radiation gives rise to acoustic cavitations to overcome the molecular attractive forces and to stimulate the mixing of molecules. This increases intimate contact among different molecules to form a highly reactive species and results in the acceleration of the reaction and improved product yields. This procedure is accomplished to stimulate several organic reactions [4-6] . In contrast to the conventional method, which affords thermal energy to the macro-system, the ultrasound-assisted process lessens reaction time, rises yield, reduces waste, and conserves energy by affording the activation energy to the microenvironment accentuates its greener impact.

Water has attracted considerable attention from organic chemists as it is a nonhazardous, inexpensive, ecologically benign, readily available, non-flammable, harmless, and versatile solvent for many chemical reactions. The isolation of the product becomes very easy in water solvents because maximum organic compounds are not soluble in water. They may be obtained in pure form only by filtration and/or recrystallization without column chromatography to avoid using hazardous solvents. “On water” synthesis is a distinctive theory of the increasing rate of organic reaction in the aqueous medium. Commonly, reactions in aqueous media involve the vigorous stirring of water-insoluble reagents due to the absence of organic co-solvents. The reason for higher yield in water is its dual behavior, i.e., as a solvent as well as a catalyst in organic reaction [7-11].

Due to their valued properties, multicomponent reactions have evolved as an effective and powerful tool in modern synthetic organic chemistry. Multicomponent reactions, which lead to fascinating heterocyclic scaffolds, are especially beneficial for developing various "drug-like" molecules [12].

Spiro compounds are an essential group of naturally occurring substances with high biological characteristics. The framework of spirooxindole is a fundamental component of many pharmacological agents and natural alkaloids such as horsfiline, mitraphylline, spirotryprotatin, gelsemine, and others [13-19]. Spirooxindoles act as anti-cancer, anti-viral, antibacterial, and anti-fungal agents. These are the major concerns for medicinal, modern organic, and natural product chemistry. The structural rigidity of spirooxindole and spirocarbon conformation induces biological activities, i.e., NITD 609 and MI77301 are used in malaria diagnosis and cancer therapy, respectively.

Among *N*-heterocyclic compounds, benzodiazepines are the most significant compounds, which developed extensive attention in medicinal chemistry due to their well-known biological and pharmacological activities [20-27] (**Figure 2.1**).



HIV protease inhibitor

Cystathionine Synthase inhibitor

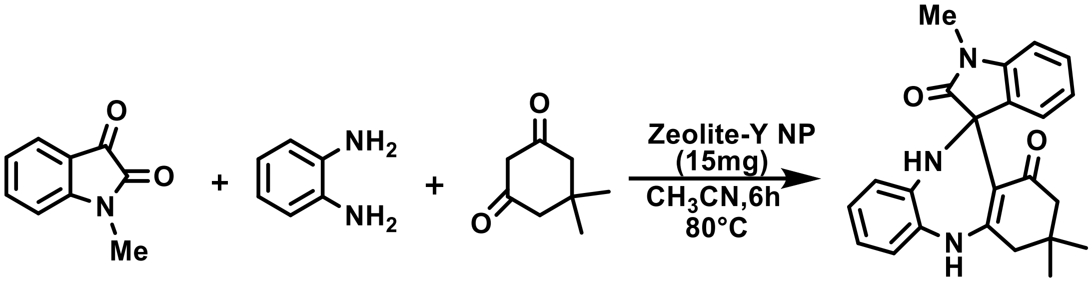
HCV NS5B polymerase inhibitor

Neoromedin B receptor antagonist

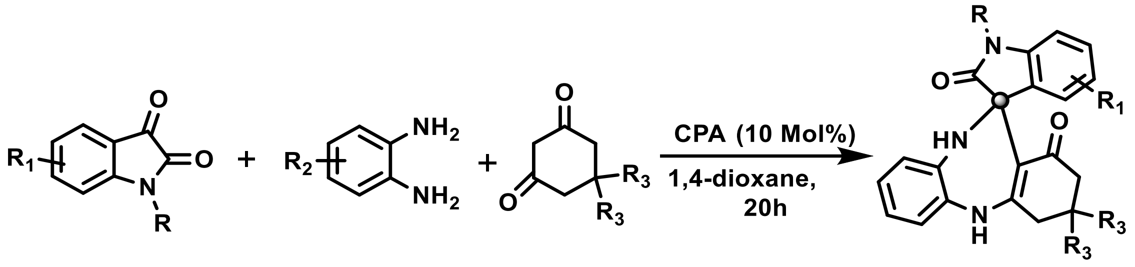
Figure 2.1 Some biologically active compounds having 1, 4-benzodiazepine scaffold

Benzodiazepine rings are one of the most extensively recommended classes of psychotropics due to their significant central nervous system (CNS) sedative activity [28]. Furthermore, benzodiazepine rings containing moiety has found to possess encouraging pharmacological properties and biological activities such as sedative, HIV-1 protease inhibiting [29, 30], anti-inflammatory [31], anti-depressive [32-35], antibiotic [36], antifungal [37, 38], insecticidal [39], anticoagulant [40-43], analgesic [44], and antiepileptic [45]. 1,4-Benzodiazepines are used to treat anxiety, insomnia, muscle spasms, alcohol withdrawal syndrome, and avoid seizures [46]. Such compounds are also used as dyes for acrylic fibres [47, 48] and in photography. Due to their great importance, several synthetic approaches have been developed **(Scheme 2.1 and 2.2)**. Previously O. S. Popovaa et al. [49] described a successive two-step reaction for synthesizing benzodiazepine rings using trifluoroacetic acid as a catalyst. Recently, Wang Shulianga et al. [50] developed a green synthesis of such a ring via a microwave-assisted multi-component reaction of isatin, diphenylamine, and tetronic acid using water as a solvent and acetic acid as a catalyst. Though, this method is associated with the use of catalyst, i.e., acetic acid.

Previous methodology

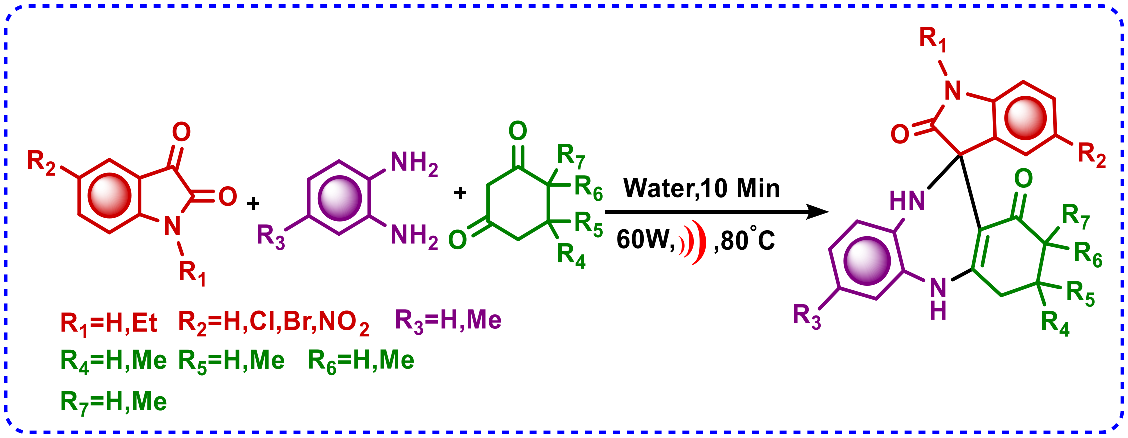


Scheme 2.1 Kajal De et al.—ChemCatChem https://doi.org/10.1002/cctc.201701487



Scheme 2.2 Wang, Shi et al.—Chem. Eur. J. https://doi.org/10.1002/chem.201403868

Current Work:



Scheme 2.3 Current procedure for the synthesis of 1, 4- benzodiazepine ring

In spite of their potential utility, most of these synthetic processes suffer from one or more serious drawbacks, such as substantial amounts of waste materials, laborious and complex work-up and purification, strongly acidic conditions, the occurrence of side reactions, low yields, high temperature, prolonged reaction time and the use of expensive reagents and a metal catalyst.

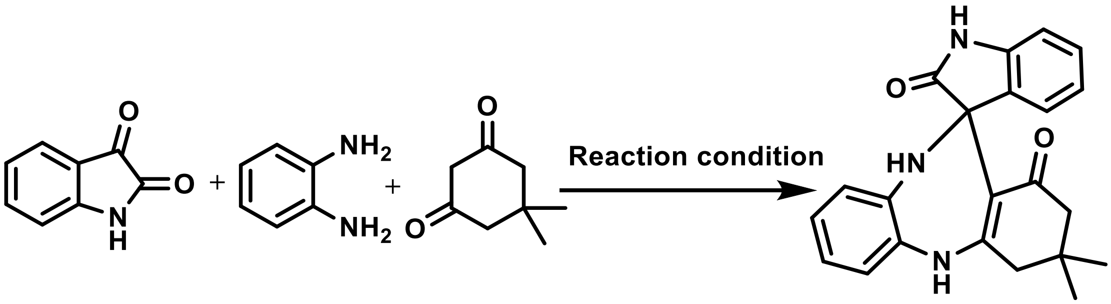
So far, the literature survey does not reveal any green protocol via ultrasonic-assisted "on water" synthesis of benzodiazepine ring. However, there is a necessity for the development of a highly efficient synthetic protocol to construct benzodiazepine ring-containing compounds.

In continuation to our research work on the synthesis of biologically interesting heterocyclic moieties [51-55] and in view of the above, it was thought worthwhile to synthesize some benzodiazepine rings by multicomponent reaction of isatin, diphenylamine, and 1,3-diketone under ultrasound irradiation in water with excellent yield (95%) **(Scheme 2.3)**.

2.2 Results and discussion

Our study was commenced by carrying out a one-pot multicomponent reaction of isatin **1** (1 mmol), 1,2-phenylenediamine **2** (1 mmol), and 5,5-dimethylcyclohexane-1,3-dione **3** (1 mmol) under conventional heating at 100˚C in water without using any catalyst and amazingly 68 % yield was obtained. Surprisingly, when a similar reaction was carried out under ultrasonic irradiation (instrument model 750W, 220V), the product was achieved with an excellent yield of 95%. To find the optimized reaction condition, various reaction parameters such as solvent effect, type of catalyst, and molar ratio were investigated by taking model reaction of isatin **1** (1 mmol) 1, 2-phenylenediamine **2** (1 mmol), and 5,5-dimethyl cyclohexane-1,3-dione **3** (1 mmol) under ultrasound irradiation at 80˚ C in water. First, the reaction was carried out without solvent and catalyst; as expected, no product was obtained even after 24 hrs. To investigate the solvent effect, the reaction was carried out in both non-polar and polar solvents (**Table 2.1**). A perusal of the table indicates that the product was not obtained with a non-polar solvent. In contrast, the product was obtained with a polar solvent like ethanol, methanol, and acetonitrile to a few extents. Furthermore, the product yield was good when the EtOH and EtOH:H_2O in ratio 1:1 and1:2 were used as solvents system, but there was a decrease in yield when the EtOH:H_2O ratio was 2:1 **(Table 2.1, Entries 5,6,7 and 8)**. This result encouraged us to do the reaction in water. The effect of various catalysts was examined, and the results are summarized **(Table 2.1)**. None of the catalysts improved the yield of the product. The results demonstrate the catalytic role of water in this reaction.

Table 2.1 Optimization reaction for the model reaction **4g**[a]



(1) (2) (3) (4g)

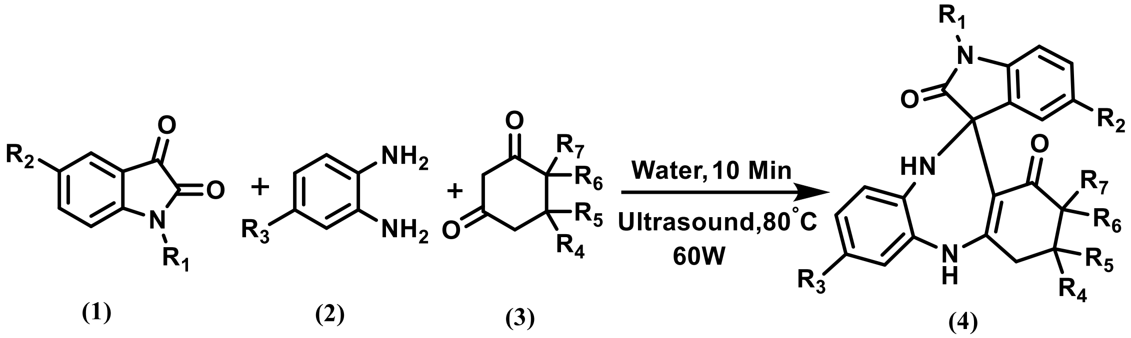
Entry	Catalyst(10mol%)	Solvent	Time (min)	Yield %[b]
1.	-	-	24 h	No reaction
2.	-	n-Hexane	50	No reaction
3.	-	Xylene	40	No reaction
4.	-	CCl_4	40	No reaction
5.	-	CH_3CH_2OH	15	38
6.	-	$C_2H_5OH:H_2O$ 1:1	15	48
7.	-	1:2	15	55
8.	-	2:1	15	43
9.	-	CH_3OH	15	35
10.	-	CH_3CN	15	26
11.	HOAc	H_2O	15	50
12.	p-TSA	H_2O	15	59
13.	TFA	H_2O	15	61

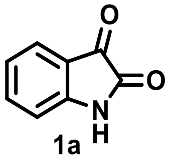
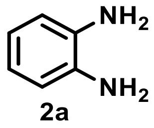
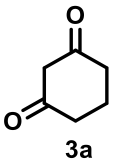
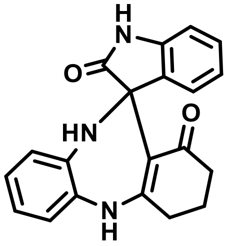
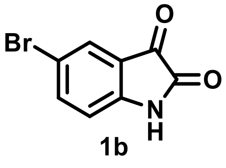
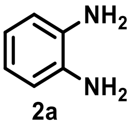
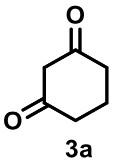
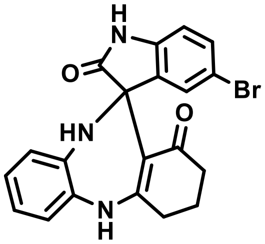
14.	$ZnCl_2$	H_2O	15	46
15.	HCl	H_2O	15	43
16.	Fe_2O_3	H_2O	15	64
17.	TiO_2	H_2O	15	51
18.	$AlCl_3$	H_2O	15	68
19.	NH_2SO_3H	H_2O	15	74
20.	**-**	**H_2O**	**10**	**95**

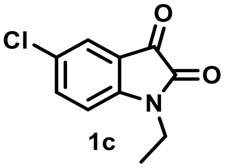
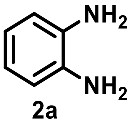
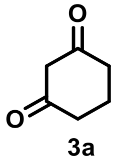
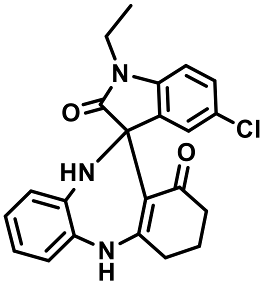
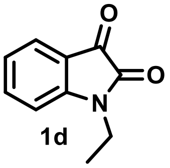
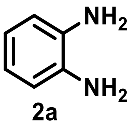
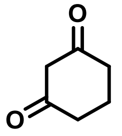
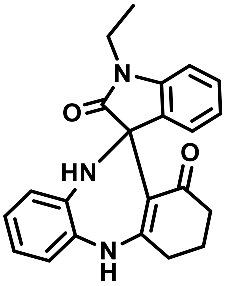
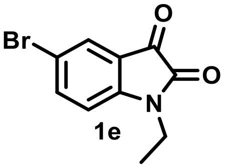
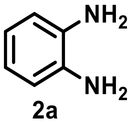
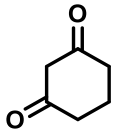
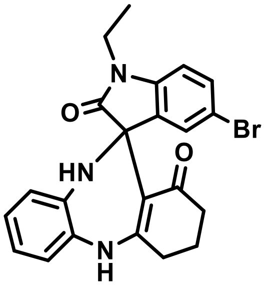
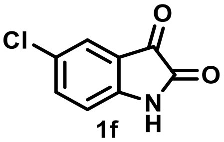
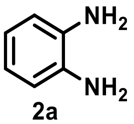
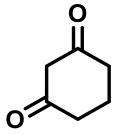
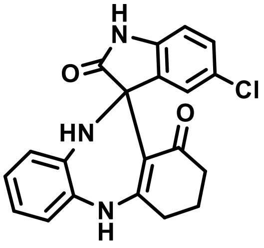
[a]Reaction condition: Isatin(1mmol), 1,2-phenylenediamine(1mmol),and 5,5-dimethylcyclohexane-1,3- dione (1mmol), under ultrasonication.
[b]Isolated yield after recrystallization.

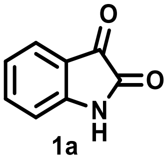
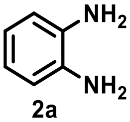
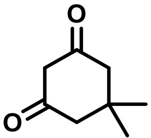
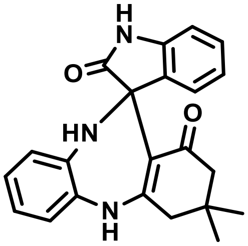
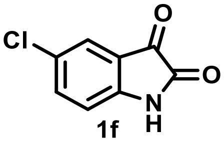
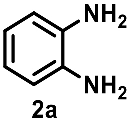
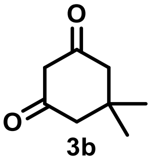
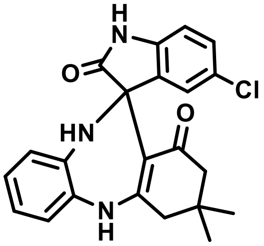
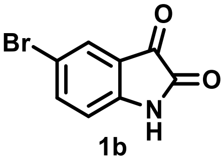
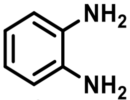
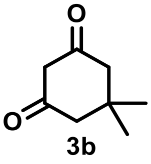
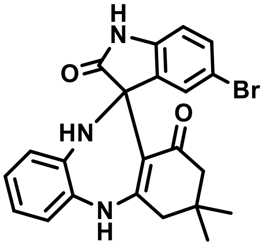
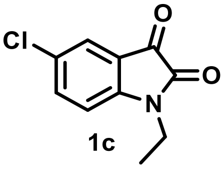
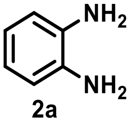
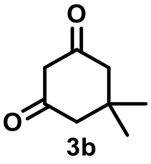
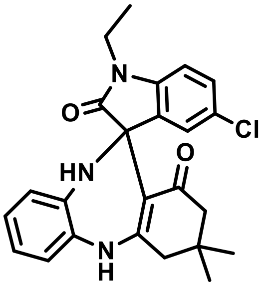
Several isatin derivatives such as isatin (**1a**), 5-bromoisatin **(1b)**, 5-chloro-1-ethylisatin **(1c)**, 1-ethylisatin **(1d)**, 5-bromo-1-ethylisatin **(1e)**, 5-chloroisatin **(1f)**, 5-nitroisatin **(1g)**, 1, 2-phenylenediamine **(2a)** 4-methyl-phenylenediamine (**2b)** were allowed to react with 1,3-cyclohexanedione (**3a)** 5,5-dimethylcyclohexane-1,3-dione **(3b)** and 4,4-dimethylcyclohexane-1,3-dione **(3c)** to validate the general applicability of this procedure under the optimized reaction condition. The results are summarized in **(Table 2.2)**. In most cases, the yield of products was good.

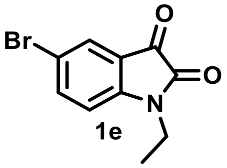
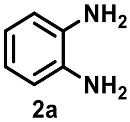
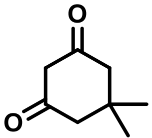
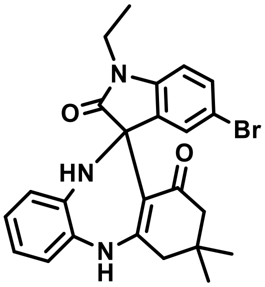
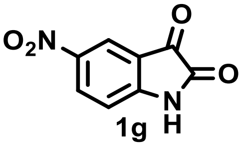
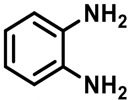
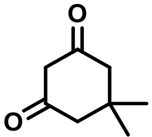
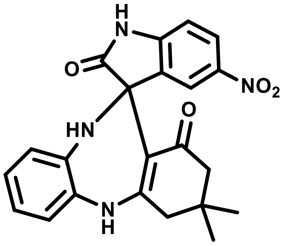
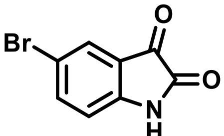
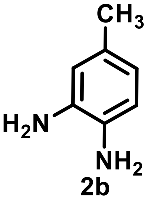
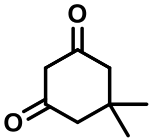
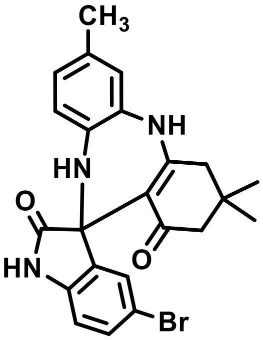
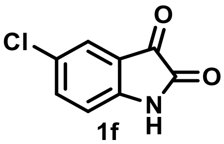
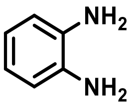
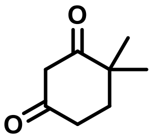
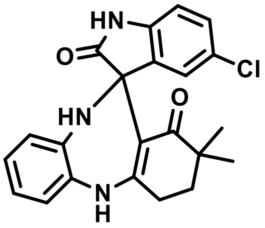
Table 2.2 Investigation of substrate scope for the synthesis of 1,4-benzodiazepine ring[a].

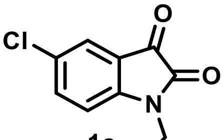
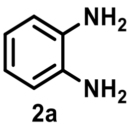
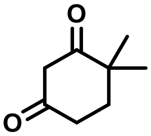
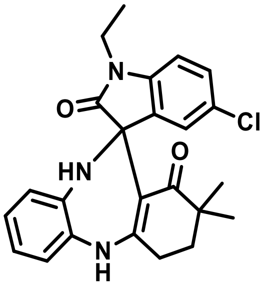
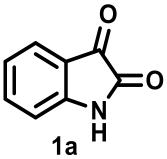
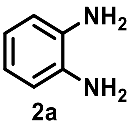
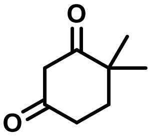
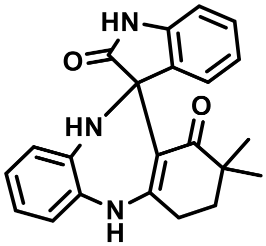
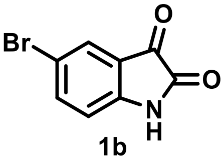
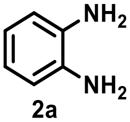
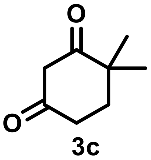
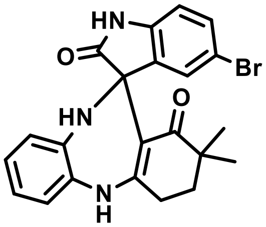


Entry	1	2	3	4[a]	Yield[b] (%)
4a	 1a	 2a	 3a		89
4b	 1b	 2a	 3a		89

4c	 1c	 2a	 3a		90
4d	 1d	 2a	 3a		89
4e	 1e	 2a	 3a		90
4f	 1f	 2a	 3a		87

4g	 1a	 2a	 3b		95
4h	 1f	 2a	 3b		92
4i	 1b	 2a	 3b		94
4j	 1c	 2a	 3b		90

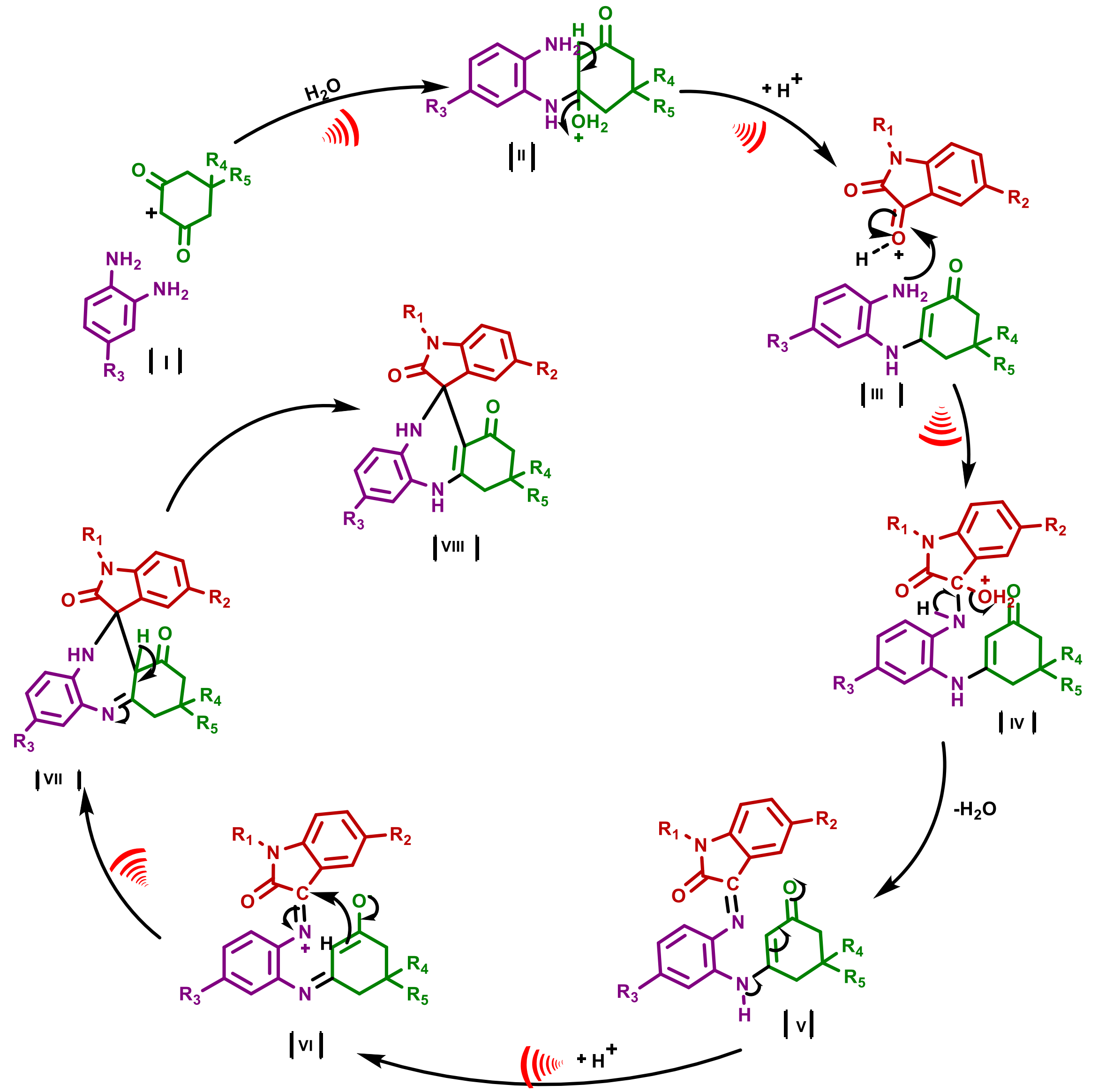
4k	 1e	 2a	 3b		91
4l	 1g	 2a	 3b		85
4m	 1b	 2b	 3b		90
4n	 1f	 2a	 3c		87

4o	 1c	 2a	 3c		89
4p	 1a	 2a	 3c		91
4q	 1b	 2a	 3c		90

[a]Reaction condition: Isatin(1mmol), 1,2-phenylenediamine(1mmol),and 5,5-dimethylcyclohexane-1,3- dione (1mmol), in water under ultrasonication.

[b]Isolated yield after recrystallization

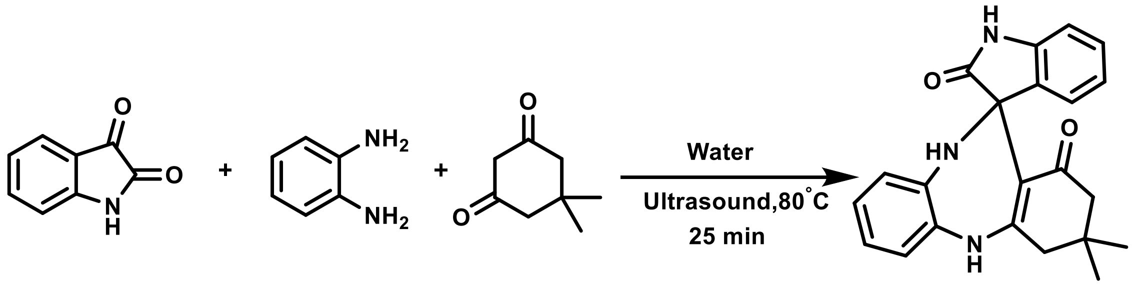
The mechanism is proposed **(Scheme 2.4)** on the basis of product isolation and reported literature. The condensation reaction of 1, 2-phenylenediamine with 1, 3-diketone in the presence of water results in intermediate formation **[III]**. This intermediate attacks at carbonyl carbon -3 of isatin to give intermediate **[IV]**, which on intramolecular cyclization gives the final product **[VIII]**.



Scheme 2.4 Proposed mechanism for the synthesis of benzodiazepine ring

2.3 Gram-Scale synthesis of benzodiazepine ring

Moreover, the practicality was validated by carrying out the model reaction on a gram scale (**Scheme 2.5**). The reaction mixture of isatin **1**(10 mmol, 1.47 g) 1,2-phenylenediamine **2**(10 mmol, 1.08 g), and 5,5-dimethyl cyclohexane-1,3- dione **3**(10 mmol, 1.40 g) in water was stirred and heated at 80˚C for 25 min under ultrasonic irradiations (monitored by TLC). The ice-cold water was added to this reaction mixture and stirred for five minutes. A solid precipitate was obtained, which was washed with water and recrystallized with ethanol to give a pure product.



(1.47g:10 mmol) (1.08g:10 mmol) (1.40g:10 mmol) Yield (88%)

(1) (2) (3) (4g)

Scheme 2.5 Gram-scale synthesis of benzodiazepine ring under ultrasound irradiation

2.4 Conclusion

In conclusion, green and efficient synthesis of benzodiazepine ring was developed *via* multicomponent reaction of isatin, 1, 2-phenylenediamine, 5,5-dimethylcyclohexane-1,3-

dione under ultrasonic irradiation in water. The present method provides good to excellent yield in a short reaction time. This method is also valid for gram-scale reactions.

2.5 Experimental section

2.5.1 Typical procedure for preparation of compound (4)

A mixture of isatin **1**(1 mmol), 1,2 phenylenediamine **2**(1 mmol), and dimedone **3**(1 mmol) was mixed with a minimum amount of water in a 50-ml beaker and subjected to ultrasound irradiation with 60 Watt power at 80 ˚C for 10 min (model no.PKS-750F) . The progress of the reaction was measured by thin-layer chromatography (ethyl acetate: hexane 1:3). After the completion of the reaction, the ice-cold water was added to the reaction mixture and stirred for 5 min. The solid precipitate was collected by filtration, washed with water, and recrystallized with ethanol to give the desired product in good yield.

2.5.2 Analytical Data

3,4,5,10-Tetrahydrospiro[dibenzo[b,e][1, 4]diazepine-11, 3′-indoline]-1,2′(2H)-dione [4a]

White solid, yield 89%, m. p. 258 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.17 (s, 1H), 9.12 (s, 1H), 7.12 (d, J=7.8 Hz, 1H), 7.00 (t, J=7.6 Hz, 1H), 6.85 (t, J=7.5 Hz, 1H), 6.74 (d, J=7.7 Hz, 2H), 6.64 (d, J=7.8 Hz, 1H), 6.54 (t, J=7.5 Hz, 1H), 6.19 (d, J=7.3 Hz, 1H), 5.44 (s, 1H), 2.71 (d, 2H), 2.16–1.83 (m, 4H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.89, 176.64, 156.79, 143.29, 137.98, 135.49, 133.57, 127.54, 123.67, 123.14, 122.21, 121.99, 120.34, 120.27, 109.79, 109.28, 66.19, 40.44, 40.36, 40.27, 40.20, 40.11, 39.94, 39.77, 39.61, 39.44, 36.72, 32.02, 21.09. . **IR (KBr) (ῡ$_{max}$/cm^{-1}):** 3242, 1954, 1661, 1583, 1475, 1252, 1184, 889 cm^{-1}; **Anal. calc. for $C_{20}H_{17}N_3O_2$**: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.62; H, 5.25; N, 12.81.

5′-Bromo-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4b]

White solid, yield 89%, m. p. 236 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.31 (s, 1H), 9.16 (s, 1H), 7.19 (m, J=8.2 Hz, 1H), 7.14 (d, J=7.9 Hz, 1H), 6.90 (t, J=7.6 Hz, 1H), 6.79 (t, J=7.5 Hz, 1H), 6.72 (d, J=8.2 Hz, 1H), 6.66 (d, J=7.7 Hz, 1H), 6.25 (s, 1H), 5.54 (s, 1H), 2.74–2.70 (m, 2H), 2.09–2.07 (m, 2H), 1.89–1.85 (m, 2H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 193.23, 176.21, 157.33, 142.64, 137.81, 137.67, 133.59, 130.11, 124.94, 124.62, 123.21, 122.45, 120.55, 112.02, 111.07, 109.04, 66.39, 40.46, 40.30, 40.13, 39.96, 39.79, 39.63, 39.46, 36.62, 31.96, 20.99. **IR (KBr) (ῡ$_{max}$/cm^{-1}):** 3266, 1946, 1662, 1578, 1456, 1258, 1195, 866 cm^{-1}; **Anal. Calc. for $C_{20}H_{16}N_3O_2Br$**: C, 58.55; H, 3.93; N, 10.24 Found: C, 58.65.; H, 3.98; N, 10.31.

5′-Chloro-1′-ethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4c]

White solid, yield 90%, m. p. 225 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 9.20 (s, 1H), 7.22–7.10 (m, 2H), 6.97 (d, J=8.3 Hz, 1H), 6.91 (s, 1H), 6.80 (s, 1H), 6.63 (d, J=7.8 Hz, 1H), 6.16

(s, 1H), 5.53 (s, 1H), 2.73 (t, 2H), 2.07 (m, 2H), 1.89–1.85 (m, 2H), 1.22 (m, 2H), 1.06 (t, 3H).**^{13}C NMR (126 MHz, DMSO-d^6)** δ 193.20, 174.39, 157.31, 142.69, 137.58, 136.71, 133.56, 127.73, 127.35, 124.71, 123.07, 122.35, 122.10, 121.81, 120.62, 109.07, 65.88, 56.50, 40.46, 40.30, 40.13, 39.96, 39.79, 39.63, 39.46, 31.95, 19.07, 18.95, 12.00. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3211, 1965, 1625, 1549, 1448, 1381, 1118, 866 cm^{-1}. **Anal. Calc. for $C_{22}H_{20}N_3O_2Cl$**: C, 67.09; H, 5.12; N, 10.67. Found: C, 67.18; H, 5.22; N, 10.72.

1′-Ethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4d]

White solid, yield 89%, m. p. 281 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 9.15 (s, 1H), 7.12 (d, J=7.9 Hz, 1H), 7.08 (t, J=7.6 Hz, 1H), 6.91 (d, J=7.7 Hz, 1H), 6.85 (t, J=7.5 Hz, 1H), 6.73 (t, J=7.4 Hz, 1H), 6.59 (t, J=7.5 Hz, 2H), 6.21 (d, J=7.2 Hz, 1H), 5.39 (s, 1H), 3.69 (m, 2H), 2.71 (t, 2H), 2.50 (s, 2H), 1.85–1.83 (m, 2H), 1.23 (t, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.64, 174.39, 156.52, 143.34, 137.51, 134.41, 133.16, 127.39, 123.43, 122.73, 121.77, 121.71, 120.41, 109.46, 107.88, 65.42, 40.01, 39.84, 39.67, 39.51, 39.34, 39.17, 39.01, 36.24, 34.13, 31.65, 30.79, 20.70, 11.84. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3145, 1925, 1645, 1523, 1446, 1224, 1121, 872 cm^{-1}; **Anal. Calc. for $C_{22}H_{21}N_3O_2$**: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.61; H, 5.95; N, 11.76.

5′-Bromo-1′-ethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4e]

White solid, yield 90%, m. p. 225 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 9.22 (s, 1H), 7.18–7.11 (m, 2H), 6.97 (d, J=8.3 Hz, 1H), 6.93–6.88 (m, 1H), 6.79 (dd, J=7.4, 6.3 Hz, 1H), 6.62 (dd, J=7.9, 1.2 Hz, 1H), 6.15 (d, J=2.2 Hz, 1H), 5.56 (s, 1H), 3.71 (m, 2H), 2.73 2.06–1.93 (m, 1H), 1.87 (d, 2H), 1.21 (t, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 193.15, 174.35, 157.26, 142.66, 137.58, 136.70, 133.53, 127.31, 124.68, 124.02, 123.18, 122.41, 121.94, 120.60, 109.58, 109.05, 65.85, 40.46, 40.38, 40.29, 40.21, 40.12, 40.05, 39.96, 39.79, 39.62, 39.46, 36.51, 34.64, 31.94, 20.97, 12.09). . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3173, 1981, 1676, 1577, 1467, 1245, 1137, 858 cm^{-1}. **Anal. Calc. for $C_{22}H_{20}N_3O_2Br$**: C, 60.28; H, 4.60; N, 9.59. Found: C, 60.38; H, 4.72; N, 9.65.

5′-Chloro-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H) -dione [4f]

White solid, yield 87%, m. p. 189 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6**) **δ** 10.33 (s, 1H), 9.18 (s, 1H), 7.14 (d, J=7.8 Hz, 1H), 7.06 (dd, J=8.2, 2.2 Hz, 1H), 6.89 (d, J=7.2 Hz, 1H), 6.79 (t, J=7.2 Hz, 2H), 6.66 (d, J=7.7 Hz, 1H), 6.13 (d, J=2.0 Hz, 1H), 5.58 (s, 1H), 2.73– 2.71 (m, 2H), 2.51 (s, 2H), 1.88–1.86 (m, 2H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 193.25, 176.32, 157.30, 142.23, 137.40, 133.56, 127.26, 124.17, 123.96, 123.24, 122.33, 122.05, 120.53, 114.29, 110.57, 109.03, 66.37, 36.62, 31.95, 20.98. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3242, 1942, 1656, 1572, 1442, 1252, 1185, 887 cm^{-1}. **Anal. Calc. for $C_{20}H_{16}N_3O_2Cl$**: C, 65.67; H, 4.41; N, 11.49. Found: C: 65.72; H: 4.45; N: 11.55.

3,3-Dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4g]

White solid, yield 95%, m. p. 275 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.21 (s, 1H), 9.10 (s, 1H), 7.18 (d, J=7.9 Hz, 1H), 7.05 (t, J=7.6 Hz, 1H), 6.90 (t, J=7.5 Hz, 1H), 6.79 (t, J=9.0 Hz, 2H), 6.69 (d, J=7.8 Hz, 1H), 6.59 (t, J=7.4 Hz, 1H), 6.24 (d, J=7.3 Hz, 1H), 5.52 (s, 1H), 2.65 (d, 2H), 2.15–1.91 (m, 2H), 1.15 (s, 3H), 1.01 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.68, 176.57, 159.79, 154.87, 143.34, 137.84, 135.54, 133.60, 127.56, 123.68, 123.14, 122.08, 121.96, 120.37, 120.23, 109.35, 108.66, 66.40, 50.19, 45.37, 40.43, 40.27, 40.10, 39.93, 39.76, 39.60, 39.43, 31.90, 28.06. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3259, 1947, 1629, 1551, 1487, 1233, 1145, 861 cm^{-1}. **Anal. Calc. for $C_{22}H_{21}N_3O_2$**: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.58; H, 5.96; N, 11.78.

5′-Chloro-3,3-dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4h]

White solid, yield 92%, m. p. 285 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.32 (s, 1H), 9.11 (s, 1H), 7.18 (dd, J=8.2, 2.0 Hz, 1H), 7.13 (d, J=7.9 Hz, 1H), 6.89 (s, 1H), 6.78 (s, 1H), 6.71 (d, J=8.2 Hz, 1H), 6.66 (d, J=7.9 Hz, 1H), 6.21 (s, 1H), 5.58 (s, 1H), 2.61 (d, 2H), 1.96 (m, 2H), 1.09 (s, 3H), 0.98 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.53, 175.69, 154.92, 142.27, 137.44, 137.13, 133.19, 129.67, 124.22, 123.53, 122.88, 121.90, 120.14, 111.50, 110.82, 107.45, 66.18, 49.60, 44.81, 40.11, 40.02, 39.94, 39.85, 39.78, 39.68, 39.61, 39.52, 39.35, 39.18, 39.02, 31.34, 27.85, 27.28, 18.61. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3244, 1951, 1637, 1546, 1557, 1264, 1171, 852 cm^{-1};**Anal. Calc. for $C_{22}H_{21}N_3O_2$**: C, 67.09; H, 5.12; N, 10.67. Found: C, 67.18; H, 5.22; N, 10.74.

5′-Bromo-3,3-dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4i]

White solid, yield 94%, m. p. 295 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.32 (s, 1H), 9.11 (s, 1H), 7.16 (m, 2H), 6.90 (t, J=7.3 Hz, 1H), 6.79 (s, 1H), 6.72 (d, J=8.1 Hz, 1H), 6.66 (d, J=7.6 Hz, 1H), 6.22 (s, 1H), 5.57 (s, 1H), 2.62 (s, 2H), 1.97 (m, 2H), 1.10 (s, 3H), 0.99 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.97, 176.13, 155.36, 142.69, 137.87, 137.55, 133.63, 130.10, 124.66, 123.97, 123.32, 122.34, 120.57, 111.94, 111.26, 107.89, 66.62, 56.50, 50.04, 40.45, 40.29, 40.21, 40.12, 39.95, 39.79, 39.62, 39.45, 31.77, 27.72, 19.02. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3266, 1948, 1644, 1551, 1478, 1251, 1165, 859 cm^{-1}; **Anal. Calc. for $C_{22}H_{20}N_3O_2Br$**: C, 60.28; H, 4.60; N, 9.59. Found: C, 60.35; H, 4.73; N, 9.68.

5′-Chloro-1′-ethyl-3,3-dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4j]

White solid, yield 90%, m. p. 240 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 9.14 (s, 1H), 7.19–7.12 (m, 2H), 6.98 (d, J=8.3 Hz, 1H), 6.94–6.88 (m, 1H), 6.80 (t, J=6.9 Hz, 1H), 6.63 (d, J=6.9 Hz, 1H), 6.14 (d, J=2.1 Hz, 1H), 5.55 (s, 1H), 3.71 (m, 2H), 2.63 (s, 2H), 1.90-2.03 (m, 2H), 1.23 (t, 3H), 1.10 (s, 3H), 0.98 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.99, 174.32, 155.37, 142.73, 137.47, 136.78, 133.58, 127.36, 124.67, 123.95, 123.36, 121.93, 121.65, 120.66, 109.76, 107.95, 66.09, 49.94, 45.27, 40.46, 40.30, 40.13, 39.96, 39.80, 39.63, 39.46, 31.84, 28.15, 27.85, 27.72, 12.01. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3261, 1968, 1642, 1547, 1465, 1237, 1165, 891 cm^{-1}. **Anal. Calc. for $C_{24}H_{24}N_3O_2Cl$**: C, 68.32; H, 5.73; N, 9.96. Found: C, 68.39; H, 5.88; N, 9.98.

5′-Bromo-1′-ethyl-3,3-dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4k]

White solid, yield 91%, m. p. 225 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 9.15 (s, 1H), 7.34–7.06 (m, 2H), 6.97 (d, J=8.3 Hz, 1H), 6.90 (s, 1H), 6.79 (s, 1H), 6.64 (s, 1H), 6.13 (d, J=2.1 Hz, 1H), 5.58 (s, 1H), 3.80–3.61 (m, 2H), 2.62 (s, 2H), 1.99–1.89 (m, 2H), 1.22 (t, 3H), 1.09 (s, 3H), 0.97 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.96, 174.30, 155.34, 142.71, 137.48, 136.78, 133.57, 127.34, 124.66, 124.05, 123.21, 122.40, 121.78, 120.66, 109.69, 107.93, 66.08, 49.94, 45.25, 40.46, 40.29, 40.13, 39.96, 39.79, 39.62, 39.46, 34.65, 31.85, 28.20, 27.78, 12.10. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3271, 1958, 1647, 1537, 1455, 1232, 1169, 888 cm^{-1};**Anal. Calc. for $C_{24}H_{24}N_3O_2Br$**: C, 61.81; H, 5.19; N, 9.01. Found: C, 61.95; H, 5.59; N, 9.78.

3,3-Dimethyl-5′-nitro-3,4,5,10-tetrahydrospiro- [dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4l]

White solid, yield 85%, m. p. 240 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.95 (s, 1H), 9.23 (s, 1H), 8.04 (m, J=8.6, Hz, 1H), 7.18 (d, J=7.8 Hz, 1H), 6.98–6.95 (m, 2H), 6.92 (t, J=7.5 Hz, 1H), 6.78 (t, J=7.4 Hz, 1H), 6.63 (d, J=7.7 Hz, 1H), 5.73 (s, 1H), 2.69 – 2.61 (m, 2H), 1.97 (m, 2H), 1.10 (s, 3H), 0.99 (s, 3H). **^{13}CNMR (126 MHz, DMSO-d^6) δ** 192.85, 176.33, 155.53, 149.69, 140.51, 136.92, 135.73, 133.31, 124.99, 123.84, 122.92, 122.27, 120.41, 116.50, 108.93, 106.88, 65.84, 49.41, 44.73, 40.02, 39.85, 39.78, 39.69, 39.52, 39.35, 39.19, 39.02, 31.34, 27.94, 27.11. . **IR (KBr) (ῡ$_{max}$/cm^{-1}):** 3296, 1988, 1674, 1581, 1498, 1279, 1191, 876 cm^{-1}; **Anal. calcd. for $C_{22}H_{20}N_4O_4$**; C: 65.34; H: 4.98; N: 13.85%. Found: C: 65.42; H: 4.88; N: 13.94%.

5′-Bromo-7-methyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4m]

White solid, yield 90%, m. p. 185 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.29 (s, 1H), 9.20–9.03 (m, 1H), 7.18 (m, 1H), 7.01 (d, J=8.1 Hz, 1H), 6.70 (m, 2H), 6.48 (s, 1H), 6.27 (m, 1H), 5.46 (s, 1H), 2.70 (t, 2H), 2.08 (s, 3H), 2.01 (m, 2H), 1.87–1.85 (m, 2H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 193.00, 176.28, 157.20, 142.66, 137.86, 137.46, 132.83, 131.00, 130.09, 124.82, 123.29, 122.96, 120.48, 112.01, 111.16, 108.73, 66.36, 40.47, 40.40, 40.30, 40.23, 40.14, 40.06, 39.97, 39.80, 39.64, 39.47, 36.64, 31.95, 20.99, 20.85. . **IR (KBr) (ῡ$_{max}$/cm^{-1}):** 3215, 1921, 1689, 1579, 1443, 1251, 1187, 876 cm^{-1}; **Anal. calcd. for $C_{21}H_{18}N_3O_2Br$**; C: 59.45; H: 4.28; N: 9.90%. Found: C: 59.62; H: 4.38; N: 9.98%.

5′-Chloro-2,2-dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4n]

White solid, yield 87%, m. p. 286 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.31 (s, 1H), 9.10 (s, 1H), 7.18 (m, J=8.2, Hz, 1H), 7.14 (m, J=8.0 Hz, 1H), 6.91– 6.87 (m, 1H), 6.79 (d, J=1.3 Hz, 1H), 6.72 (d, J=8.2 Hz, 1H), 6.68–6.65 (m, 1H), 6.22 (d, J=2.0 Hz, 1H), 5.57 (s, 1H), 2.61 (d, 2H), 1.97 (m, 2H), 1.09 (s, 3H), 0.98 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.97, 176.13, 155.36, 142.69, 137.86, 137.55, 133.63, 130.10, 124.65, 123.96, 123.32, 122.34, 120.57, 111.94, 111.26, 107.89, 66.62, 50.04, 45.26, 40.45, 40.37, 40.28, 40.21, 40.12, 40.04, 39.95, 39.78, 39.61, 39.45, 31.77, 27.72, 18.99. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3289, 1975, 1655, 1561, 1535, 1227, 1147, 878 cm^{-1}; **Anal. calcd. for $C_{22}H_{20}N_3O_2Cl$**; C: 67.09; H: 5.12; N: 10.67%. Found: C: 67.16; H: 5.18; N: 10.73%.

5′-Chloro-1′-ethyl-2,2-dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4o]

White solid, yield 89%, m. p. 225 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 9.14 (s, 1H), 7.22–7.11 (m, 3H), 6.97 (d, J=8.3 Hz, 1H), 6.93–6.87 (m, 1H), 6.79 (m, J=7.7 Hz, 1H), 6.63 (m, J=7.9 Hz, 1H), 6.13 (d, J=2.2 Hz, 1H), 5.55 (s, 1H), 3.70–3.58 (m, 2H), 2.62 (s, 2H), 1.96 (m, 2H), 1.22 (t, 3H), 1.10 (s, 3H), 0.97 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.97, 174.29, 155.35, 142.70, 137.45, 136.76, 133.56, 127.33, 124.65, 124.04, 123.21, 122.41, 121.77, 120.64, 109.68, 107.93, 66.08, 49.94, 45.53, 40.45, 40.28, 40.20, 40.11, 40.04, 39.95, 39.78, 39.61, 39.44, 34.66, 31.84, 28.18, 12.09. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3251, 1978, 1646, 1537, 1448, 1257, 1175, 893 cm^{-1}. **Anal. Calc. for $C_{24}H_{24}N_3O_2Cl$**: C, 68.32; H, 5.73; N, 9.96. Found: C, 68.35; H, 5.79; N, 9.99.

2,2-Dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4p]

White solid, yield 91%, m. p. 270 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.14 (s, 1H), 9.03 (s, 1H), 7.12 (m, J=8.0 Hz, 1H), 7.00 (m, 1H), 6.89–6.80 (m, 1H), 6.73 (m, J=8.6 Hz, 2H), 6.64 (m, J=7.9 Hz, 1H), 6.54 (m, 1H), 6.19 (d, J=7.3 Hz, 1H), 5.43 (s, 1H), 2.60 (d, 2H), 1.96

(m, 2H), 1.09 (s, 3H), 0.96 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.66, 176.56, 154.84, 143.33, 137.83, 135.54, 133.60, 127.54, 123.66, 123.14, 122.07, 121.94, 120.36, 120.28, 109.34, 108.66, 66.41, 50.20, 45.39, 40.45, 40.37, 40.28, 40.21, 40.12, 40.04, 39.95, 39.78, 39.62, 39.45, 31.89, 28.06, 19.01. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3251, 1977, 1658, 1542, 1493, 1223, 1155, 879 cm^{-1}; **Anal. calcd. for $C_{22}H_{21}N_3O_2$**; C: 73.52; H: 5.89; N: 11.69%. Found: C: 73.65; H: 5.88; N: 11.75%.

5′-Bromo-2,2-dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-d ione [4q]

White solid, yield 90%, m. p. 287 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.30 (s, 1H), 9.10 (s, 1H), 7.14 (m, *J* = 8.0 Hz, 1H), 7.06 (m, *J* = 8.2 Hz, 1H), 6.89 (d, *J* = 0.7 Hz, 1H), 6.77 (m, *J* = 7.8, 2H), 6.67 (d, 1H), 6.10 (d, *J* = 7.2 Hz, 1H), 5.57 (s, 1H), 2.61 (s, 2H), 1.97 (m, 2H), 1.09 (s, 3H), 0.98 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.97, 176.13, 155.36, 142.69, 137.86, 137.55, 133.63, 130.10, 124.65, 123.96, 123.32, 122.34, 120.57, 111.94, 111.26, 107.89, 66.62, 50.04, 45.26, 40.45, 40.37, 40.28, 40.21, 40.12, 40.04, 39.95, 39.78, 39.61, 39.45, 31.77, 18.99. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3280, 1942, 1652, 1558, 1465, 1273, 1183, 861 cm^{-1}; **Anal. calcd. for $C_{22}H_{20}N_3O_2Br$**; C: 60.28; H: 4.60; N: 9.59%. Found: C: 60.24; H: 4.52; N: 9.53%.

2.5.3 Spectral Data of Product 3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3'-indoline]-1,2'(2H)-dione (4a)

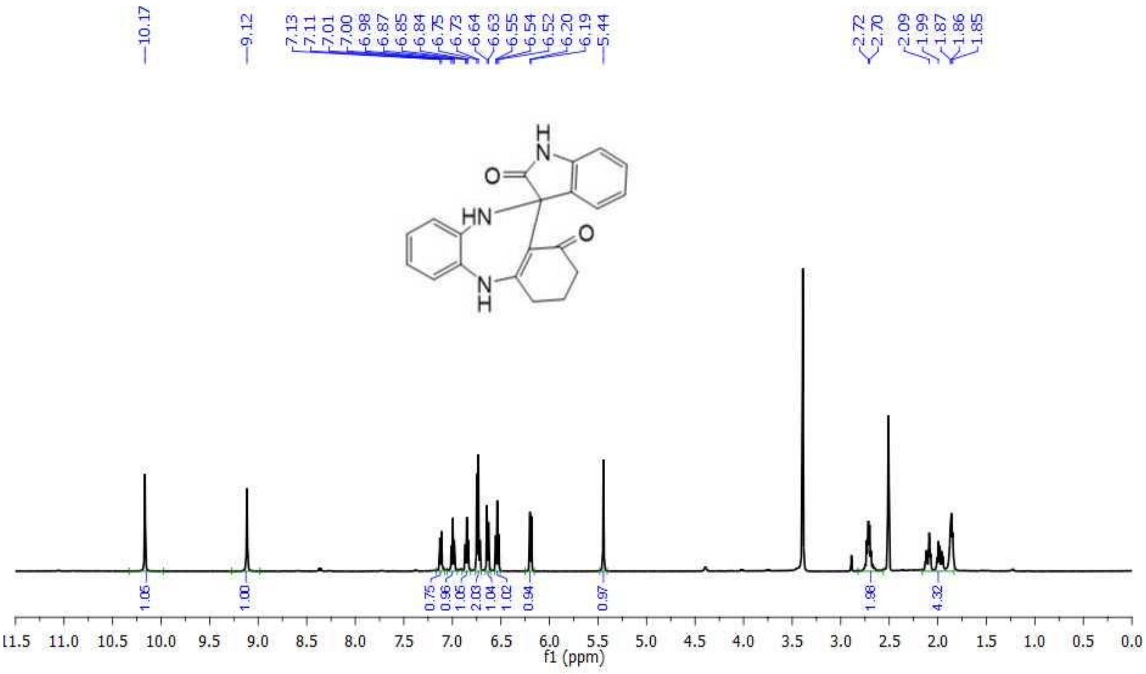


Figure 2.2 ^{1}H NMR of 3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3'-indoline]-1,2'(2H)-dione **(4a)**

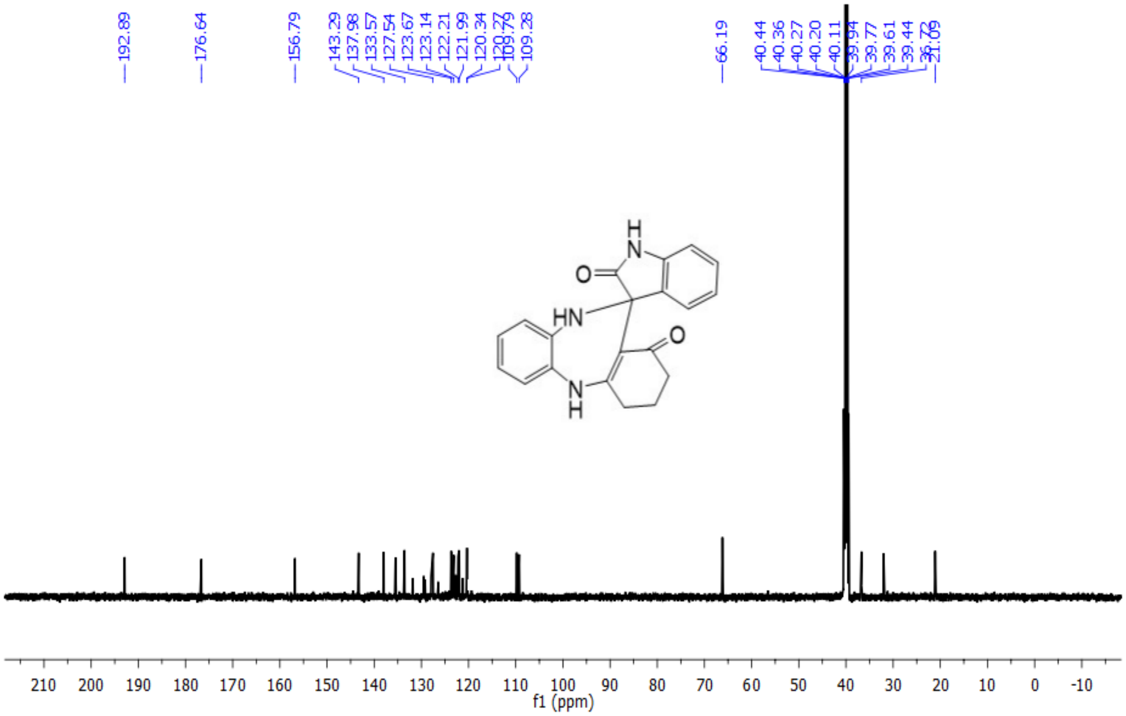


Figure 2.3 ^{13}C NMR of 3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3'-indoline]-1,2'(2H)-dione **(4a)**

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CHAPTER 3

GRINDING INDUCED CATALYST FREE, MULTICOMPONENT SYNTHESIS OF INDOLOINDOLE PYRIMIDINE

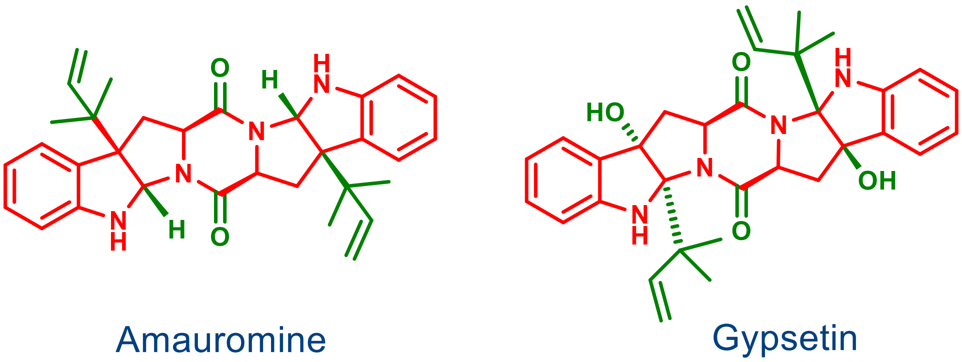
Grinding induced catalyst-free, multicomponent synthesis of indoloindole pyrimidine

3.1 Introduction

Multicomponent reactions have risen as a successful and incredible tool in current synthetic organic chemistry, because of their esteemed properties, multicomponent reactions have risen as a successful and incredible tool in current synthetic organic chemistry. Multicomponent reactions give rise to fascinating heterocyclic scaffolds and are advantageous for developing several ‘‘drug-like” molecules [1, 2].

Indole is one of the most essential and abundant nitrogen-containing heterocycles in natural and medicinal products [3]. Compounds having an indole unit show a wide range of biological activities, including antiviral [4], antitumor [5], anticonvulsant [6], anti-inflammatory [7, 8], anti-bacterial [9], and cardiovascular activities [10] .

Pyrimidine and its derivatives play a significant role in numerous pharmacological and biological activities, such as antibacterial, anticonvulsant, antiviral, antifungal, and anticancer properties [11, 12]. They are also a fundamental part of nucleic acid RNA and DNA [13]. Derivatives of pyrimidine have been utilized to produce metal-cage complexes in coordination chemistry and function as CDK 4 inhibitors [14]. Substituted pyrimidines are usually found in naturally occurring and biologically active compounds like avitriptan and voriconazole [15]. Furthermore, the substitution of the indole with an extra heterocyclic ring-like pyrimidine [16], imidazole [17], oxadiazine pyridine [18], oxazole [19], pyrazole [20], and dihydroimidazole, produced a variety of biologically active compounds. Considering the resourceful pharmaceutical properties of indole and pyrimidine moieties and enhancing indole's biological and pharmacological activity, we synthetically attached the pyrimidine moiety to obtain potent molecules with better biological activity. Some examples containing indole moieties are given below **(Figure. 3.1)**.



Amauromine

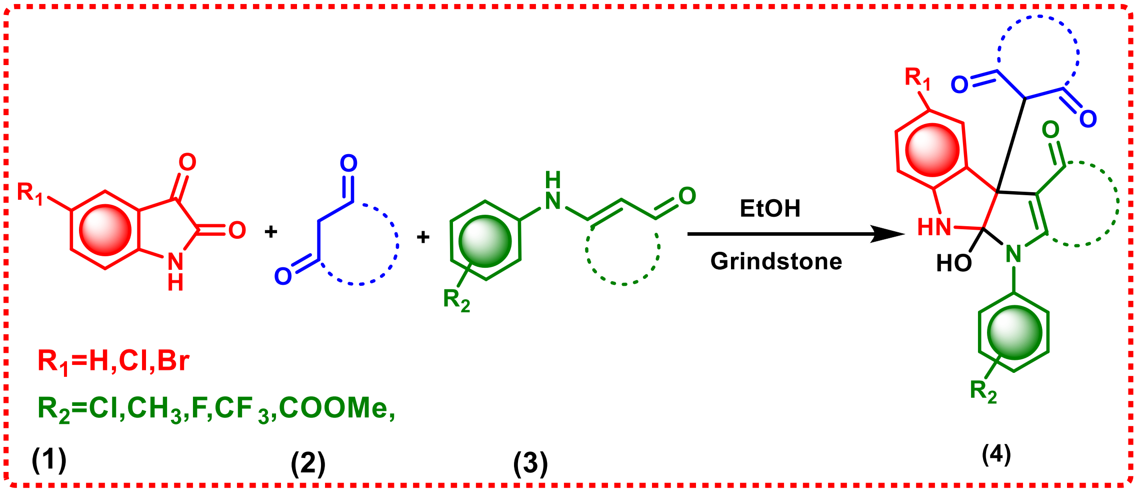
Gypsetin

Figure 3.1 Few natural products having indole moieties.

Due to its fascinating biological properties, several methodologies have been developed for the construction of indoloindolpyrimidine derivatives [21]. Nevertheless, many of these approaches have shortcomings, such as harsh reaction conditions, restricted accessibility of starting materials, and the use of costly metal catalysts. Therefore, developing effective and new methods for synthesizing indoloindolpyrimidine derivatives by easily accessible starting materials is of great significance. Enaminones are versatile and powerful building blocks that have been extensively used in synthesizing a variety of biologically active heterocycles [22].

Simple grinding methods using mortar and pestle have taken a central place as a highly valuable approach with the advantages of a simple experimental setup, energy-efficient, economical, and ecologically favorable procedure, and the accessible complexity of the very large number of compounds [23, 24].

In view of the above and as a part of our ongoing research on the synthesis of biologically active heterocyclic compounds [25-27], we report herein an efficient and new protocol for the synthesis of indoloindolpyrimidine derivatives through a one-pot, multicomponent reaction of isatin derivatives (**1**), 1,3 diketones (**2**) and enaminones (**3**) under the grinding condition for 2 h with excellent yield **(86–93% yields, Scheme 3.1)**.

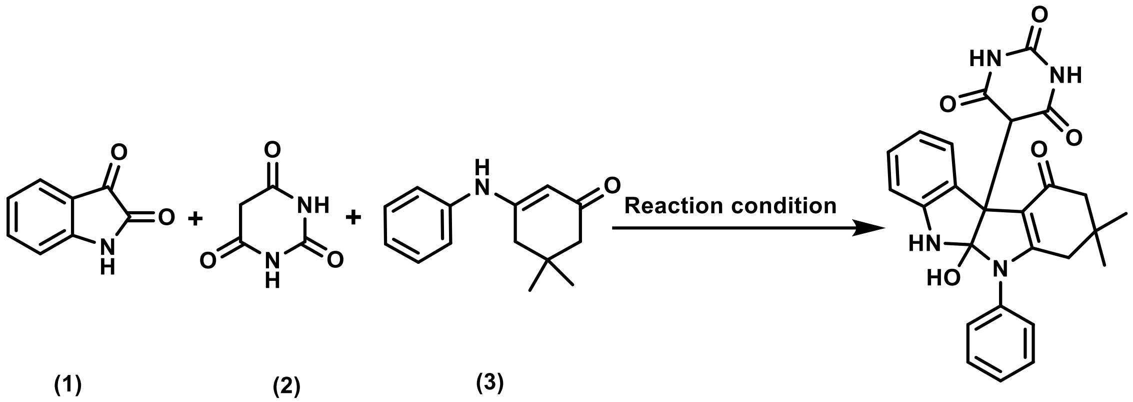


Scheme 3.1 Synthesis of indoloindole pyrimidine derivatives

3.2 Results and Discussion

We have commenced our study to optimize the reaction condition for the preparation of indoloindole pyrimidine via grindstone methodology using isatin (**1**), barbituric acid (**2**), and enaminone (**3)** as a model reaction. Initially, the model reaction was carried out without solvent and catalyst, but it was observed (using TLC) that the reaction did not proceed. A similar reaction was carried out in a few drops of EtOH at room temperature with various catalysts like *p*-TSA, sulfamic acid, L-proline, Sc(OTf)$_3$, CuCl, Et$_3$N, t-BuOK (**Table 3.1, Entries 2–8**) the reaction proceeds satisfactorily. Further, the same reaction was carried out in different solvents like aprotic and protic, i.e., DMF, DMSO, acetone, toluene, CH_3CN, H_2O, and the molar ratio of EtOH : H_2O at room temperature without the addition of any catalyst, the expected product was observed with low yield (**Table 3.1, Entries 9–18**). Amazingly, when the reaction was carried out in 2–4 drops (approximately 0.2 ml) of ethanol at room temperature without any catalyst, an excellent yield of product (93%) was obtained within 2h (**Table 3.1, Entry 19**). Our methodology has the advantage not only of a higher yield but also of the shortest reaction time. This procedure was best because the liquid-assisted grinding method is better than the dry grinding methodology.

Table 3.1 Optimization condition for the model reaction **4c**[a].



(1) (2) (3)

(4c)

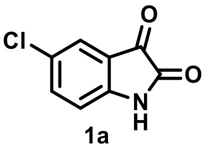
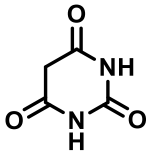
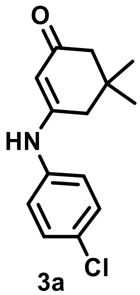
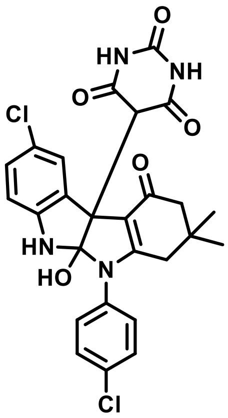
Entry	Catalyst (mol%)	Solvent(drop)	Time(h)	Yields[b] (%)
1.	-	-	6	-
2.	p-TSA (10%)	EtOH	3	80
3.	Sulfamic acid (10%)	EtOH	3	82
4.	L-proline (10%)	EtOH	5	16
5.	$Sc(OTf)_3$ (10%)	EtOH	3	33
6.	CuCl (10%)	EtOH	3	27
7.	Et_3N (10%)	EtOH	4	78

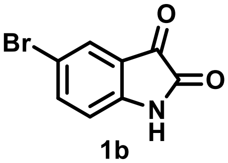
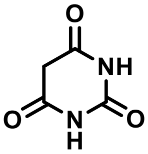
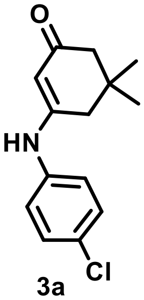
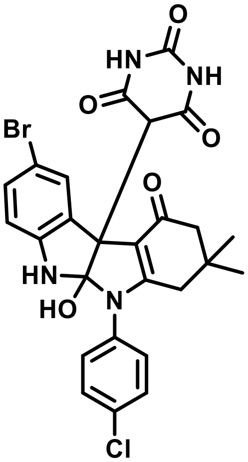
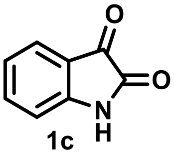
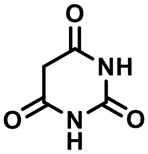
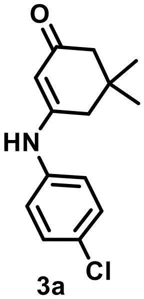
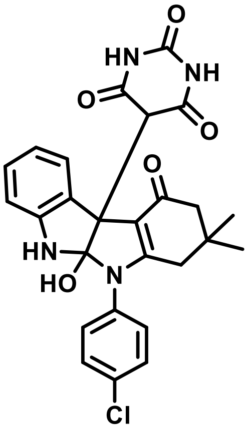
8.	t-BuOK (10%)	EtOH	3	10
9.	None	DMF	3	-
10.	None	DMSO	6	-
11.	None	Acetone	2	-
12.	None	Toluene	5	-
13.	None	CH_3CN	4	75
14.	None	H_2O	6	-
15.	None	EtOH:H_2O (1:1)	3	-
16.	None	2:1	3	10
17.	None	5:1	3	20
18.	None	8:1	3	50
19.	**None**	**EtOH**	**2**	**93**

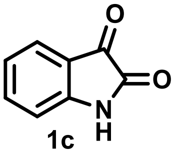
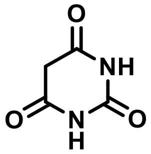
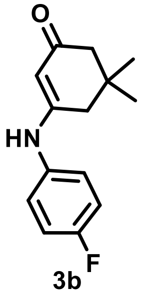
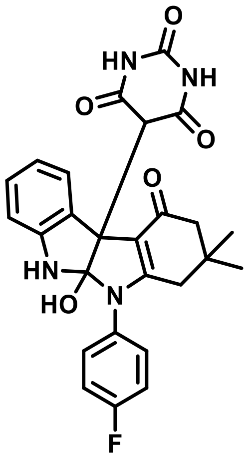
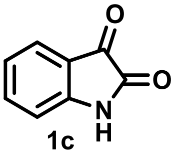
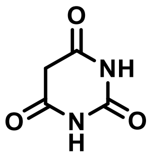
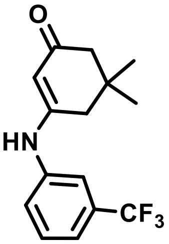
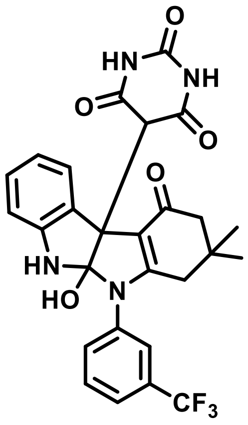
[a]Reaction condition: Isatin(1mmol), barbituric acid (1mmol),and enaminone (1mmol), under grinding.
[b]Isolated yield after recrystallization.

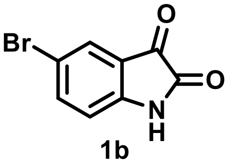
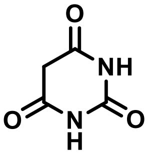
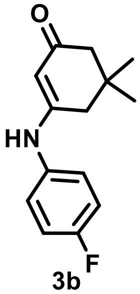
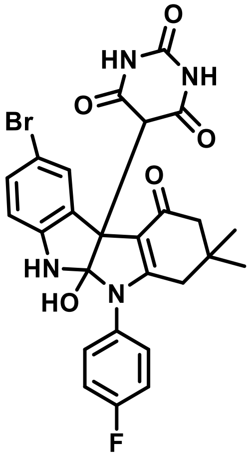
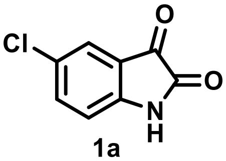
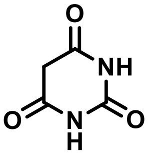
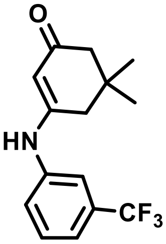
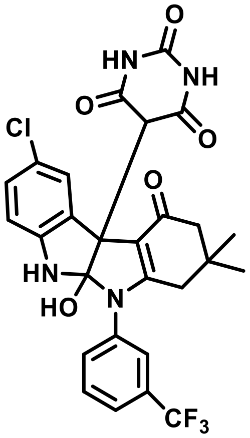
In order to extend the scope of this methodology, a wide range of isatins such as 5-chloro Isatin (**1a**),5-bromo Isatin (**1b**), Isatin (**1c**), barbituric acid (**2a**), and enaminone such as 3-((4-chlorophenyl)amino)-5,5-dimethylcyclohex-2-en-1-one (**3a**), 3-((4-fluorophenyl)amino)-5,5-dimethylcyclohex-2-en-1-one (**3b**),5,5-dimethyl-3-(((trifluoromethyl)phenyl)amino)cyclohex-2-en-1-one (**3c**),methyl4-((5,5-dimethyl-3-oxocyclohex-1-en-1-yl)amino)benzoate (**3d**), 5,5-dimethyl-3-(p-tolylamino)cyclohex-2-en-1-one (**3e**) were investi-gated under optimal conditions to afford the product in excellent yield (86-93%, **Table 3.2**).

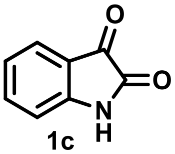
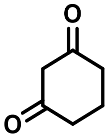
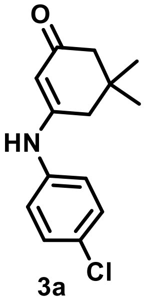
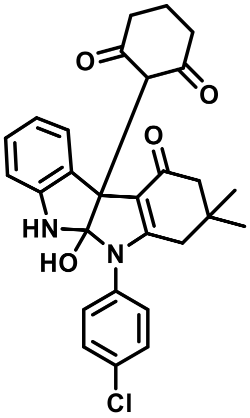
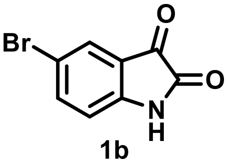
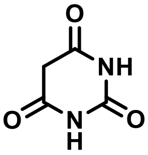
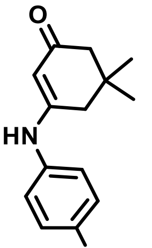
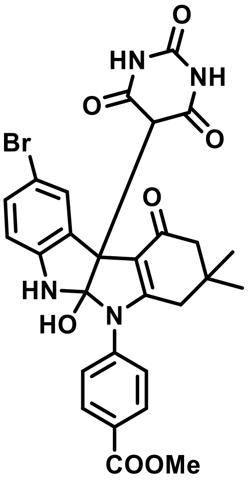
Table 3.2 Investigation of substrate scope for the synthesis of Indoloindole pyrimidine[a]

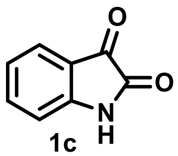
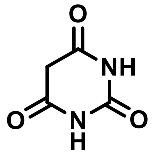
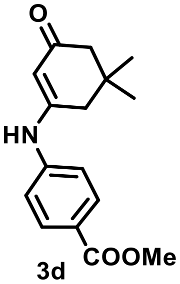
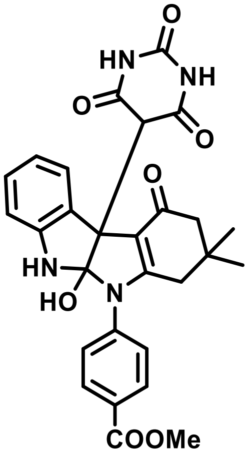
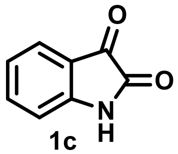
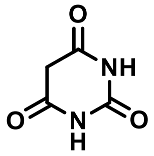
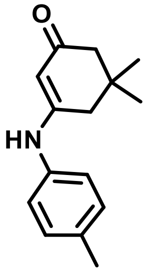
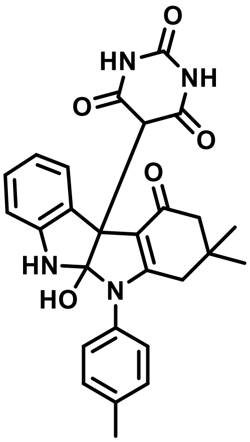
Entry	**1**	**2**	**3**	**4[a]**	**Yield[b](%)**
4a	 **1a**	 **2a**	 **3a**		**88**

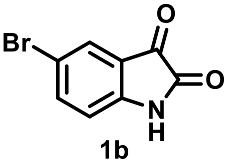
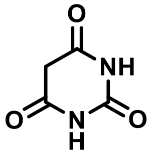
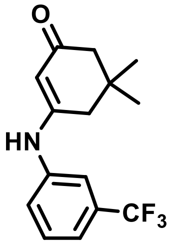
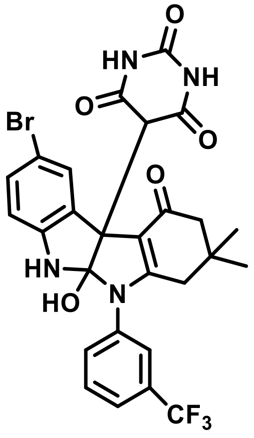
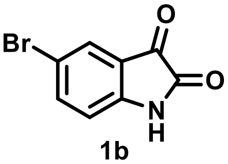
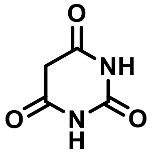
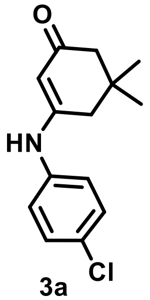
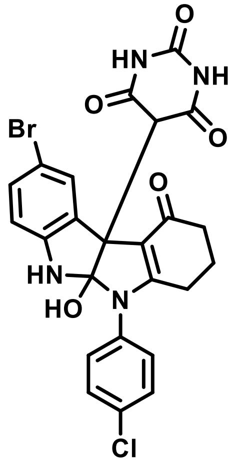
4b	 1b	 2a	 3a		93
4c	 1c	 2a	 3a		91

4d	 1c	 2a	 3b		90
4e	 1c	 2a	 3c		90

4f	 1b	 2a	 3b		91
4g	 1a	 2a	 3c		87

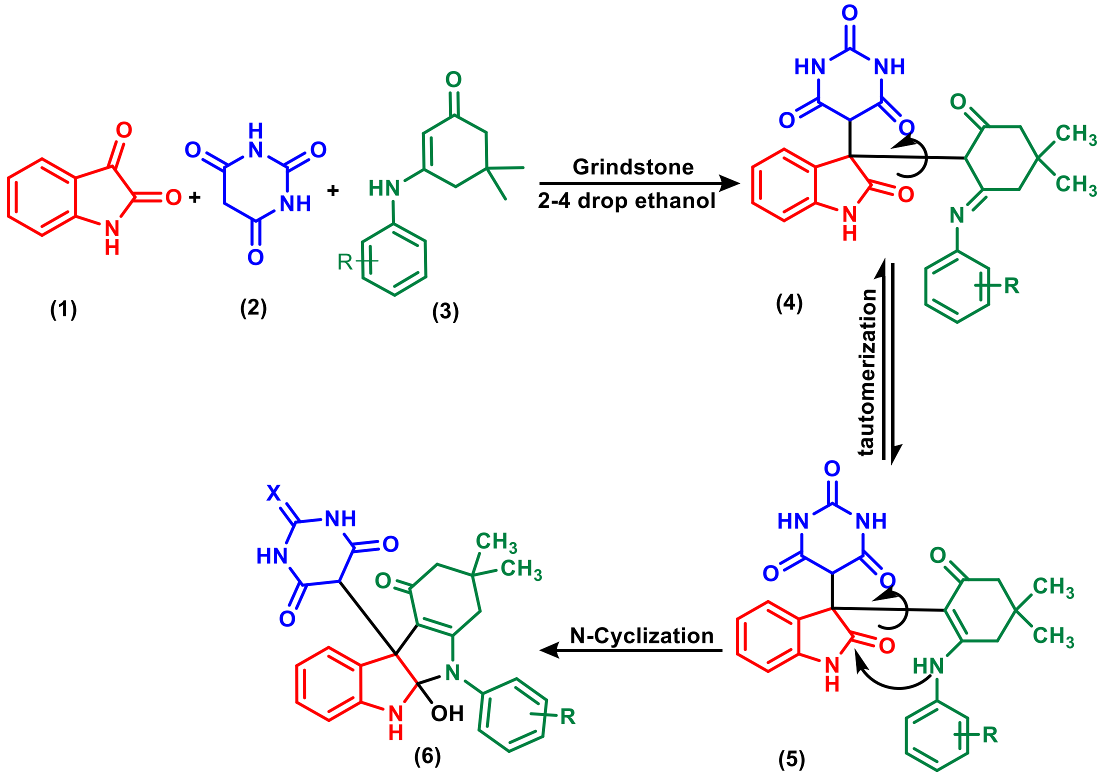
4h	 1c	 2b	 3a		86
4i	 1b	 2a	 3d		91

4j	 1c	 2a	 3d		92
4k	 1c	 2a	 3e		86

4l	 **1b**	 **2a**	 **3c**		**89**
4m	 **1b**	 **2a**	 **3a**		**87**

[a]Reaction condition: Isatin(1mmol), barbituric acid (1mmol),and enaminone (1mmol), under grinding.
[b]Isolated yield after recrystallization.

A suitable reaction mechanism is proposed based on product isolation and represented in **Scheme 3.2**. Initially, the Knoevenagel adduct is formed by the reaction of barbituric acid and isatin; after then, a Michael-type addition takes place via enamine and gives an open-chain intermediate. This intermediate undergoes imineenamine tautomerization and N-cyclization via the attack to the carbonyl group of amidic isatin produces **6 (Scheme 3.2)**.



Scheme 3.2 Plausible reaction mechanism

3.3 Conclusion

In conclusion, the present article describes the catalyst-free multicomponent synthesis of indoloindole pyrimidine via grinding methodology in a few drops of ethanol. This current approach offers some distinctive benefits such as eco-friendly, green protocol, short reaction times, good yields, and simple workup.

3.4 Experimental section

3.4.1 General experimental procedure for the synthesis of compound (4)

In this procedure, a mixture of isatin (1 mmol), enaminone (1 mmol), and diketone (1 mmol) was grinded in a specific size of mortar and pestle in the presence of a few drops (2–4 drops or 0.2 ml) of ethanol (3.43 mmol). The progress of the reaction was monitored by thin-layer chromatography (ethyl acetate: hexane 6:4). After the completion of the reaction, the product was recrystallized with hot ethanol to give the desired product in good yield.

3.4.2 Analytical data

5-(9-Chloro-5-(4-chlorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (4a)

Cream powder, yield 88%, m. p. 218 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.61 (s, 1H), 10.42 (s, 1H), 10.09 (s, 1H), 7.95 (d, 1H), 7.68-7.63 (m, 3H), 7.60-7.59 (m, 1H), 7.48 (m, 1H), 7.32(m, 2H), 5.97 (s, 1H), 3.34 (br,1H), 3.07 (d, 2H), 3.04 – 2.90 (m, 2H), 1.13 (s, 6H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 165.24, 160.68, 150.09, 149.25, 144.25, 137.95, 134.79, 131.19, 130.83, 129.65, 128.94, 127.68, 125.98, 125.45, 124.63, 123.85, 121.51, 90.64, 47.27, 40.56, 40.47, 40.39, 40.30, 40.23, 40.13, 39.97, 39.80, 39.63, 39.47, 33.04, 28.12. ; **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3725, 3414 (OH, NH), 2936 (CH), 1667, 1564 (C=O), 1251 (C-O), 763 (Ar). **Anal. Calc. for $C_{26}H_{22}Cl_2N_4O_5$:** C, 57.68; H, 4.10; N, 10.35. Found C,

57.75; H, 4.32; N, 10.61. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{22}Cl_2N_4O_5$, 541.3850; found, 541.3846.

5-(9-Bromo-5-(4-chlorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione(4b)

Cream powder, yield 93%, m. p. 221 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.60 (s, 1H), 10.42 (s, 1H), 10.09 (s, 1H), 7.91 (d, 1H), 7.80 (d, 1H), 7.65 – 7.62 (m, 3H), 7.33 (d, 2H), 5.97 (s, 1H), 3.34 (br,1H)3.01 (d, 4H), 1.13 (s, 6H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 165.24, 160.79, 151.57, 149.28, 144.43, 137.94, 134.66, 132.23, 130.94, 128.95, 127.73, 127.07, 126.50, 125.42, 124.61, 121.51, 119.72, 91.09, 47.30, 40.48, 40.40, 40.31, 40.23, 40.14, 39.98, 39.81, 39.64, 39.47, 33.02, 28.10. **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3745, 3423 (OH, NH), 2946 (CH), 1657, 1565 (C=O), 1257 (C-O), 767 (Ar). **Anal. Calc. for $C_{26}H_{22}BrClN_4O_5$:** C, 53.31; H, 3.79; N, 9.56. Found C, 53.52; H, 3.91; N, 9.86. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{22}BrClN_4O_5$, 585.8390; found 585.8386.

5-(5-(4-Chlorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione(4c)

Cream powder, yield 91%, m. p. 216 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.58 (s, 1H), 10.37 (s, 1H), 10.06 (s, 1H), 7.94 (d, 1H), 7.70 – 7.64 (m, 3H), 7.60 (m, 1H), 7.50 (m, 1H), 7.36 – 7.27 (m, 2H), 5.92 (s, 1H), 3.33 (br,1H), 3.06-3.09 (d, 2H), 2.96-2.99 (d, 2H), 1.14 (s, 6H).^{13}**C NMR (126 MHz, DMSO-d^6) δ** 165.87, 159.81, 150.10, 148.30, 145.75, 138.18, 135.80, 129.27, 128.81, 128.53, 127.43, 126.89, 125.45, 125.07, 124.83, 124.38, 121.51, 90.75, 47.38, 40.57, 40.48, 40.40, 40.31, 40.24, 40.15, 40.07, 39.98, 39.81, 39.64, 39.48, 33.00, 28.0 . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3727, 3417 (OH, NH), 2933 (CH), 1667, 1562 (C=O), 1251 (C-O), 765 (Ar). **Anal. Calc. for $C_{26}H_{23}ClN_4O_5$:** C, 61.60; H, 4.57; N, 11.05. Found C, 62.25; H, 4.83; N, 10.78. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{23}ClN_4O_5$, 506.9430; found, 506.9424.

5-(5-(4-Fluorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione(4d)

Cream powder, yield 90%, m. p. 230 ˚C, ^{1}**H NMR (500 MHz, DMSO-d^6) δ** 10.56 (s, 1H), 10.27 (s, 1H), 10.05 (s, 1H), 7.94 (d, 1H), 7.68 – 7.59 (m, 4H), 7.51 – 7.47 (m, 1H), 7.09 (t, 2H), 5.92 (s, 1H), 3.33 (br,1H), 3.20 – 2.88 (m, 4H), 1.14 (s, 6H). ^{13}**C NMR (126 MHz, DMSO-d^6) δ** 165.62, 159.79, 159.50, 157.60, 150.10, 148.18, 145.81, 135.95, 135.67, 129.23, 128.52, 126.83, 125.52, 125.15, 124.94, 124.35, 121.70, 121.64, 115.54, 115.36, 90.90, 47.43, 40.58, 40.49, 40.42, 40.33, 40.25, 40.16, 40.08, 39.99, 39.82, 39.66, 39.49, 32.99, 28.10. **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3735, 3453 (OH, NH), 2961 (CH), 1696, 1595 (C=O), 1236 (C-O), 773 (Ar). **Anal. Calc. for $C_{26}H_{23}FN_4O_5$:** C, 63.67; H, 4.73; N, 11.42. Found C, 63.92; H, 4.67; N, 11.67. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{23}FN_4O_5$, 490.4914; found, 490.4910.

5-(5a-Hydroxy-3,3-dimethyl-1-oxo-5-(3-(trifluoromethyl)phenyl)-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione(4e)

Cream powder, yield 90%, m. p. 216 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.56 (d, 2H), 10.01 (s, 1H), 8.07 (s, 1H), 7.96 (d, 1H), 7.85 (d, 1H), 7.67 (t, 1H), 7.60 (d, 1H), 7.51 (q, 2H), 7.41 (d,1H), 5.94 (s, 1H), 3.34 (br,1H), 3.20 – 2.87 (m, 4H), 1.14 (s, 6H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 166.28, 159.83, 157.18, 150.00, 148.41, 145.81, 144.01, 139.95, 135.54, 130.13, 129.66, 129.30, 128.57, 126.99, 125.40, 124.99, 124.77, 124.45, 123.43, 122.85, 120.33, 115.99, 90.84, 47.37, 43.53, 40.49, 40.32, 40.24, 40.15, 39.99, 39.82, 39.65, 39.49, 37.36, 33.01, 28.23. **IR (KBr) ($\bar{υ}_{max}$/cm^{-1}):** 3457, 3429, 3062 (OH, NH), CH (2892), 1672, 1582 (C=O), 1266 (C-O); 756 (Ar). **Anal. Calc. for $C_{27}H_{23}F_3N_4O_5$:** C, 60.00; H, 4.29; N, 10.37. Found C, 60.12; H, 4.41; N, 10.67. **HRMS** (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{27}H_{23}F_3N_4O_5$, 540.4992; found, 540.4987.

5-(9-Bromo-5-(4-fluorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione(4f)

Cream powder, yield 91%, m. p. 220 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.59 (s, 1H), 10.33 (s, 1H), 10.07 (s, 1H), 7.91 (d, 1H), 7.80 (d, 1H), 7.72 – 7.59 (m, 3H), 7.39 (s, 1H), 7.11 (t, 2H), 5.97 (s, 1H), 3.33 (br, 1H), 3.22 – 2.81 (m, 4H), 1.13 (s, 6H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 164.99, 160.78, 150.07, 144.44, 136.10, 134.82, 132.19, 130.93, 119.67, 115.70, 115.52, 90.76, 47.32, 40.49, 40.42, 40.33, 40.25, 40.16, 40.09, 39.83, 39.66, 39.49, 33.01, 28.08, 23.27. **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3459, 3096 (OH, NH), 2972 (CH), 1632, 1563 (C=O)**,** 1195(C-O). **Anal. Calc. for $C_{26}H_{22}BrFN_4O_5$:** C, 54.85; H, 3.89; N, 9.84. Found C, 54.96; H, 3.78; N, 9.77. **HRMS** (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{26}H_{22}BrFN_4O_5$, 569.3874; found, 569.3872.

5-(9-Chloro-5a-hydroxy-3,3-dimethyl-1-oxo-5-(3-(trifluoromethyl)phenyl)-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione(4g)

Cream powder, yield 87%, m. p. 216 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.59 (s, 2H), 10.02 (s, 1H), 8.05 – 7.88 (m, 2H), 7.84 (d, 1H), 7.71 (d, 1H), 7.51 (m, 2H), 7.43 (d, 1H), 5.99 (s, 1H), 3.35 (br, 1H), 3.03 (d, 4H), 1.14 (s, 6H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 165.64, 160.72, 149.96, 144.27, 139.72, 134.54, 131.29, 130.87, 130.26, 129.71, 125.89, 125.54, 123.76, 123.42, 90.58, 47.24, 40.49, 40.41, 40.32, 40.25, 40.15, 39.98, 39.82, 39.65, 39.48, 34.42, 33.05, 22.77, 15.30. **Anal. Calc. for $C_{27}H_{22}ClF_3N_4O_5$:** C, 56.41; H, 3.86; N, 9.74. Found C, 56.66; H, 3.71; N, 9.93. **HRMS** (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{27}H_{22}ClF_3N_4O_5$, 574.9412; found, 574.9408.

2-(5-(4-Chlorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)cyclohexane-1,3-dione(4h)

Cream powder, yield 86%, m. p. 241 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.98 (s, 1H), 7.32 (s, 1H), 7.12– 7.08 (m, 1H), 7.01 – 6.96 (m, 2H), 6.85-6.79 (m, 3H), 6.69 – 6.66 (m, 1H), 3.99 (s, 1H), 3.34 (br, 1H), 2.45 – 2.41 (m, 1H), 2.19 – 2.05 (m, 8H), 1.87 – 1.69 (m, 7H). ^{13}**C NMR (126 MHz, DMSO-d^6) δ** 204.30, 194.79, 182.46, 170.49, 144.85, 133.77, 127.89, 121.88, 121.80, 112.97, 109.70, 100.98, 59.63, 47.13, 40.82, 40.60, 40.51, 40.44, 40.35, 40.27, 40.18, 40.11, 40.01, 39.85, 39.68, 39.51, 37.23, 35.67, 29.55, 20.58, 20.07. **Anal. Calc. for $C_{27}H_{26}ClN_2O_4$:** C, 67.85; H, 5.48; N, 5.86. Found C, 67.69; H, 5.62; N, 5.51. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{27}ClN_2O_4$, 490.9840; found, 490.9835.

Methyl-4-(9-bromo-5a-hydroxy-3,3-dimethyl-1-oxo-10b(2,4,6-trioxohexahydro-pyrimid-in-5-yl)-2,3,4,5a,6,10b-hexahydro-1H-indolo[2,3-b]indol-5-yl)benzoate(4i)

Cream powder, yield 91%, m. p. 232 ˚C, ^{1}**H NMR (500 MHz, DMSO-d^6) δ** 10.62 (d, 2H), 9.99 (s, 1H), 7.91 (t, 3H), 7.81 (d, 1H), 7.73 (d, 2H), 7.67 (s, 1H), 5.98 (s, 1H), 3.85 (s, 3H), 3.41 (br, 1H), 2.95 (s, 4H), 1.14 (s, 6H). ^{13}**C NMR (126 MHz, DMSO-d^6) δ** 166.39, 165.71, 160.80, 150.02, 149.40, 144.44, 143.31, 134.48, 132.27, 130.97, 130.58, 127.00, 126.42, 125.48, 124.80, 124.54, 119.78, 119.44, 58.84, 52.35, 51.11, 47.28, 42.03, 40.50, 40.33, 40.17, 40.00, 39.83, 39.67, 39.50, 34.36, 33.04, 31.72, 28.13, 26.41, 19.02. **Anal. Calc. for $C_{28}H_{25}BrN_4O_7$:** C, 55.18; H, 4.13; N, 9.19. Found C, 55.73; H, 4.33; N, 9.31. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{25}BrN_4O_7$, 609.4330; found, 609.4327.

Methyl 4-(5a-hydroxy-3,3-dimethyl-1-oxo-10b-(2,4,6-trioxohexahydropyrimidin-5-yl)-2,3,4,5a,6,10b-hexahydro-1H-indolo[2,3-b]indol-5-yl)benzoate(4j)

Cream powder, yield 92%, m. p. 228 ˚C, ^{1}**H NMR (500 MHz, DMSO-d^6) δ** 11.11 (s, 1H), 10.58 (d, 1H), 9.96 (s, 1H), 7.95 (d, 1H), 7.88 (d, 2H), 7.75 (d, 2H), 7.70 – 7.63 (m, 1H), 7.61

(d, 1H), 7.57 – 7.47 (m, 1H), 5.92 (s, 1H), 3.85 (s, 3H), 3.36 (br, 1H), 3.03 (m, 4H), 1.14 (s, 6H).**^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 166.43, 159.82, 151.19, 150.05, 147.77, 145.81, 143.58, 135.59, 130.47, 129.29, 128.57, 127.85, 126.94, 125.40, 124.98, 124.55, 119.41, 52.32, 47.39, 43.93, 40.49, 40.42, 40.33, 40.25, 40.16, 39.99, 39.83, 39.66, 39.49, 33.02, 28.14. **Anal. Calc. for $C_{28}H_{26}N_4O_7$:** C, 63.39; H, 4.49; N, 10.56. Found C, 63.68; H, 4.32; N, 10.41. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{26}N_4O_7$, 530.5370; found, 530.5368.

5-(5a-Hydroxy-3,3-dimethyl-1-oxo-5-(p-tolyl)-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione(4k)

Cream powder, yield 86%, m. p. 219 ˚C, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.56 (d, 1H), 10.12 (s, 2H), 8.10 – 6.80 (m, 8H), 5.97 (s, 1H), 3.33 (br, 1H), 3.02 (d, 3H), 2.43 – 2.06 (m, 4H), 1.13 (s, 6H). **Anal. Calc. for $C_{26}H_{25}N_4O_5$:** C, 65.95; H, 5.32; N, 11.83. Found C, 65.61; H, 5.12; N, 11.41.

5-(9-Bromo-5a-hydroxy-3,3-dimethyl-1-oxo-5-(3-(trifluoromethyl)phenyl)-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione(4l)

Cream powder, yield 89%, m. p. 226 ˚C, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.59 (s, 2H), 10.01 (s, 1H), 8.09 – 7.35 (m, 7H), 5.98 (s, 1H), 3.38 (br, 1H), 3.02 (d, 4H), 1.13 (s, 6H). **Anal. Calc. for $C_{27}H_{22}BrF_3N_4O_5$:** C, 52.36; H, 3.58; N, 9.05. Found C, 52.92; H, 3.21; N, 9.47.

5-(9-Bromo-5-(4-chlorophenyl)-5a-hydroxy-1-oxo-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (4m)

Cream powder, yield 87%, m. p. 218 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 11.63 (s, 1H), 11.06 (s, 1H), 10.67 (s, 1H), 9.33 – 8.68 (m, 2H), 8.45 – 7.88 (m, 2H), 7.87 – 7.35 (m, 3H), 7.00 (m, 1H), 5.56 (s, 1H), 3.35 (br, 1H), 3.06 (s, 4H), 2.23 (d, 2H). **Anal. Calc. for $C_{24}H_{18}BrClN_4O_5$:** C, 51.68; H, 3.25; N, 10.04. Found C, 51.92; H, 3.23; N, 10.47.

3.4.3 Spectral Data of Product 5-(9-chloro-5-(4-chlorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydroindolo[2,3-b]indol-10b(2H)-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (4a)

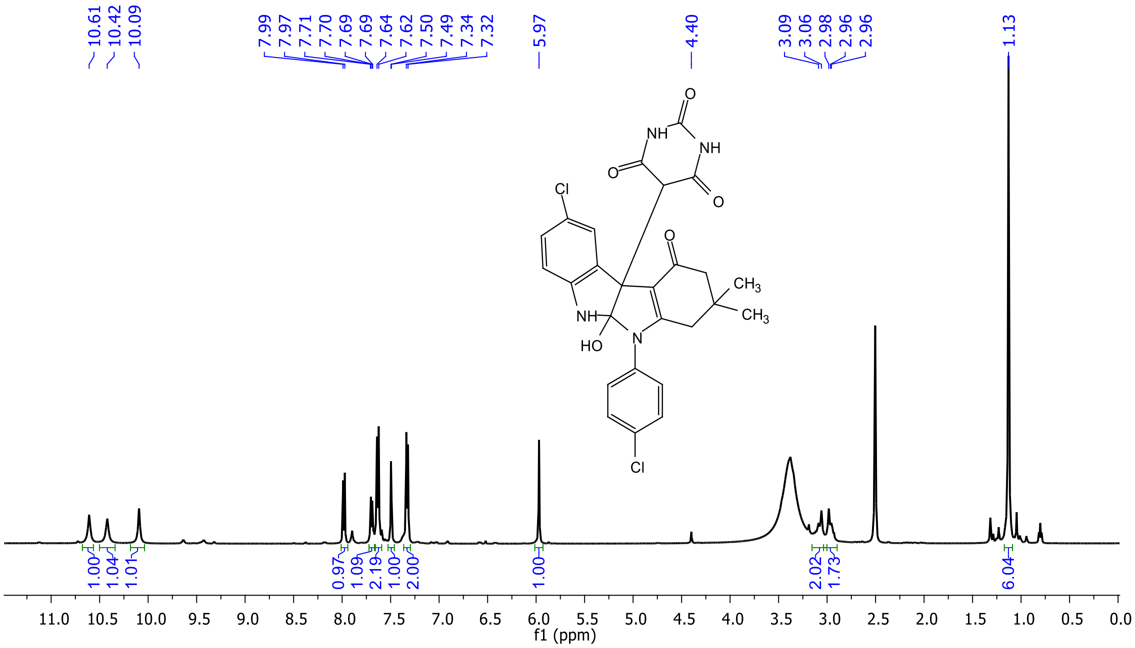


Figure 3.2 ^{1}H NMR of 5-(9-chloro-5-(4-chlorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydroindolo[2,3-b]indol-10b(2H)-yl)pyrimidine-2,4,6(1H,3H,5H)-trione **(4a)**

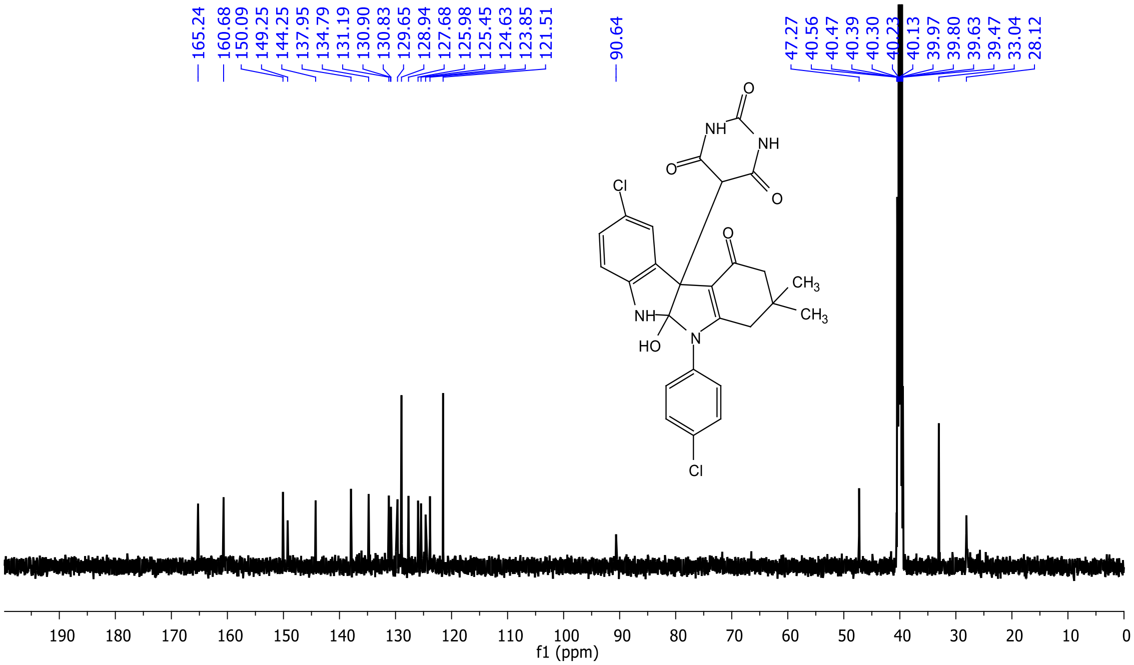


Figure 3.3 ^{13}C NMR of 5-(9-chloro-5-(4-chlorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydroindolo[2,3-b]indol-10b(2H)-yl)pyrimidine-2,4,6(1H,3H,5H)-trione **(4a)**

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CHAPTER 4

VISIBLE -LIGHT TRIGGERED SYNTHESIS OF SPIRO [INDOLINE-3,4’-QUINOLINE] VIA OXIDATIVE COUPLING OF INDOLE WITH ENAMINONE AND MALONONITRILE

Visible-light triggered synthesis of spiro [indoline-3,4’-quinoline] via oxidative coupling of indole with enaminone and malononitrile

4.1 Introduction

In the last few years, there has been a great demand for the effective synthesis of green, environmentally friendly, and metal-free approaches for preparing organic compounds [1]. At this time, chemists are more attracted towards visible light irradiation to synthesize organic compounds due to more valuable demands as it is low cost, environmentally friendly, green, non-toxic, easy to handle, and a renewable energy source [2,3].

Currently, multicomponent synthesis has more advantages for modern organic synthetic chemistry. In multicomponent reactions (MCRs), three or more starting reactants are mixed in one pot and give highly complex molecules in one step. It is easy to separate the compound, reduce time, diminish costs, and provide a good yield compared to multistep synthesis [4,5].

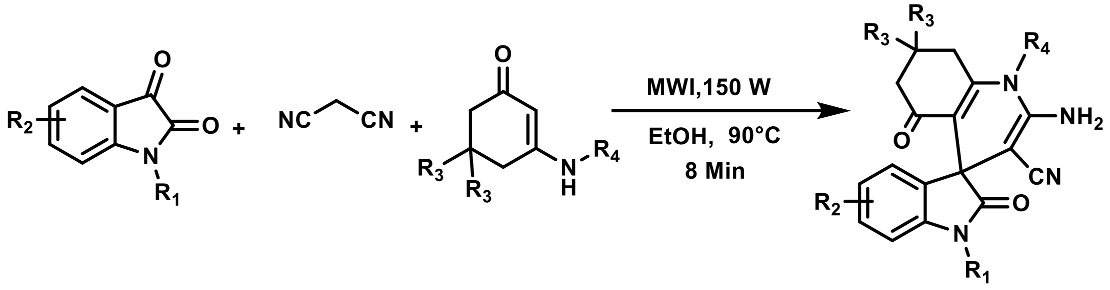
Visible-light-initiated multicomponent synthesis has also attracted considerable attention over the past years for the fast and proficient synthesis of several organic compounds. This approach is more helpful in preparing various chemical libraries, which are usually used for drugs for biological activity [6,7].

Spiro-indolo-quinoline heterocyclic compounds have much more application in medicine [8], natural product [9], agrochemical [10], therapeutic agent [11], bioorganic molecules and also play a vital role in biological activity such as antiasthmatic [12], anti-HIV [13], antihypertensive [14], anti-inflammatory [15], antitumor [16], antituberculosis [17], and antimalarial properties [18]. Various types of naturally occurring plants also have spiroindole heterocyclic compounds. The spiroindoles are a more striking moiety in organic and medicinal chemistry and also show various biological applications in antimycobacterial [19], antitumor [20], antitubercular, antifungal [21], antioxidant agents [22,23] anti-inflammatory, anticancer, analgesic, antimalarial, and antiviral activities. Isatin is important in the heterocyclic compound, having much exciting activity and being used for many chemical transformations [24,25]. The combination of visible light with multicomponent synthesis is an efficient operation to access suitable new organic molecule.

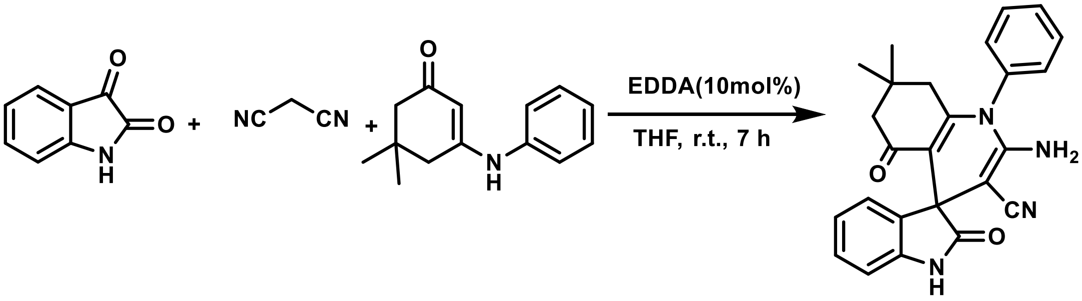
Due to the importance of such a compound, some synthetic protocols for constructing spiro[indoline-3,4'-quinoline] have been reported **(Scheme 4.1)**.

Previous work

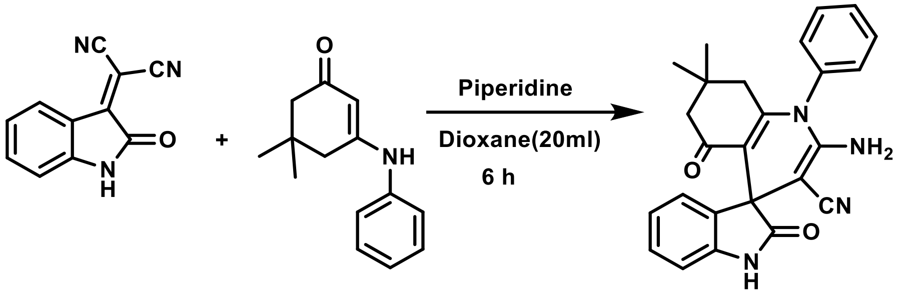
(a) S.-L. Zhu, K. Zhao, X.-M. Su, S.-J. Ji, Synthetic Communications 2009, 39, 1355



(b) S. R. Kang, Y. R. Lee, Synthesis **2013**, 45, 2593

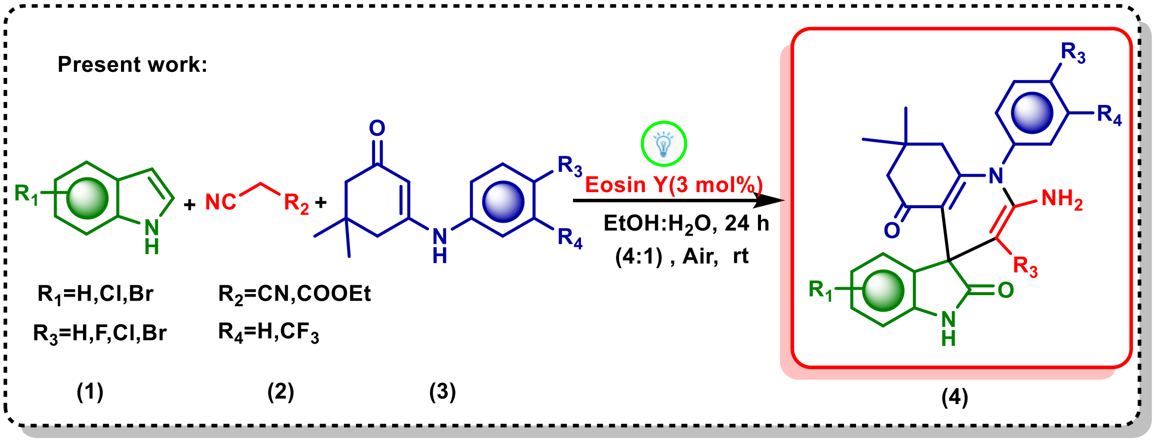


(c) S. A. S. Ghozlan, M. F. Mohamed, A. G. Ahmed, S. A. Shouman, Y. M. Attia, I. A. Abdelhamid, Archiv der Pharmazie **2015**, 348, 113



Scheme 4.1 Synthesis of spiro[indoline-3,4'-quinoline] by previous method

We advocate an appealing design to create a new ecologically friendly organic synthesis approach that uses visible light as its primary energy source [26]. To reduce the negative environmental impact of metal catalysts, we have developed a one-pot, multicomponent synthesis that uses visible light, a photocatalyst, and a green solvent[27]. Here we report multicomponent synthesis of 2'-amino-1'-(4-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile derivative under visible light irradiation via oxidative coupling of indole with enaminone and active methylene compounds in excellent yield (75-84%) **(Scheme 4.2)**.



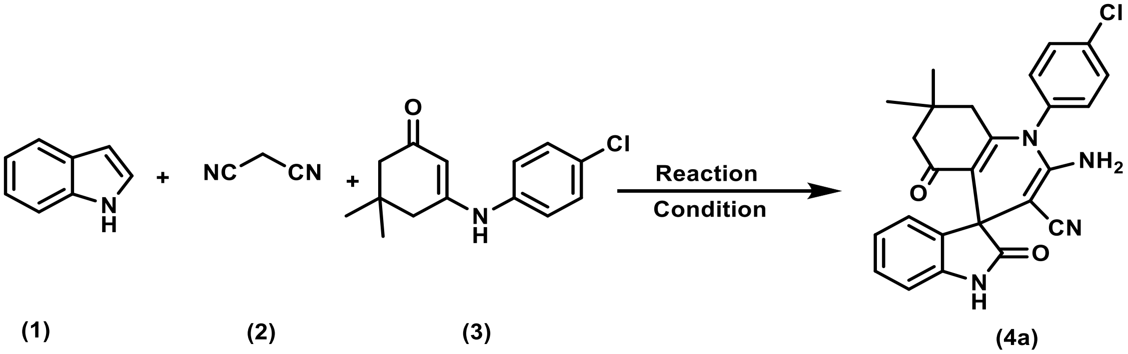
Scheme 4.2 Synthesis of Spiro[indoline-3,4-quinoline] Derivatives

4.2 Results and Discussion

Primarily in our study, we choose a model reaction for carrying out a one-pot multicomponent reaction of indole **1** (1 mmol), malononitrile **2** (1 mmol), and enaminone **3** (1 mmol) in the presence of various catalysts, solvent and LEDs lamps. Firstly, we investigated the reaction in a different solvents like THF, DMSO, DMF, and CH_3CN under 8W white LED and using eosin Y as a catalyst. We obtained a trace amount of the product after 24 h (**Table 4.1, Entries 1- 4**). Further, a similar reaction was examined in CH_2Cl_2, H_2O, EtOAc, and EtOH in the presence of eosin Y. It was found that ethanol is a superior solvent to others to form the desired product (**Table 4.1, Entries 5-8**). We also investigated the same protocol in the various molar ratio of ethanol and water (2:1, 3:1, 4:1, 5:1), and the product yield was good in 4:1 ratio **(Table 4.1, Entries 9-12)**. Subsequently, after selecting a solvent, we dedicated ourselves to studying the consequence of many visible light sources on the reaction. Now different intensities of LED, such as 8W, 12W, 15W, 20W, and 30W, were optimized under ethanol: water (4:1) system(**Table 4.1, Entries 13-17**). Amazingly, 84% product yield was obtained in 24 h under 22W white LED **(Table 4.1, Entry 16)**. After increasing light intensities, the yield was constant (**Table 4.1, Entry 17**). A similar reaction was carried out in various catalysts like piperidine, ethylenediamine, and trimethylamine were optimized, and 56%, 41%, 28% yields were obtained, respectively (**Table 4.1, Entries 18-20**). Further, we optimized our model reaction using some photocatalysts like rhodamine B and rose bengal and got 27% and 38% yields (**Table 4.1 Entries 21-22**). Unfortunately, there was the formation of only a trace amount of the product in the presence of 8W blue and green LED (**Table 4.1, Entries 23, 24**). However, as soon as the same protocol was performed in the dark for 24h, no product was obtained (**Table 4.1, Entry 25**). The reaction was also tried in sunlight without white LEDs, and we got an 11% yield of product (**Table**

4.1, Entry 26). Finally, we also tried the same procedure for 24 h stirring without white LEDs and did not obtain the expected product (**Table 4.1, Entry 27**).

Table 4.1 Optimization condition for the synthesis of Spiro[indoline-3,4 -quinoline] derivatives **4a**[a]



Entry	Various Conditions For Reaction	Catalyst (3 Mol%)	Solvent	Time (h)	Yield[b] (%)
1.	8 W white LEDs	Eosin Y	THF	24	12
2.	8 W white LEDs	Eosin Y	DMSO	24	9
3.	8 W white LEDs	Eosin Y	DMF	24	11
4.	8 W white LEDs	Eosin Y	CH_3CN	24	12
5.	8 W white LEDs	Eosin Y	CH_2Cl_2	24	11
6.	8 W white LEDs	Eosin Y	H_2O	24	15
7.	8 W white LEDs	Eosin Y	EtOAc	24	9
8.	8 W white LEDs	Eosin Y	EtOH	24	34

9.	8 W white LEDs	Eosin Y	EtOH:H_2O (2:1)	24	54
10.	8 W white LEDs	Eosin Y	EtOH:H_2O (3:1)	24	60
11.	8 W white LEDs	Eosin Y	EtOH:H_2O (4:1)	24	65
12.	8 W white LEDs	Eosin Y	EtOH:H_2O (5:1)	24	65
13.	12 W white LEDs	Eosin Y	EtOH:H_2O (4:1)	24	68
14.	15 W white LEDs	Eosin Y	EtOH:H_2O (4:1)	24	72
15.	20 W white LEDs	Eosin Y	EtOH:H_2O (4:1)	24	75
16.	**22 W white LEDs**	**Eosin Y**	**EtOH:H_2O (4:1)**	**24**	**84**
17.	30 W white LEDs	Eosin Y	EtOH:H_2O (4:1)	24	84
18.	22 W white LEDs	Piperidine	EtOH:H_2O (4:1)	24	56

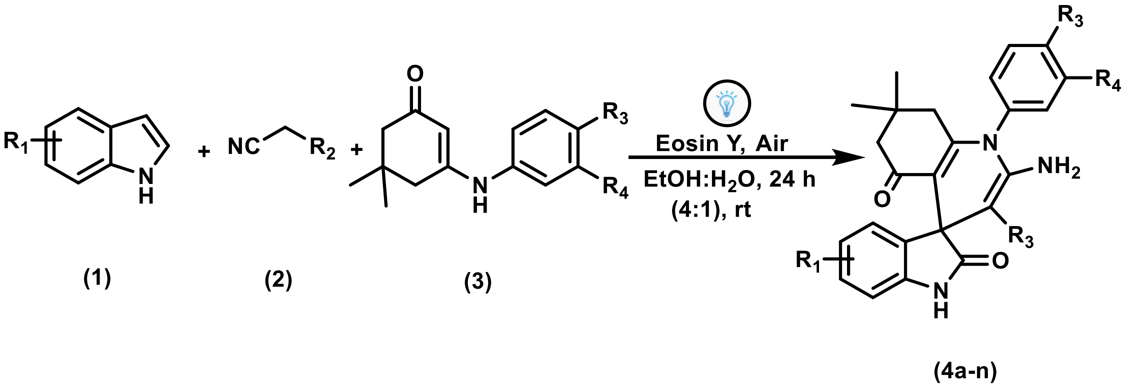
19.	22 W white LEDs	Ethylenediamine	$EtOH:H_2O$ (4:1)	24	41
20.	22 W white LEDs	Triethylamine	$EtOH:H_2O$ (4:1)	24	28
21.	22 W white LEDs	Rhodamine B	$EtOH:H_2O$ (4:1)	24	27
22.	22 W white LEDs	Rose bengal	$EtOH:H_2O$ (4:1)	24	38
23.	22 W white LEDs	Eosin Y	H_2O	24	Trace
24.	8 W blue LEDs	Eosin Y	$EtOH:H_2O$ (4:1)	24	Trace
25.	8 W green LEDs	Eosin Y	$EtOH:H_2O$ (4:1)	24	Trace
26.	Dark	Eosin Y	$EtOH:H_2O$ (4:1)	24	NA
27.	Sunlight instead of white LEDs	Eosin Y	$EtOH:H_2O$ (4:1)	6	11
28.	Stirring without white LEDs	Eosin Y	$EtOH:H_2O$ (4:1)	24	NA

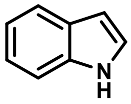
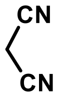
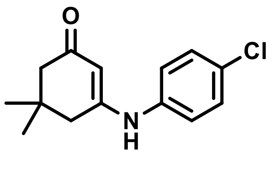
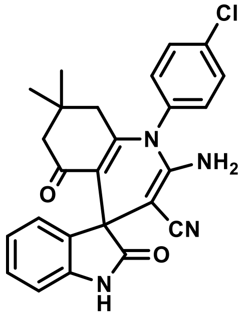
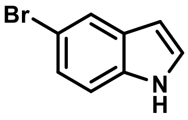
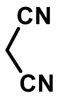
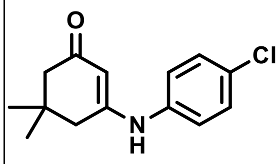
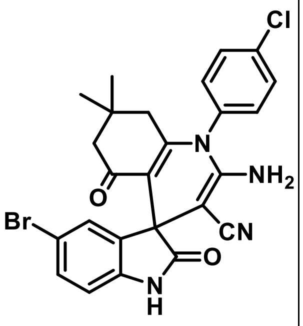
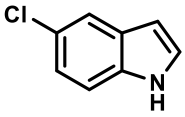
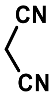
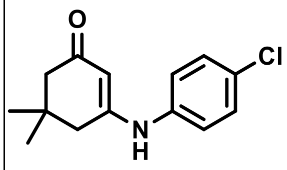
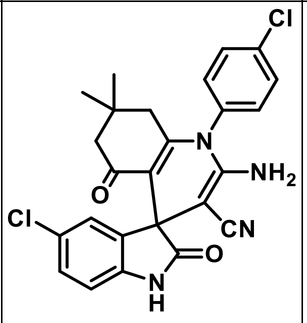
[a]Experimental condition: Indole(1mmol), malononitrile (1mmol), enaminone (1mmol), solvents (5ml) , room temperature,under various visible light irradiation

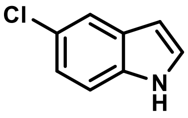
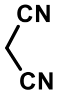
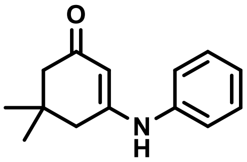
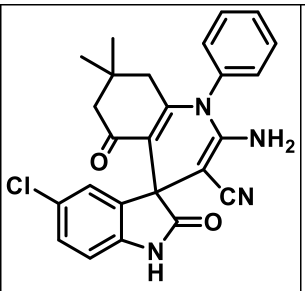
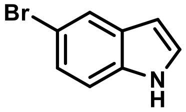
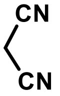
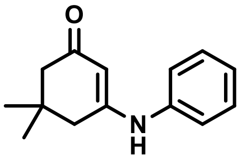
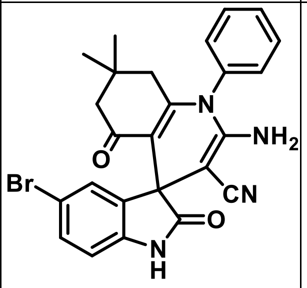
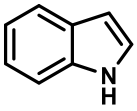
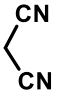
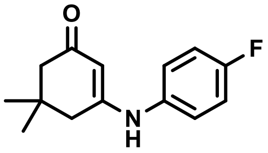
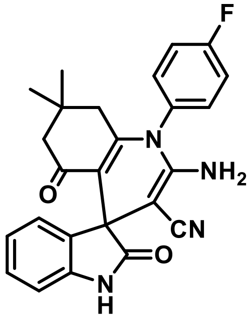
[b] Isolated yields, [c] NA- no reaction

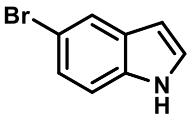
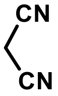
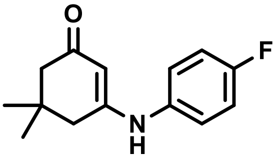
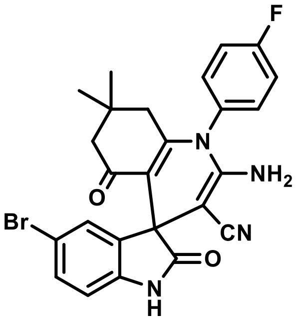
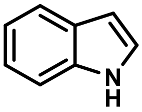
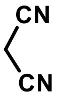
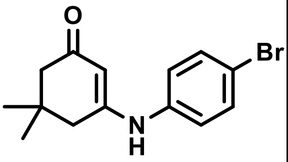
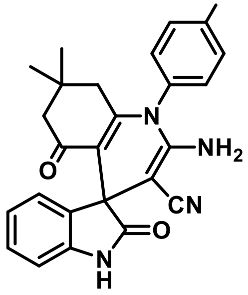
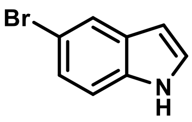
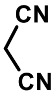
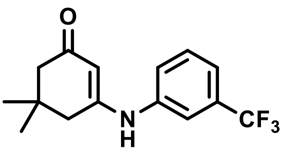
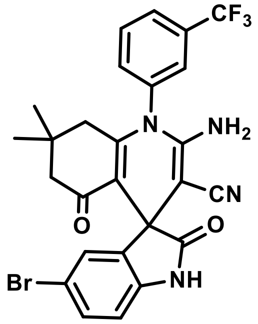
With the aim of extending the opportunity of this approach, various indole **(1a)**, 5-bromoindole **(1b)** and 5-chloroindole **(1c),** active methylene compounds like malononitrile **(2a)** and ethyl cyanoacetate **(2b**) were allowed to react with 3-((4-chlorophenyl)amino)-5,5-dimethylcyclohex-2-en-1-one **(3a)**, 5,5-dimethyl-3-(phenyl- amino)cyclohex-2-en-1-one **(3b)**, 3-((4-fluorophenyl)amino)-5,5-dimethylcyclohex-2-en-1-one **(3c)**, 3-((4-bromophenyl)amino)-5,5-dimethylcyclohex-2-en-1-one **(3d)**, 5,5-dimethyl-3-((3-(trifluoromethyl)phenyl)amino)cyclohex-2-en-1-one **(3e)**, 6-(phenyl- amino)pyrimidine-2,4(1H,3H)-dione **(3f)** and 3-((2-chlorophenyl)amino)-5,5-dimethyl- cyclohex-2-en-1-one **(3g)** under optimal conditions, and the reaction proceeds smoothly in all cases to provide the product (**Table 4.2**).

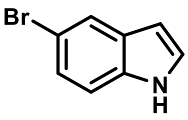
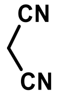
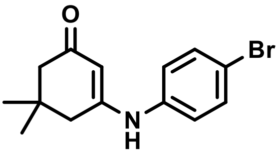
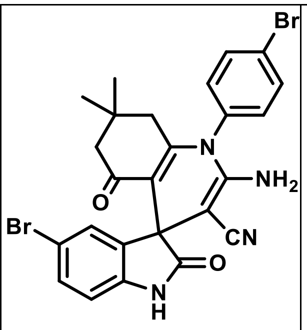
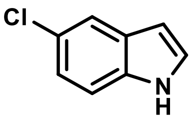
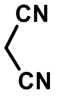
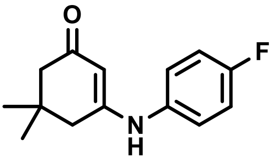
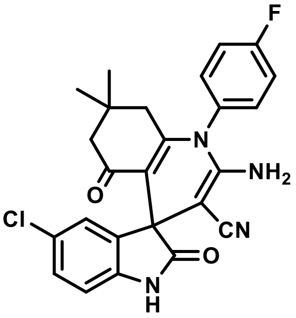
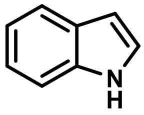
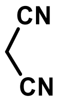
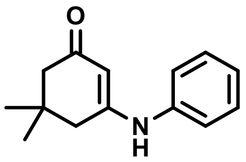
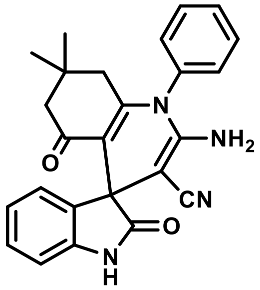
Table 4.2 Library of compounds and versatility of reaction[a]

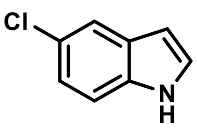
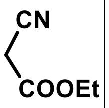
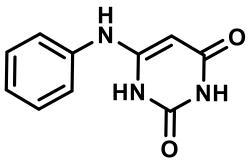
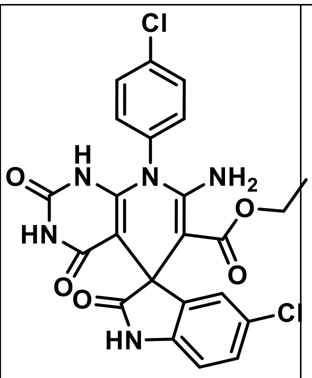
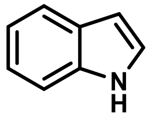
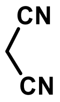
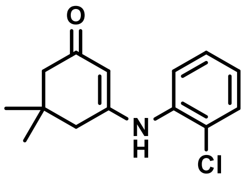
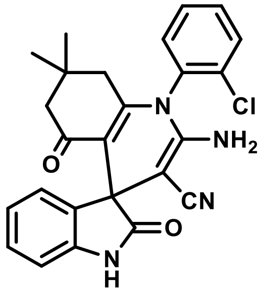


Entry	1	2	3	4[a]	Yield[b] (%)
4a	 1a	 2a	 3a		84
4b	 1b	 2a	 3a		83
4c	 1c	 2a	 3a		80

4d	 1c	 2a	 3b		**78**
4e	 1b	 2a	 3b		**82**
4f	 1a	 2a	 3c		**81**

4g	 **1b**	 **2a**	 **3c**		**80**
4h	 **1a**	 **2a**	 **3d**		**83**
4i	 **1b**	 **2a**	 **3e**		**79**

4j	 1b	 2a	 3d		82
4k	 1c	 2a	 3c		79
4l	 1a	 2a	 3b		83

4m	 **1c**	 **2b**	 **3f**		**74**
4n	 **1a**	 **2a**	 **3g**		**81**

[a]Experimental condition: Indole (1mmol), malononitrile (1mmol), enaminone (1mmol), solvents (5ml), room temperature,under various visible light irradiation ,

[b] Isolated yields,

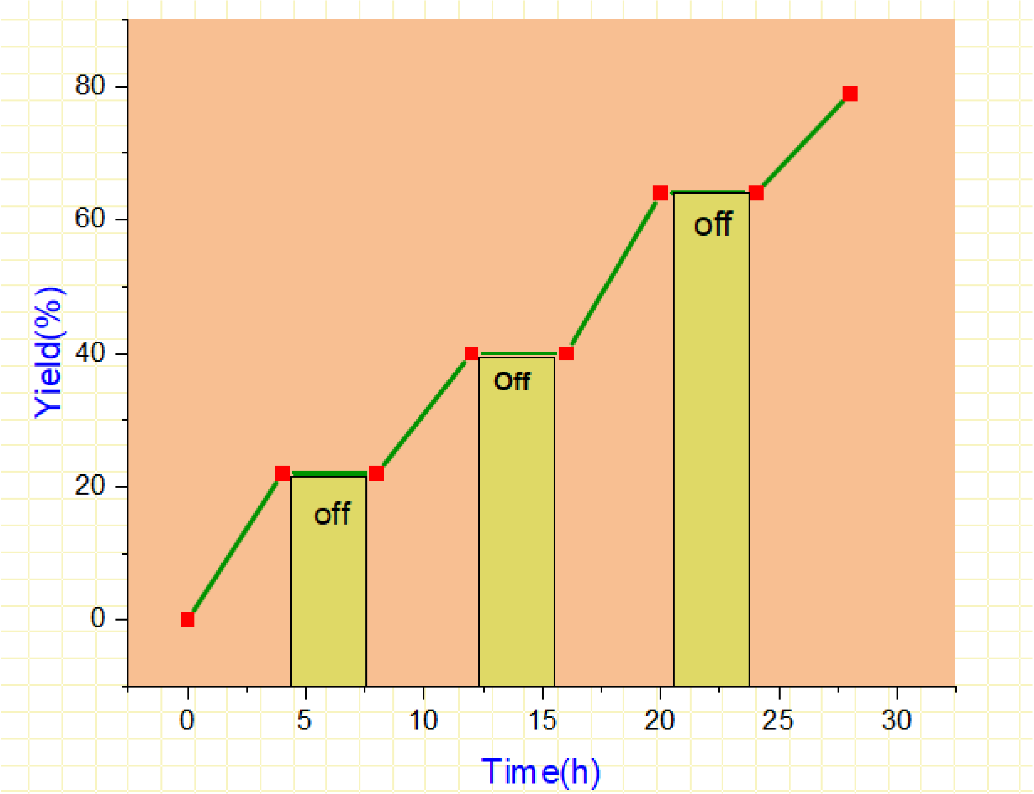
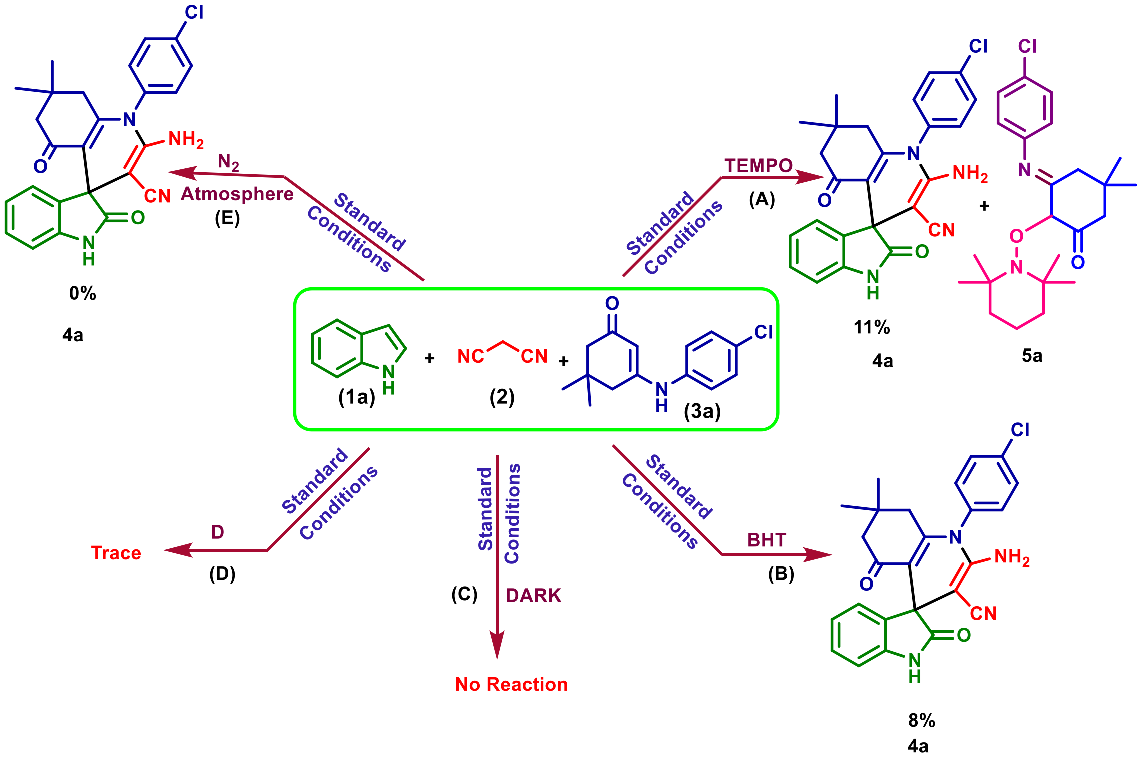
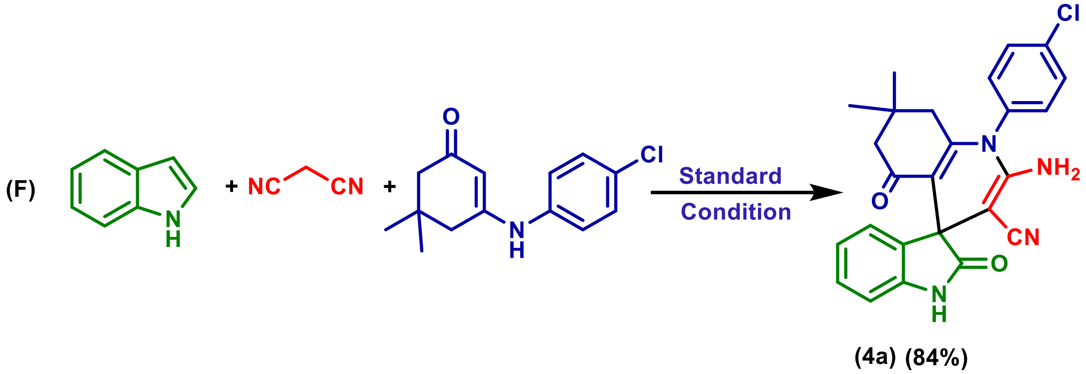


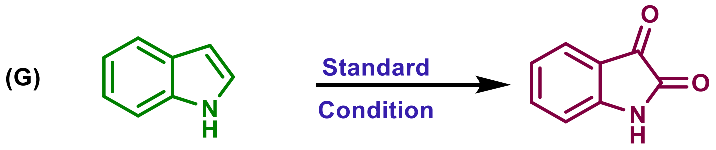
Figure 4.1 The experiment showed the effect of "On-off" switching of the visible light source on reaction

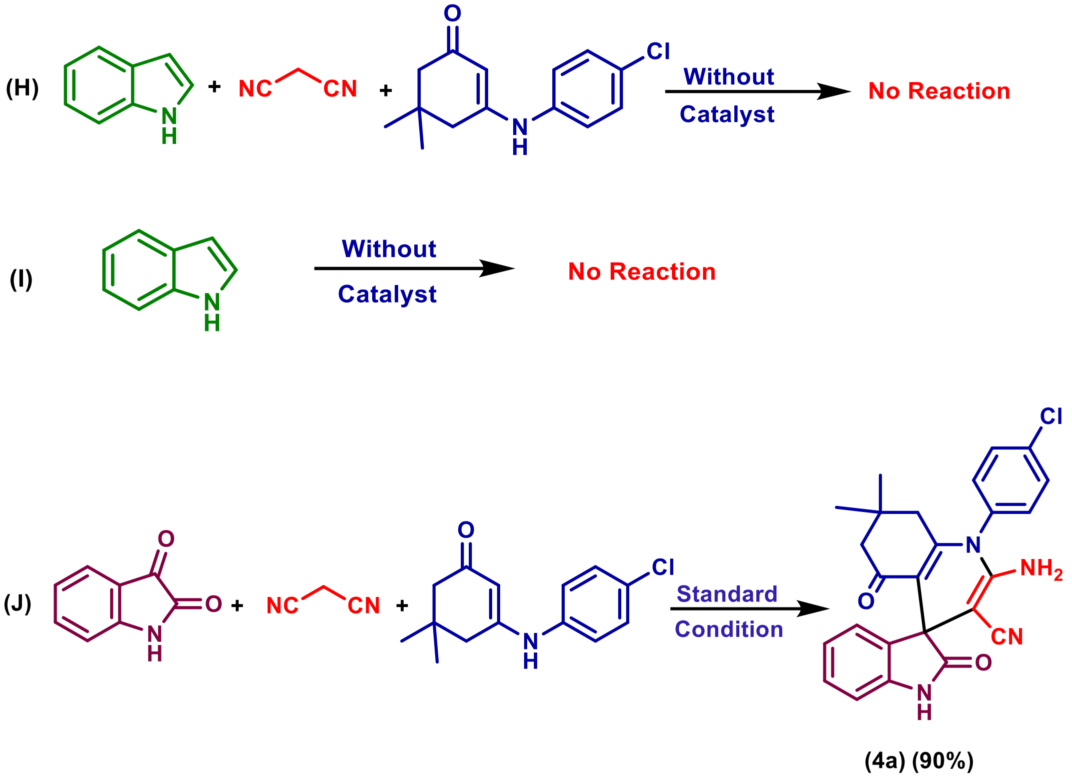
We experimented with mechanistic pathways with a broad substrate scope and optimized reaction conditions, and conducted a few control experiments (**Scheme 4.3**). Initially, we conducted a thermal reaction of indole (1 mmol), malononitrile (1 mmol), and enaminone (1 mmol) in standard conditions and got a trace amount of product, and also no reaction happened when performed in dark conditions. This result confirms the importance of visible light for this reaction. No product was obtained as soon as the reaction was performed in nitrogen. This indicates that there is a role of oxygen in this reaction. Further, radical scavengers like TEMPO and BHT were added to the reaction mixture under standard conditions, and the yield of the product spiro [indoline-3,4'-quinoline] was suppressed due to the formation of **5a** (confirmed through HRMS data). This result ensured that the reaction went via a free radical mechanism. The on-off experiment **(Figure 4.1)** was carried out to explore the effect of visible light on the reaction. This experiment shows that the reaction got significantly promoted by visible light irradiation.

More control experiments were conducted to determine the reaction's pathway. Under the standard condition, the reaction of indole (**1a**), malononitrile **(2),** and enaminone **(3a)** were carried out and produced product **4a** in an 84 % yield (**Scheme 4.3, reaction F**). The reaction of indole was carried out under standard conditions alone to identify the intermediate, and the intermediate, isatin (VII), was produced (**Scheme 4.3, reaction G**). By analyzing it using ^{1}H and ^{13}C NMR spectroscopy, the intermediate (VII) production was verified. However, comparable conditions were used for the reaction of isatin (VII) enaminone and malononitrile. The 90% yield of product **4a** (**Scheme 4.3, reaction J**), along with reaction **I**, supports isatin's ability to operate as an intermediate (VII).


Cl
NH2
CN
O
N
H
O
N2
Atmosphere
(E)
Standard
Conditions
0%
4a
TEMPO
(A)
Standard
Conditions
Cl
N
NH2
CN
O
N
H
O
+
Cl
N
O
N
O
11%
4a
5a
O
NC
CN
+
+
Cl
N
H
N
H
(1a)
(2)
(3a)
Standard
Conditions
D
Trace
(D)
Standard
Conditions
(C)
DARK
No Reaction
Standard
Conditions
BHT
(B)
Cl
N
NH2
CN
O
N
H
O
8%
4a

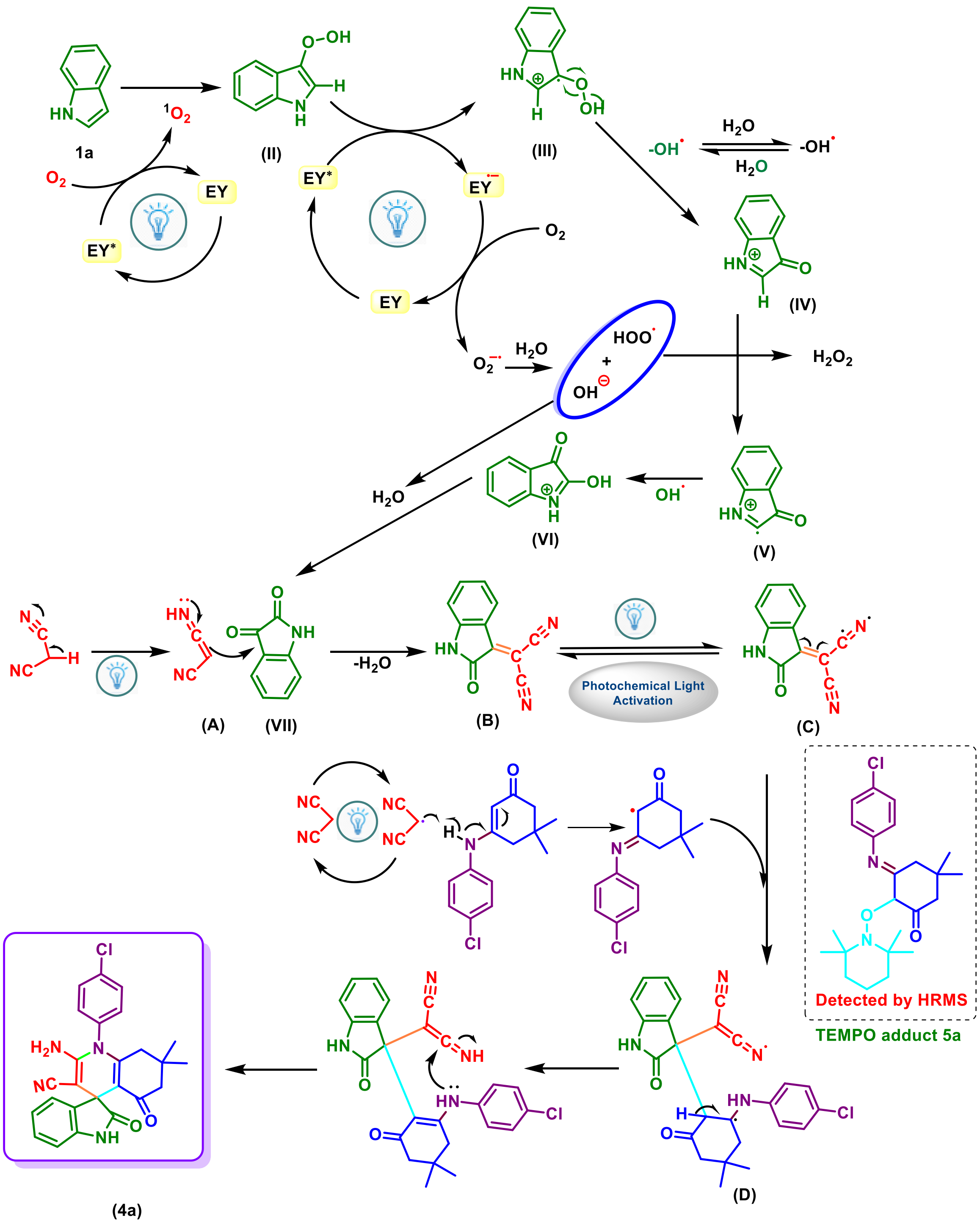

(F)
N
H
+ NC
CN
+
O
Cl
N
H
Standard
Condition
Cl
N
NH2
O
CN
O
N
H
(4a) (84%)


(G)
N
H
Standard
Condition
O
O
N
H



Scheme 4.3 Control experiment for reaction

Based on the study, previous reports, and control experiments, a plausible mechanism was sketched out (**Scheme 4.4**) for this light-promoted three-component reaction [28-30]. Eosin Y was transformed into excited Eosin Y (EY*) when exposed to visible light (EY). Singlet oxygen is created when oxygen quenches the excited form of eosin Y (EY*), which then interacts with indole (I) to create peroxo species (II). In the second photocatalytic cycle, species (II) were oxidised to produce species (III) of peroxoindole and radical anion $EY^{\cdot -}$ By cleaving up different species, the cation (IV) and hydroxyl radical were created one after the other (III). Hydrogen atom from the (IV) is abstracted by the formed hydroxyl radical, which produces (V). It has been reported that the excited state of eosin Y has an $E^0_{(red)}$ of -1.32 V versus SCE, which is more than enough to reduce oxygen to its superoxide radical anion ($E^0_{(red)}$ is -0.56 V vs SCE). In order to create superoxide radical anion, $EY^{\cdot -}$ reduced oxygen. When the radical anion reacts with water, hydroxide anions and peroxide radicals are produced. The species (VI) (by the release of a water molecule) and the radical species (V) and hydroxyl radical combined to produce the intermediate (VII). Further intermediate (**A)** is formed by the photoexcitation or tautomerization of malononitrile in ethanol. After that, knoevenagel condensation takes place by isatin and intermediate **A** and gives the cyanoolefin intermediate **B** with water removal. The formation of intermediate **B** is confirmed through ^{1}H NMR and ^{13}C NMR spectra. Then this intermediate is activated by visible light to generate a free radical intermediate **C**. The hydrogen of enaminone is acidic, which is abstracted by malononitrile and generates a radical. This radical is rearranged and combined with intermediate **C** to form the intermediate **D** through carbon-carbon bond formation. Consequently, intermediate **D** is intramolecularly cyclized to give the desired product (**4a**).



Scheme 4.4 Proposed reaction mechanism

4.3 Conclusion

We have developed the visible light-mediated multicomponent synthesis of spiro[indoline-3,4'-quinoline] derivative in ethanol using a 22W LED lamp without a catalyst. This present method provides some characteristic profits such as catalyst-free, low cost, environmentally friendly, green, non-toxic, easy to handle, and visible light as a renewable energy source.

4.4 Experimental section

4.4.1 Typical procedure for the preparation of compound (4)

Indole **1** (1.0 mmol), malononitrile **2** (1.0 mmol), and enaminone **3** (1.0 mmol) were stirred at room temperature under visible light irradiation of 22 W white LED in the presence of eosin Y by using ethanol: water (4:1) (5.0 ml) as a solvent. After the completion of the reaction (monitored by TLC), the reaction mixture was filtered and washed with water to yield a solid product. Then, the crude product was recrystallized from ethanol to afford the pure product **4**.

4.4.2 Analytical Data

2'-Amino-1'-(4-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (4a)

White solid, m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.21 (s, 1H), 7.66 (d, *J* = 7.7 Hz, 2H), 7.51 (s, 2H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 7.6

Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 5.56 (br. s, 2H, NH_2), 2.12 (m,2H), 1.88 (m, 2H), 0.89 (s, 3H), 0.82 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.38, 179.92, 152.15, 151.58, 141.92, 137.12, 135.39, 134.99, 132.47, 130.77, 128.14, 123.69, 121.83, 119.40, 110.94, 109.29, 61.25, 49.79, 48.97, 41.80, 40.49, 40.32, 40.16, 39.99, 39.82, 39.66, 39.49, 32.60, 28.73, 27.04. **IR (KBr, cm^{-1}) :** 3325, 3310 (NH_2), 2175 (CN), 1741 (CO), 1635 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{22}ClN_4O_2$, 445.1431 ; found,445.1426.

2'-Amino-5-bromo-1'-(4-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (4b)

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.36 (s, 1H), 7.41 (m, *J* = 7.6 Hz, 6H), 6.73 (d, *J* = 7.8 Hz, 1H), 5.65 (br. s, 2H, NH_2), 2.15 – 1.78 (m, 4H), 0.89 (s, 3H), 0.85 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.59, 179.63, 152.71, 151.66, 141.42, 139.56, 135.16, 135.06, 132.60, 130.85, 130.73, 126.55, 119.26, 113.64, 111.21, 110.15, 60.30, 49.66, 49.48, 41.82, 40.48, 40.32, 40.15, 39.98, 39.82, 39.65, 39.48, 32.64, 28.28, 27.56. **IR (KBr, cm^{-1}) :** 3325, 3316 (NH_2), 2183 (CN), 1738 (CO), 1643 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}BrClN_4O_2$, 523.0536 ; found,523.0533.

2'-Amino-5-chloro-1'-(4-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (4c)

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.36 (s, 1H), 7.66 (d, *J* = 7.7 Hz, 4H), 7.31 – 7.14 (m, 2H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.66 (br. s, 2H, NH_2), 2.19 – 1.75 (m, 4H), 0.89 (s, 3H), 0.85 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.58, 179.77, 152.69, 151.67, 141.00, 139.17, 135.18, 135.06, 132.60, 130.73, 127.99, 125.89, 123.89, 119.26, 110.63, 110.17, 60.32, 49.67, 49.50, 41.82, 40.49, 40.32, 40.15, 39.99, 39.82, 39.65, 39.49, 32.63, 28.32, 27.53. **IR (KBr, cm^{-1}) :** 3328, 3312 (NH_2), 2182 (CN), 1751 (CO), 1648 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}Cl_2N_4O_2$, 479.1041 ; found,479.1039.

2'-Amino-5-chloro-7',7'-dimethyl-2,5'-dioxo-1'-phenyl-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (4d)

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.36 (s, 1H), 7.76 – 7.34 (m, *J* = 7.8 Hz, 5H), 7.29 – 7.14 (m, 2H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.44 (br. s, 2H, NH_2), 2.14 – 1.83 (m, 4H), 0.88 (s, 3H), 0.84 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.57, 179.77, 152.89, 151.67, 141.02, 139.19, 136.23, 130.74, 130.55, 130.47, 128.01, 125.89, 123.80, 119.24, 110.66, 110.10, 60.48, 56.50, 49.65, 49.50, 41.85, 40.49, 40.41, 40.32, 40.25, 40.16, 39.99, 39.82, 39.66, 39.49, 32.62, 28.26, 27.58. **IR (KBr, cm^{-1}) :** 3328, 3321 (NH_2), 2179 (CN), 1748 (CO), 1639 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{22}ClN_4O_2$, 445.1431; found, 445.1429.

2'-Amino-5-bromo-7',7'-dimethyl-2,5'-dioxo-1'-phenyl-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (4e)

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.37 (s, 1H), 7.79 – 6.59 (m, *J* = 7.8 Hz, 8H), 5.44 (br. s, 2H, NH_2), 2.21 – 1.75 (m, 4H), 1.05 (m, 3H), 0.84 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.57, 179.63, 152.90, 151.66, 141.45, 139.58, 136.21, 130.87, 130.74, 130.54, 130.48, 126.46, 119.24, 113.63, 111.25, 110.09, 60.49, 56.50, 49.65, 49.48, 41.85, 40.50, 40.33, 40.16, 40.00, 39.83, 39.66, 39.50, 32.63, 28.22, 27.62. **IR (KBr, cm^{-1}) :** 3323, 3316 (NH_2), 2190 (CN), 1755 (CO), 1655 (CO); **HRMS** (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{25}H_{22}BrN_4O_2$, 489.0926 ; found, 489.0925.

2'-Amino-1'-(4-fluorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (4f)

White solid, m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.21 (s, 1H), 7.57 – 7.34 (m, *J* = 7.6 Hz, 4H), 7.29 – 7.00 (m, *J* = 7.4 Hz, 2H), 7.00 – 6.67 (m, 2H), 5.52 (br. s, 2H, NH_2), 2.25 – 2.03 (m, 2H), 1.87 (m, 2H), 0.89 (s, 3H), 0.82 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.38, 179.96, 163.85 (d, J = 251.2 Hz), 161.88, 152.40, 151.72, 141.91, 137.15, 132.69 (dd, J = 13.6, 8.8 Hz), 128.13, 123.70, 121.83, 119.44, 117.62 (d, J = 18.4 Hz), 110.88, 109.28, 61.15, 49.77, 48.96, 41.82, 40.48, 40.31, 40.14, 39.98, 39.81, 39.64, 39.47, 32.56, 28.75, 27.05. **^{19}F NMR (471 MHz, DMSO-d^6) δ** -111.40. **IR (KBr, cm^{-1}) :** 3315, 3310 (NH_2), 2210 (CN), 1740 (CO), 1643 (CO); **HRMS** (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{25}H_{22}FN_4O_2$, 429.1726; found, 429.1724.

2'-Amino-5-bromo-1'-(4-fluorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (4g)

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.36 (s, 1H), 7.92 – 6.61 (m, *J* = 7.9 Hz, 7H), 5.61 (br. s, 2H, NH_2), 2.00 (m, 4H), 1.07 – 0.88 (m, 3H), 0.84 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.59, 179.66, 163.72 (d, J = 260.2 Hz) 152.95, 151.80, 141.42, 139.59, 133.00, 132.45 (d, J = 8.8 Hz), 130.84, 126.54, 119.30, 117.61 (d, J = 18.1 Hz), 111.20, 110.11, 60.22, 49.64, 49.48, 41.83, 40.48, 40.31, 40.15, 39.98, 39.81, 39.65, 39.48, 33.63, 32.60, 31.11, 28.29, 27.57. **^{19}F NMR (471 MHz, DMSO-d^6) δ** -111.36. **IR (KBr, cm^{-1}) :** 3321, 3311 (NH_2), 2193 (CN), 1738 (CO), 1642 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}BrFN_4O_2$, 507.0831; found, 507.0828.

2'-Amino-1'-(4-bromophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (4h)

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.29 (s, 1H), 7.61 (d, *J* = 7.6 Hz, 4H), 7.42 – 6.94 (m, 3H), 6.72 (d, *J* = 8.1 Hz, 1H), 5.59 (br. s, 2H, NH_2), 2.08 – 1.77 (m, 4H), 0.85 (s, 3H), 0.80 (s, 3H). **IR (KBr, cm^{-1}) :** 3322, 3314 (NH_2), 2175 (CN), 1742 (CO), 1651 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{22}BrN_4O_2$, 489.0926 ; found, 489.0923. Due to less solubility, we are not able to take the ^{13}C NMR .

2'-Amino-5-bromo-7',7'-dimethyl-2,5'-dioxo-1'-(3-(trifluoromethyl)phenyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (4i)

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.46 (d, 1H), 7.97 (t, *J* = 7.5 Hz, 3H), 7.37 (d, *J* = 7.9 Hz, 3H), 6.73 (s, 1H), 5.70 (br. s, 2H, NH_2), 2.00 (d, 4H), 1.01 (s, 3H), 0.85 (d, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.65, 178.16, 165.11, 159.35, 152.53, 141.45, 137.03, 135.10, 131.40 (q, J = 32.2 Hz), 130.87, 126.43 (q, J = 250.2 Hz), 119.26, 115.46, 113.69, 111.66, 111.18, 60.51, 57.19, 50.40, 49.61, 47.52, 40.47, , 40.30, 40.23, 40.14, 39.97, 39.80, 39.63, 39.47, 32.64, 28.00, 27.64. **^{19}F NMR (471 MHz, DMSO-**

d^6) δ -111.43. **IR (KBr, cm^{-1}) :** 3323, 3316 (NH_2), 2190 (CN), 1755 (CO), 1655 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{21}BrF_3N_4O_2$, 557.0799; found, 557.0796.

2'-Amino-5-bromo-1'-(4-bromophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (4j)

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.30 (s, 1H), 7.61 (s, *J* = 7.8 Hz, 3H), 7.47 – 7.20 (m, *J* = 7.4 Hz, 3H), 6.68 (d, *J* = 7.6 Hz, 1H), 5.59 (br. s, 2H, NH_2), 1.96 (m, 4H), 0.85 (s, 3H), 0.80 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.62, 179.67, 152.74, 151.70, 141.49, 139.61, 135.22, 135.11, 132.65, 130.90, 130.78, 126.60, 119.29, 113.68, 111.25, 61.29, 51.16, 49.72, 41.87, 40.56, 40.39, 40.23, 40.06, 39.89, 39.73, 39.56, 32.69, 28.32, 27.62. **IR (KBr, cm^{-1}) :** 3318, 3310 (NH_2), 2180 (CN), 1746 (CO), 1635 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}Br_2N_4O_2$, 567.0031; found, 567.0030.

2'-Amino-5-chloro-1'-(4-fluorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (4k)

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.36 (s, 1H), 7.72 (s, *J* = 7.8 Hz, 1H), 7.47 – 7.37 (m, 4H), 7.30 (m, *J* = 8.2, 1.9 Hz, 1H), 6.74 (t, *J* = 7.3 Hz, 1H), 5.61 (br. s, 2H, NH_2), 2.06 (m, 2H), 1.95 (d, 2H), 0.90 (s, 3H), 0.85 (s, 3H). **^{19}F NMR (471 MHz, DMSO-d^6) δ** -111.42. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}ClFN_4O_2$, 463.1337; found, 463.1335. Due to less solubility, we are not able to take the ^{13}C NMR.

2'-Amino-7',7'-dimethyl-2,5'-dioxo-1'-phenyl-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (4l)

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.22 (s, 1H), 7.70 – 7.44 (m, *J* = 7.6 Hz, 5H), 7.22 – 7.10 (m, *J* = 7.3 Hz, 2H), 6.95 – 6.76 (m, 2H), 5.34 (br. s, 2H, NH_2), 2.12 (m, 2H), 1.88 (m, 2H), 0.88 (s, 3H), 0.82 (s, 3H). **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{23}N_4O_2$, 411.1821; found, 411.1819. Due to less solubility, we are not able to take the ^{13}C NMR.

Ethyl 7'-amino-5-chloro-8'-(4-chlorophenyl)-2,2',4'-trioxo-2',3',4',8'-tetrahydro-1'H-spiro[indoline-3,5'-pyrido[2,3-d]pyrimidine]-6'-carboxylate (4m)

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.09 (s, 1H), 7.70 (d, *J* = 7.4 Hz, 2H), 7.44 (d, *J* = 8.9 Hz, 1H), 7.17 (s, *J* = 7.6 Hz 1H), 6.97 (m, *J* = 7.2 Hz, 3H), 6.64 (br. s, 2H, NH_2), 3.69 (m, 2H), 2.09 – 2.03 (m, 2H), 1.90 (d, 1H), 1.80 (d, 1H), 1.11 – 0.93 (m, 3H), 0.84 (m, 3H), 0.78 (s, 3H). **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{18}Cl_2N_5O_5$, 514.0685; found, 514.0681. Due to less solubility, we are not able to take the ^{13}C NMR.

2'-Amino-1'-(2-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (4n)

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.39 (s, 1H), 7.66 (m, *J* = 7.8 Hz, 7H), 7.27 – 7.06 (m, 4H), 6.98 (d, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 7.6Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 2H), 2.05 (m, *4*H), 1.04 (s, 3H), 1.00 (s, 3H). **HRMS** (ESI-TOF) m/z: $[M + H]^+$

calcd for $C_{25}H_{22}ClN_4O_2$, 445.1431; found, 445.1429. Due to less solubility, we are not able to take the ^{13}C NMR.

Isatin (intermediate) (VII)

Orange precipitate, m.p. 190°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 11.22 (s, 1H), 7.90 (d, J=7.8 Hz, 1H), 7.60 (t, J=7.8 Hz, 1H), 7.18 (t, J=7.8 Hz, 1H), 6.90 (d, J=7.7 Hz, 1H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 178.76, 160.35, 149.12, 138.25, 129.86, 128.68, 114.86, 112.56.

4.4.3 Spectral Data of Product 2'-Amino-1'-(4-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (4a)

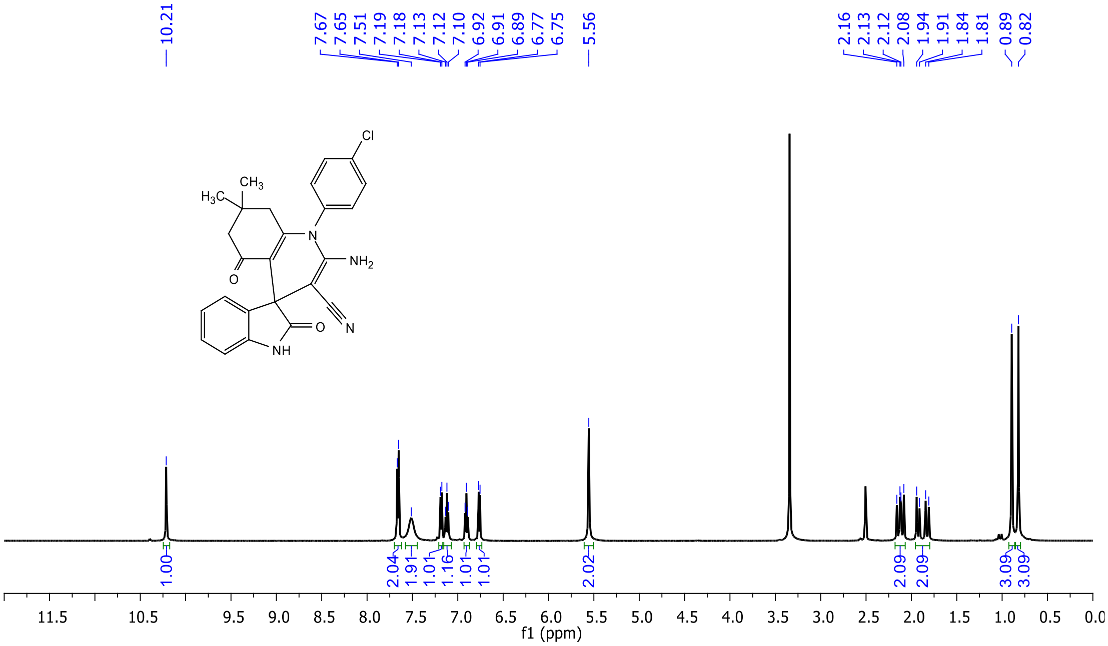


Figure 4.2 ^{1}H NMR 2'-Amino-1'-(4-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile **(4a)**

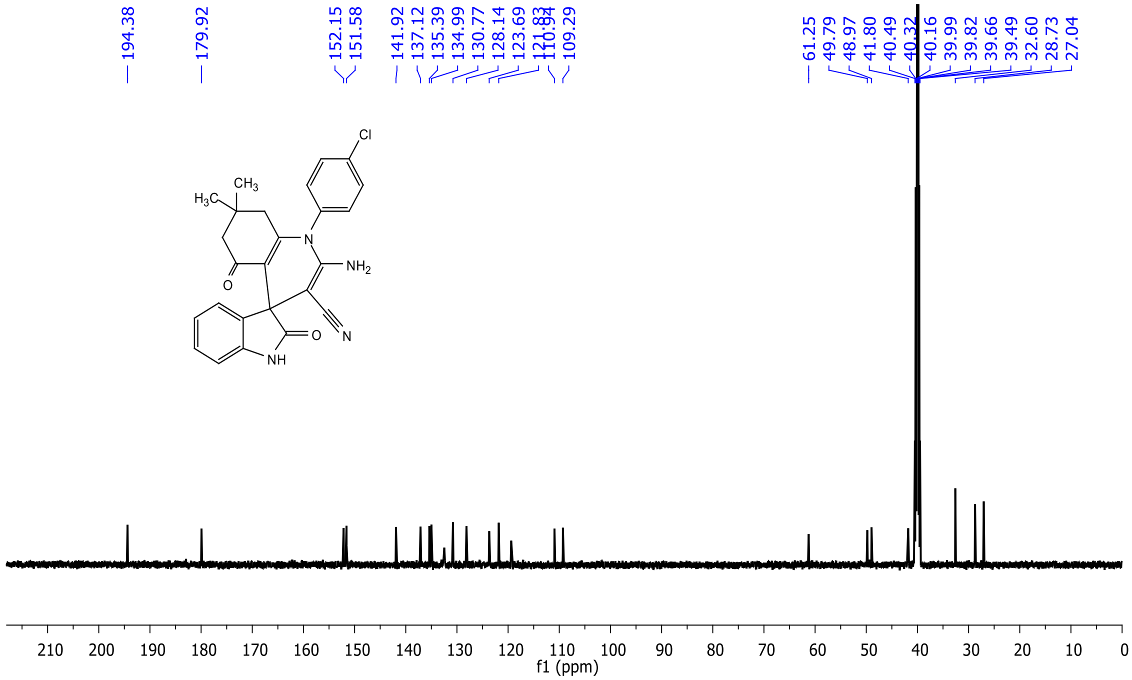
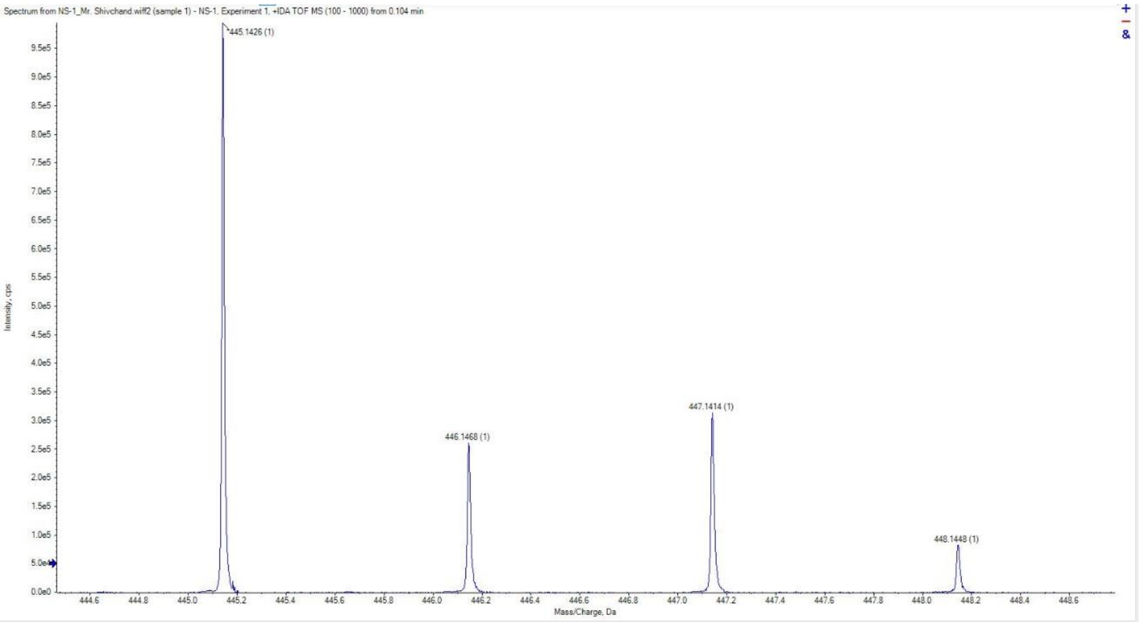


Figure 4.3 ^{13}C NMR 2'-Amino-1'-(4-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile **(4a)**

4.4.4 Copies of HRMS data of product (4a)



Spectrum from NS-1_Mr. Shivchand.wiff2 (sample 1) - NS-1. Experiment 1, +IDA TOF MS (100 - 1000) from 0.104 min

Figure 4.4 HRMS data of 2'-Amino-1'-(4-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile **(4a)**

HRMS data of product (4b)

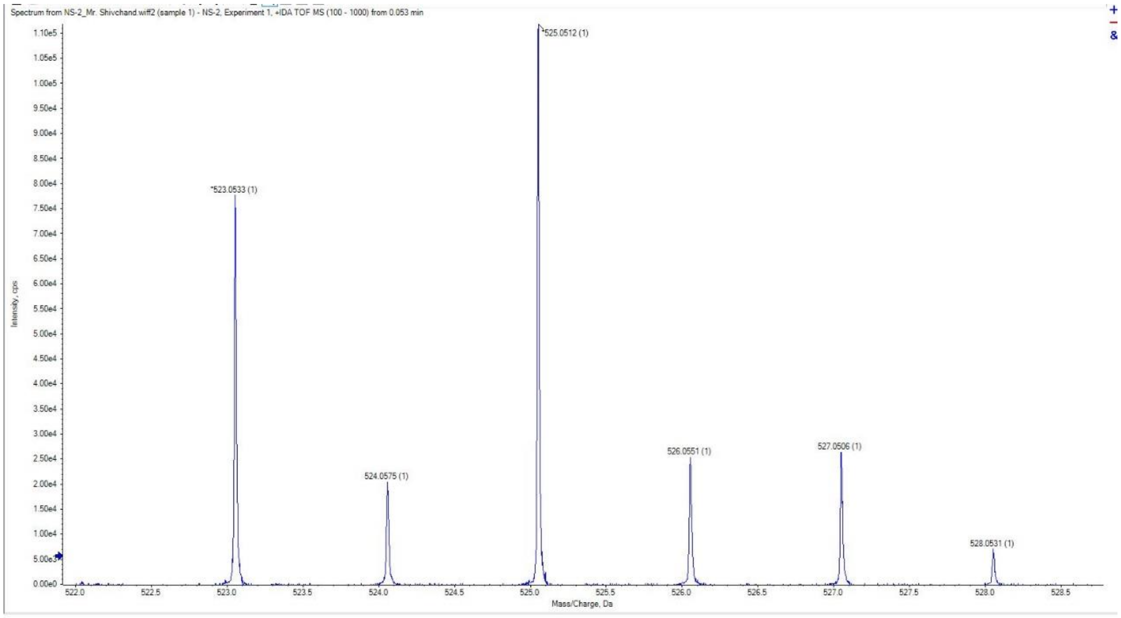


Figure 4.5 HRMS data of 2'-amino-5-bromo-1'-(4-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile **(4b)**

HRMS data of product (5a)

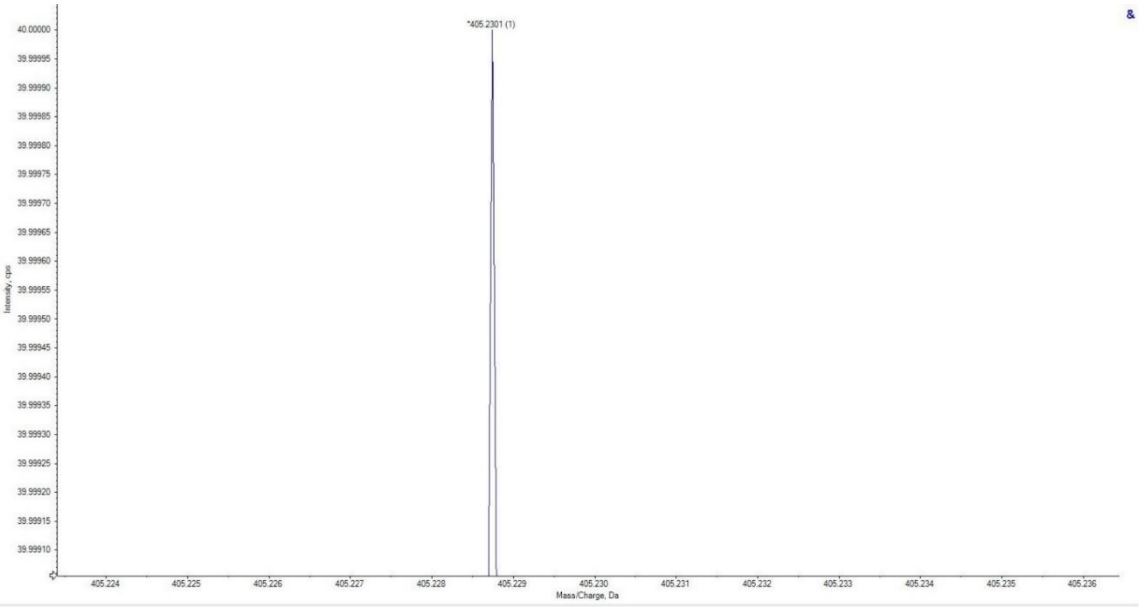


Figure 4.6 HRMS data of (E)-3-((4-chlorophenyl)imino)-5,5-dimethyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)cyclohexan-1-one **(5a)**

4.4.5 Data of UV-Visible absorption Spectra

UV-visible spectroscopy of reaction solution was recorded on a SHIMADZU UV-1800 UV-visible spectrophotometer. The sample was prepared by mixing of indole, malononitrile, and enaminone derivatives in methanol solvent [Conc. reaction mixture = 1.25×10-4mol/L] in a light path quartz UV cuvette.

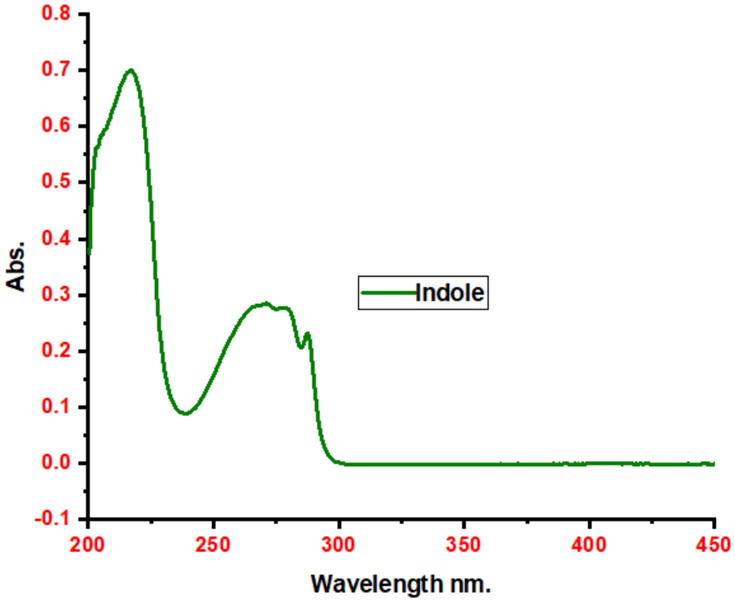


Figure 4.6 UV spectrum of Indole in methanol

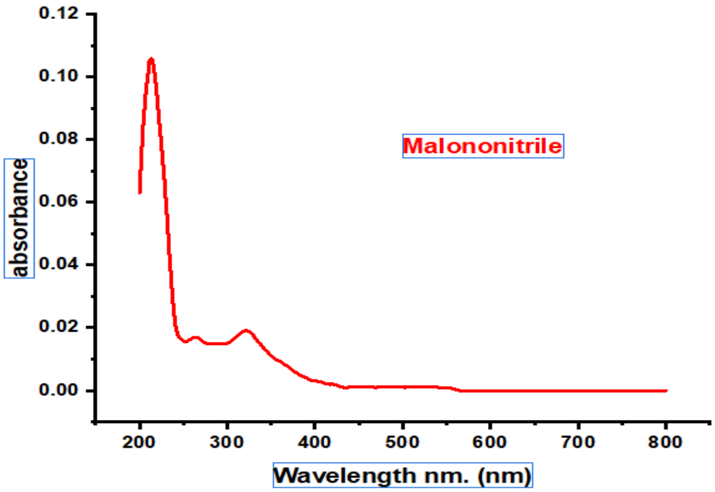


Figure 4.7 UV spectrum of Malononitrile in methanol

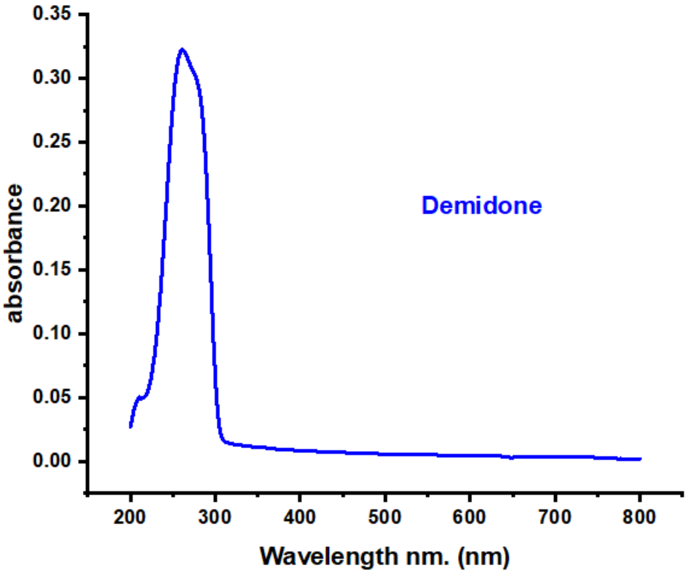


Figure 4.8 UV spectrum of Demidone in methanol

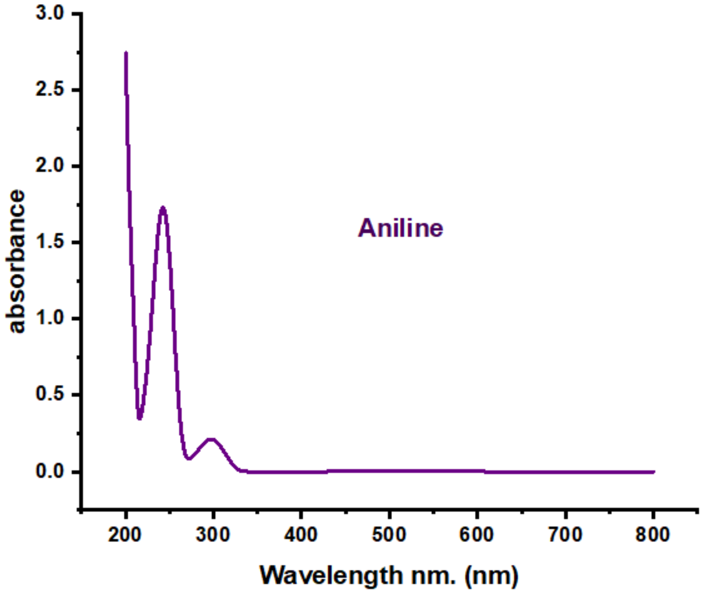


Figure 4.9 UV spectrum of Aniline in methanol

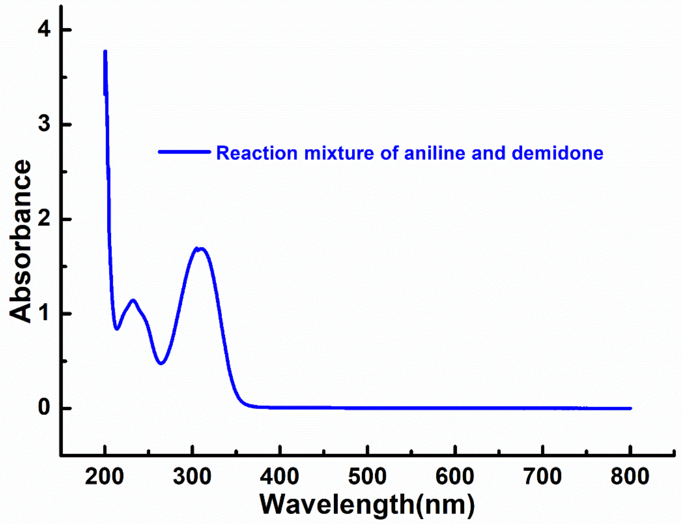


Figure 4.10 UV spectrum of reaction mixture of aniline and demidone in methanol

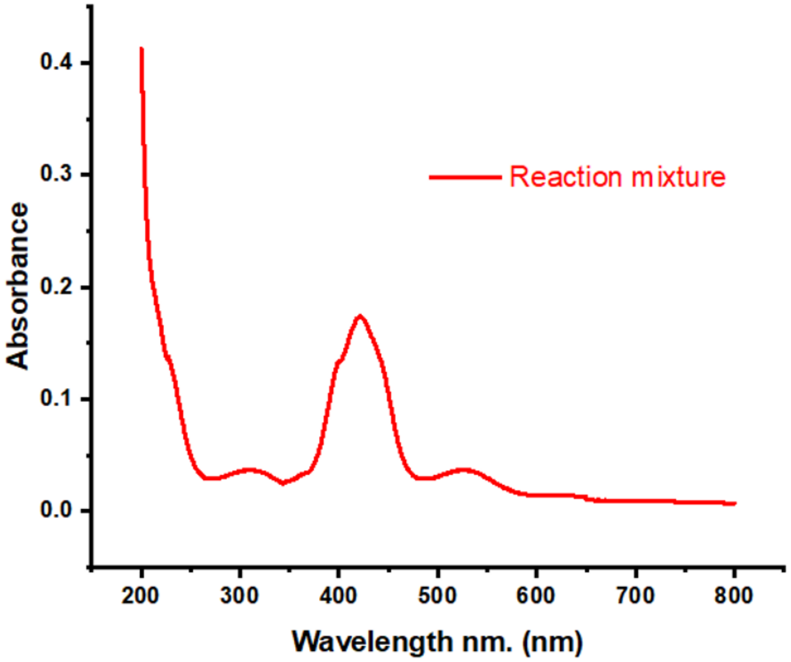
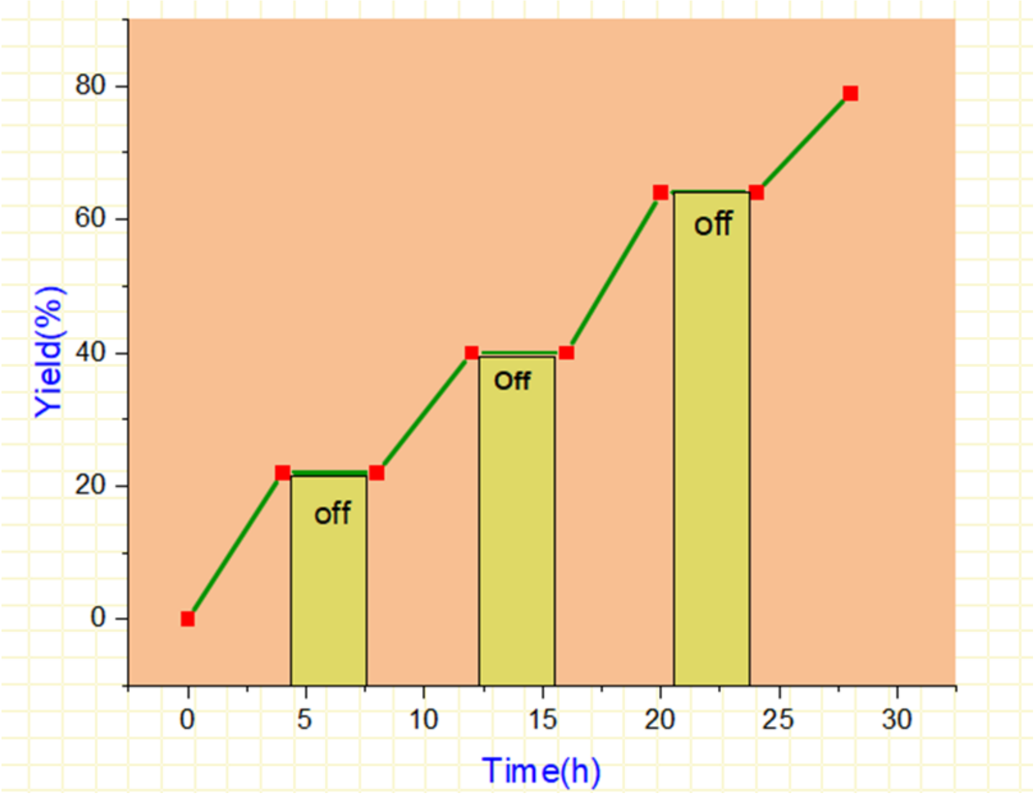


Figure 4.11 UV spectrum of reaction mixture in methanol

4.4.6. ON/OFF experiments

The reaction between Indole **1**, malononitrile **2**, and enaminone **3** was conducted under the standard conditions on a 0.25 mmol scale. The reaction mixture was subjected to sequential periods of stirring under visible light irradiation (22 W white LED) followed by stirring in the absence of light. At each time point, one reaction system was suspended, which was then purified with column chromatography on silica gel (Ethyl acetate: hexane) to give the corresponding products **4**. The yield of **4** was measured by weight of the product.



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CHAPTER 5

ONE-POT FOUR-COMPONENT SYNTHESIS OF SPIRO[INDOLINE-3,4'-QUINOLINE] DERIVATIVE USING DABCO AS A GREEN CATALYST

One-pot four-component synthesis of spiro[indoline-3,4’-quinoline] derivative using DABCO as a green catalyst

5.1 Introduction

The philosopher’s stone is catalysis in chemical industries, which acts as a driving force for chemical reactions [1, 2]. Catalysts play an important role in forming an extensive range of value-added products crucial to humans. A coherent and scientific design of proficient catalysts is vital to improving the performance of chemical reactions. The synthetic procedures can be planned in a more powerful, ecological, and cheap fashion through the attentive use of catalysts. There are two types of catalysts, i. e. homogenous and heterogeneous, based on the nature of catalysts and reactants. A homogenous catalyst retains a similar phase with the reactants as a heterogeneous catalyst [3, 4]. Homogeneous catalysis is becoming more critical to industrial and organic chemists [5] and offers benefits like improved selectivity, increased activity, and avoiding mass transfer limitations, which may permit lower temperatures [6].

Diazabicyclo [2.2.2] octane (DABCO) is a weak base and ligand and is used as a catalyst in several chemical reactions [7]. It is a cage-like small diazabicyclic molecule that has medium hindrance. Alternatively, it is also utilized in several reactions, such as the Baylis-Hillman reaction [8], N- methylation of indoles, Lu’s type cycloaddition umpolung addition, etc. [9]. Organic chemists are more attracted to using DABCO as a catalyst because it is cheap, commercially available, safe, and non-toxic [10].

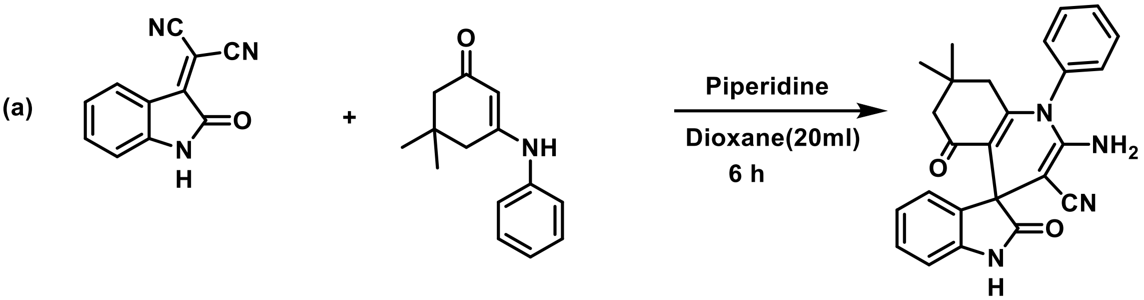
A moment ago, heterocyclic compounds containing Quinolone moiety had attracted much more attention of organic chemists due to its various industrial application[11], for example, in agrochemical [12], medicine [13], therapeutic agent [14], natural product [15], ligands in transition metal complexes [16], functional materials[17], organic light-emitting diodes[18], electrochemical storage devices [19], dyes [20], chemosensors [21], therapeutic agents, bioorganic, food colorants and pH indicators [22]. Additionally, quinolone derivatives are also significant biologically active compounds that show substantial biological activities like tuberculosis (TB) [23], antimicrobial [24], anti-HIV [25], anthelmintics [26], anti-inflammatories [27], antitumor [28], and antimalarial [29]. One of the most important quinolone derivatives, i.e., spiroindole, is found in many natural products and attracted the chemist's attention owing to its many biological activities [30] like antitubercular [31], antitumor [32], antimicrobial [33], antifungal [34], antimycobacterial [35], and antioxidant agents [36], etc. Isatin is the core unit of spiroindole molecule that shows many biological activities and is also utilized to synthesize several heterocyclic compounds, including spiroindole [37].

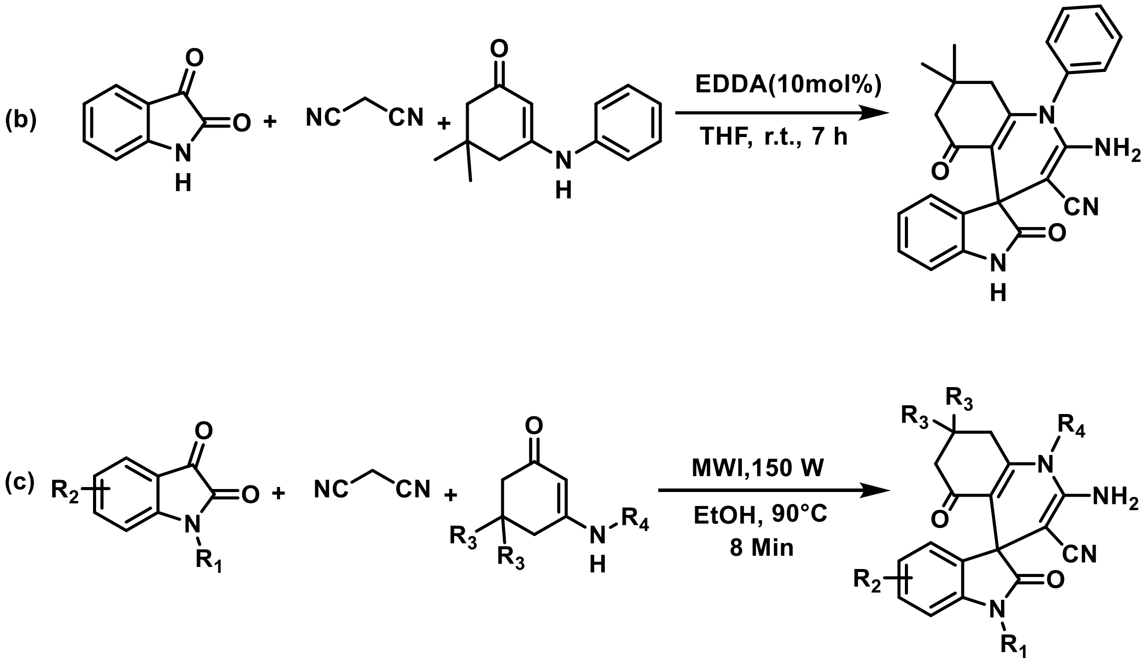
Multicomponent reactions are an essential tool for designing complex molecules in a single step to afford the target compounds, for example, spiroindole derivatives, etc., which combine most of the atoms of the starting materials [38] without intermediate isolation. MCRs are more potent than the conventional multi-step method because of their energy efficiency, better atom economy, simple operation, and excellent yield [39]. This approach is environmentally friendly, time-saving, and has more straightforward and affordable purification procedures [40].

Due to the importance of spiro [Indoline-3, 4’-Quinoline] derivatives, various synthetic approaches have been described [41-43]. However these methods are pretty helpful, but there are some drawbacks. Thus, there is space to design a new procedure that might work better than others. As far as we know, there is no report on the synthesis of spiroindole via a four-component reaction of amine, 1, 3-diketone, isatin, and active methylene compounds (malononitrile and ethyl acetoacetate) using non-toxic and cheap catalyst DABCO.

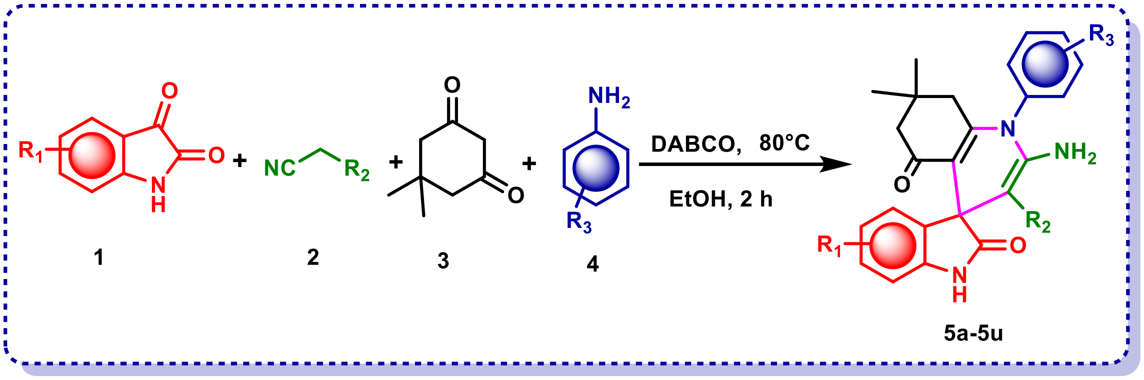
In light of the above and as a part of our research interest in developing the new synthetic approach [44], we have reported here the four-component reaction of amine, 1,3-diketone, isatin, and active methylene compounds (malononitrile and ethyl acetoacetate) to provide spiroindole using DABCO as a catalyst **(Scheme 5.1)**.

Previous Work:





This Work

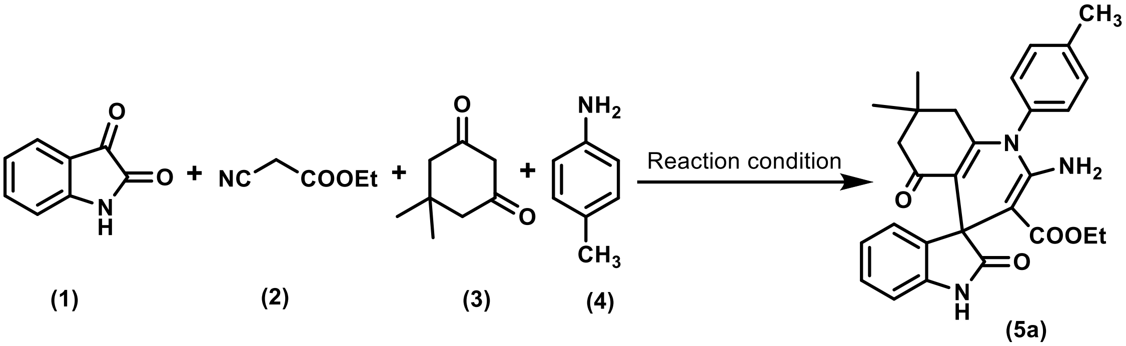


Scheme 5.1 Strategies for the synthesis of Spiro [Indoline-3, 4’-Quinoline]

5.2 Results and discussion

Mainly for optimization, a model reaction was chosen for carrying out a one-pot multicomponent reaction of amine (1mmol), dimedone (1mmol), isatin (1mmol), and malononitrile (1mmol) using DABCO in the presence of ethanol. Initially, the reaction was investigated using 10 mol% of different catalysts like Triethylamine, Piperidine, Imidazole, K_2CO_3, NaH, DBN and DBU, but they provided only 41, 62, 23, 65, 38, 52, and 56%, respectively (**Table 5.1, Entries 1-7**). Surprisingly 82% yield was obtained with 10 mol% of DABCO (**Table 5.1, Entry 8**). Now the amount of catalyst was examined, and it was found that 20 mol% of DABCO provided maximum yield, i.e., 95% yield of the product (**Table 5.1, Entry 10).** Various solvents like H_2O, THF, DMSO, DMF, Toluene, and CH_3CN were successfully examined, but none of them could provide the desired yield of the product. (**Table 5.1, Entries 13-18**). The reaction was also examined without catalyst (**Table 5.1, Entry 19**), without solvent (**Table 5.1, Entry 20**), and without both catalyst and solvent (**Table 5.1, Entry 21**). Only a trace amount of product was obtained without catalyst, while no product was formed in the last two cases (**Table 5.1, Entries 20, 21**). Finally, the temperature was also optimized, and it was found that 80^oC was the best for the reaction (**Table 5.1, Entries 22-24**).

Table 5.1 Optimization condition for the synthesis of Spiro [Indoline-3, 4'-Quinoline] **5a**$^{(a)}$



Entry	Catalyst (Mol %)	Solvent	Temp.	Time(h)	Yield$^{(b)}$ (%)
1)	Triethylamine (10)	EtOH	80^0C	6	41
2)	Piperidine (10)	EtOH	80^0C	6	62
3)	Imidazole (10)	EtOH	80^0C	6	23
4)	K_2CO_3 (10)	EtOH	80^0C	6	65
5)	NaH (10)	EtOH	80^0C	6	38
6)	DBN (10)	EtOH	80^0C	2	52
7)	DBU (10)	EtOH	80^0C	2	56
8)	DABCO (10)	EtOH	80^0C	2	82
9)	DABCO (15)	EtOH	80^0C	2	88
10)	**DABCO (20)**	**EtOH**	**80^0C**	**2**	**95**
11)	DABCO (25)	EtOH	80^0C	2	90
12)	DABCO (5)	EtOH	80^0C	2	74
13)	DABCO (20)	H_2O	80^0C	2	32

14)	DABCO (20)	THF	80^0C	2	24
15)	DABCO (20)	DMSO	80^0C	2	15
16)	DABCO (20)	DMF	80^0C	2	13
17)	DABCO (20)	Toluene	80^0C	18	NA
18)	DABCO (20)	CH$_3$CN	80^0C	18	NA
19)	---------	EtOH	80^0C	24	Trace
20)	DABCO (20)	-----	80^0C	24	NA
21)	---------	-------	80^0C	24	NA
22)	DABCO (20)	EtOH	100^0C	2	85
23)	DABCO (20)	EtOH	120^0C	6	53
24)	DABCO (20)	EtOH	60^0C	6	40

[a]Experimental condition: Isatin(1 mmol), ethylcyanoacetate (1 mmol), dimedone (1 mmol), aniline (1 mmol), solvents (5 ml) , 80^0C, 2 hrs under DABCO (20 mol%) as a green catalyst

[b] isolated yields, [c] NA- no reaction

To find the effect of the molar proportion of the reaction mixture on the yield of the product and type of the product, a different molar proportion of the reactant was taken for the reaction (**Table 5.2**). The perusal of Table 5.2 indicates that there is no effect on the type of reaction at any proportion, and the best result was obtained when the molar proportion of all substrates (1, 2, 3, 4) was 1:1:1:1 (**Table 5.2, Entry 1)**.

Table 5.2 Effect of molar proportion of reaction mixture(a)

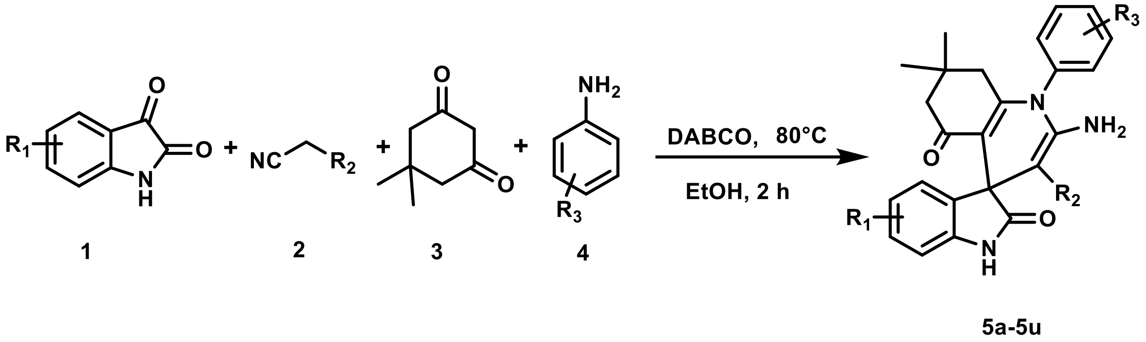
Isatin (mmol)	**Ethyl cyanoacetate (mmol)**	**Dimedone (mmol)**	**Aniline (mmol)**	**Time (hrs)**	**Yield[b] (%)**
1	1	1	1	24	95%
1	2	1	1	24	NA
2	1	1	1	24	NA
1	1	2	1	24	NA
1	1	1	2	24	NA

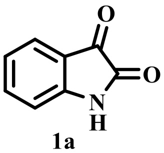
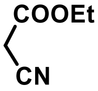
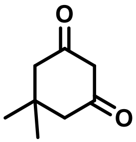
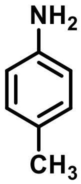
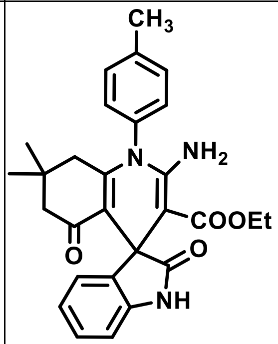
[a]Experimental condition: Isatin(1 mmol), ethylcyanoacetate (1 mmol), dimedone (1 mmol), aniline (1 mmol), solvents (5 ml) , 80^0C, 2 hrs under DABCO (20 mol%) as a green catalyst

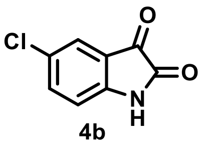
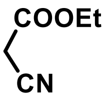
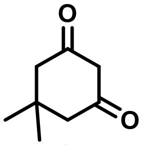
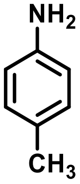
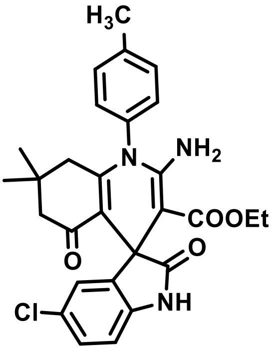
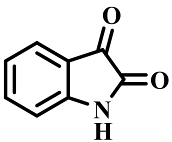
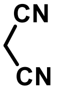
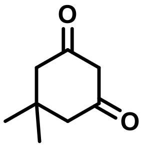
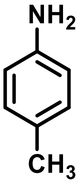
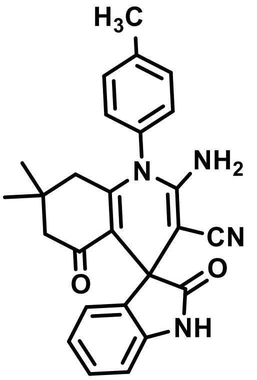
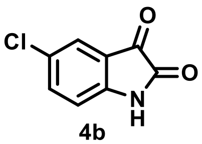
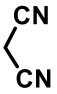
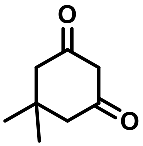
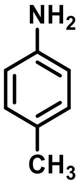
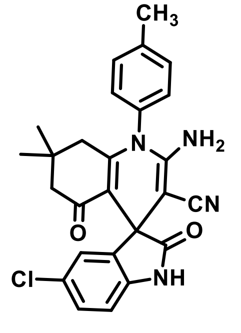
[b] isolated yields, [c] NA- no reaction

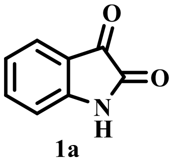
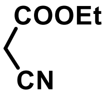
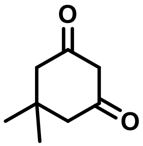
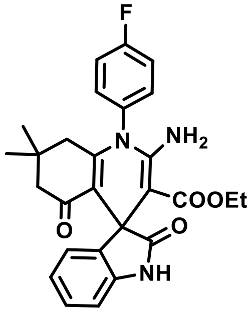
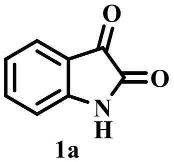
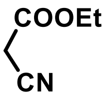
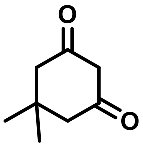
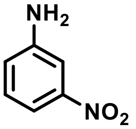
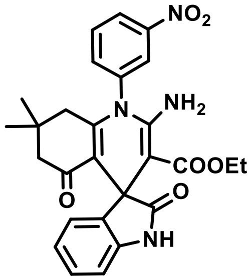
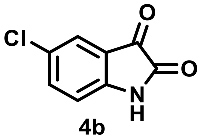
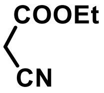
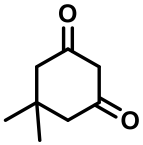
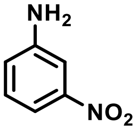
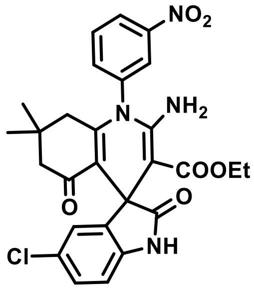
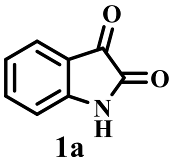
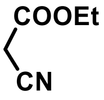
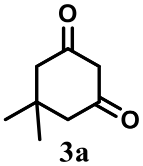
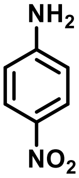
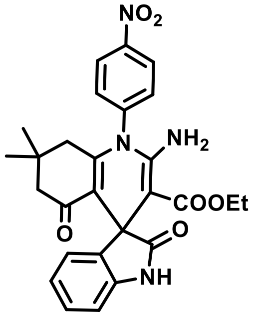
After optimizing reaction conditions, we explored the reaction's breadth and limitations in terms of isatin (**1a**), 5-bromoisatin **(1b)**, 5-chloroisatin **(1c),** and active methylene compounds like malononitrile **(2a)** and ethyl aceto- acetate **(2b)** react with dimedone **(3a)** and various amines like p-toluidine**(4a)**, 4-fluoroaniline**(4b)**, 3-nitroaniline**(4c)**, 4-nitroaniline**(4d)**, 3-chloroaniline**(4e)**, 4-(trifluoromethyl)aniline**(4f)**, 4-methoxyaniline**(4g)**. The reaction proceeds smoothly in all cases. However, when barbituric acid was substituted for malononitrile, the product's nature altered, and indoloindole was generated instead of spirocompounds (**Scheme 5.2**). Some more reactions were carried out to confirm the formation of indoloindole [41].

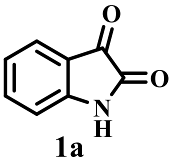
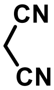
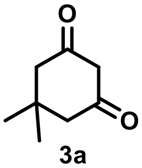
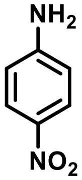
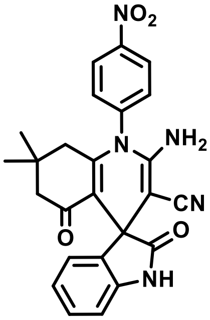
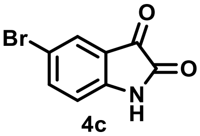
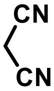
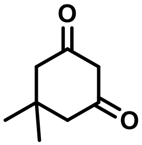
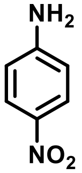
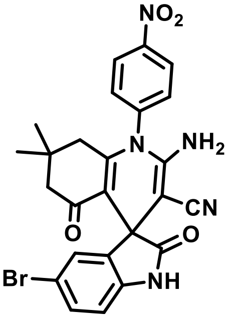
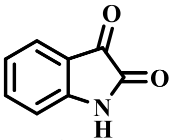
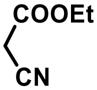
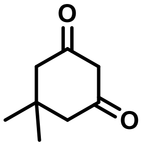
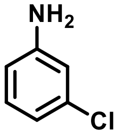
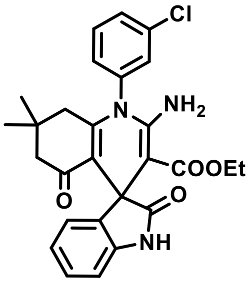
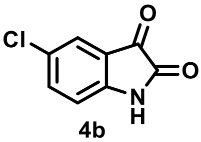
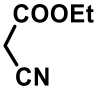
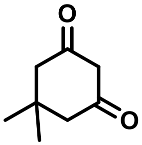
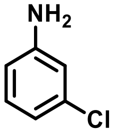
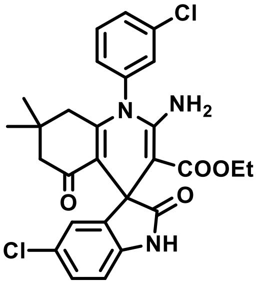
Table 5.3 Exploration of substrate scope for the synthesis of Spiro [Indoline-3, 4'-Quinoline][a]

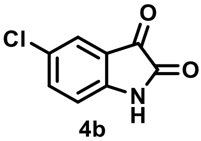
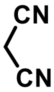
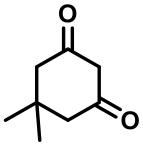
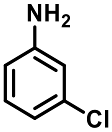
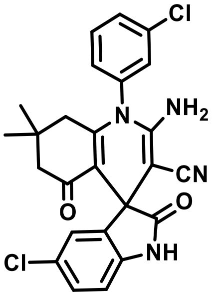
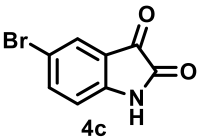
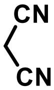
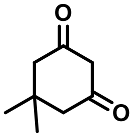
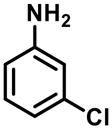
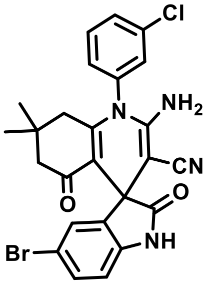
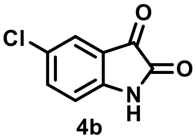
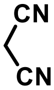
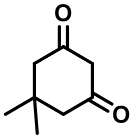
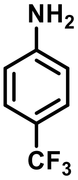
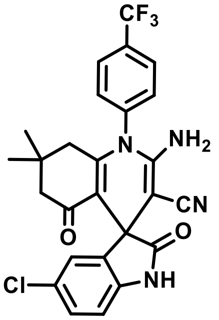
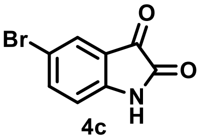
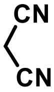
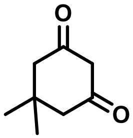
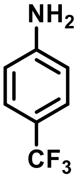
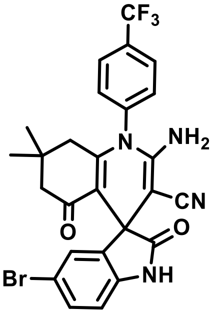


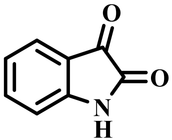
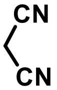
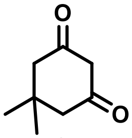
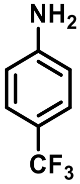
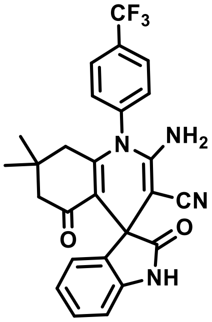
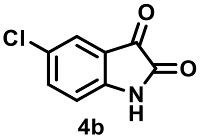
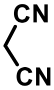
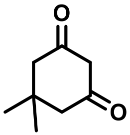
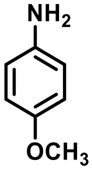
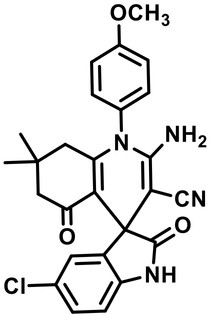
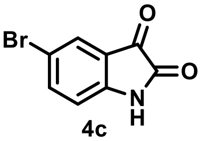
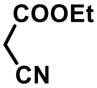
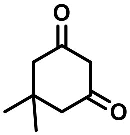
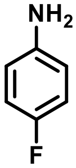
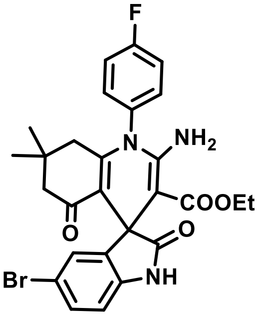
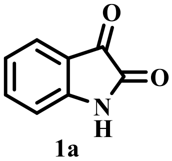
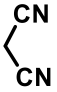
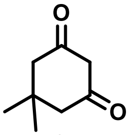
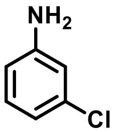
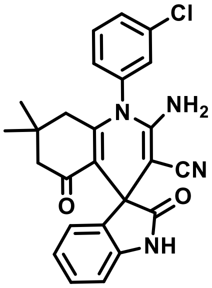
Entry	1	2	3	4	5[a]	Yield[b] (%)
4a	 1a	 2b	 3a	 4a		88

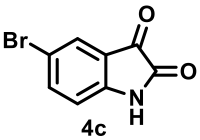
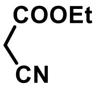
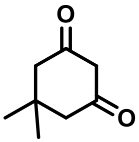
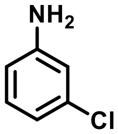
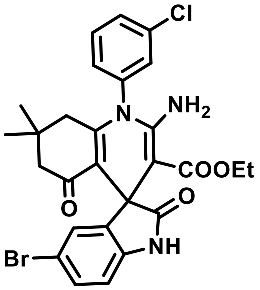
4b	 4b	 2b	 3a	 4a		**86**
4c	 1a	 2a	 3a	 4a		**88**
4d	 4b	 2a	 3a	 4a		**84**

4e	 1a	 2b	 3a	 4b		**82**
4f	 1a	 2b	 3a	 4c		**84**
4g	 4b	 2b	 3a	 4c		**80**
4h	 1a	 2b	 3a	 4d		**85**

4i	 **1a**	 2a	 3a	 4d		**88**
4j	 4c	 2a	 3a	 4d		**86**
4k	 **1a**	 2b	 3a	 4e		**83**
4l	 4b	 2b	 3a	 4e		**82**

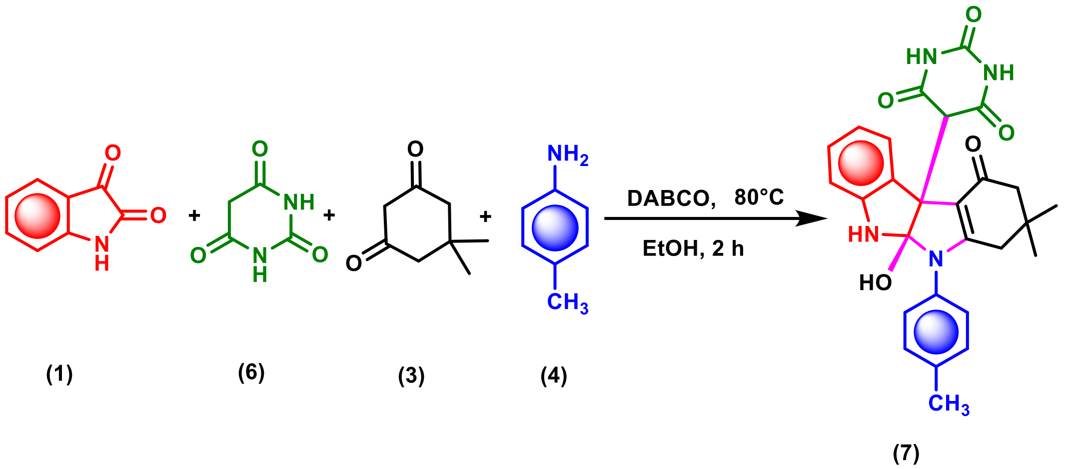
4m	 4b	 2a	 3a	 4e		**83**
4n	 4c	 2a	 3a	 4e		**85**
4o	 4b	 2a	 3a	 4f		**88**
4p	 4c	 2a	 3a	 4f		**88**

4q	 1a	 2a	 3a	 4f		**88**
4r	 4b	 2a	 3a	 4g		**87**
4s	 4c	 2b	 3a	 4b		**84**
4t	 1a	 2a	 3a	 4e		**86**

4u	 4c	 2b	 3a	 4e		**86**

[a]Experimental condition: Isatin(1 mmol), ethylcyanoacetate (1 mmol), dimedone (1 mmol), aniline (1mmol), solvents (5ml) , 80^0C, 2 hrs, under DABCO (20mol%) as a green catalyst

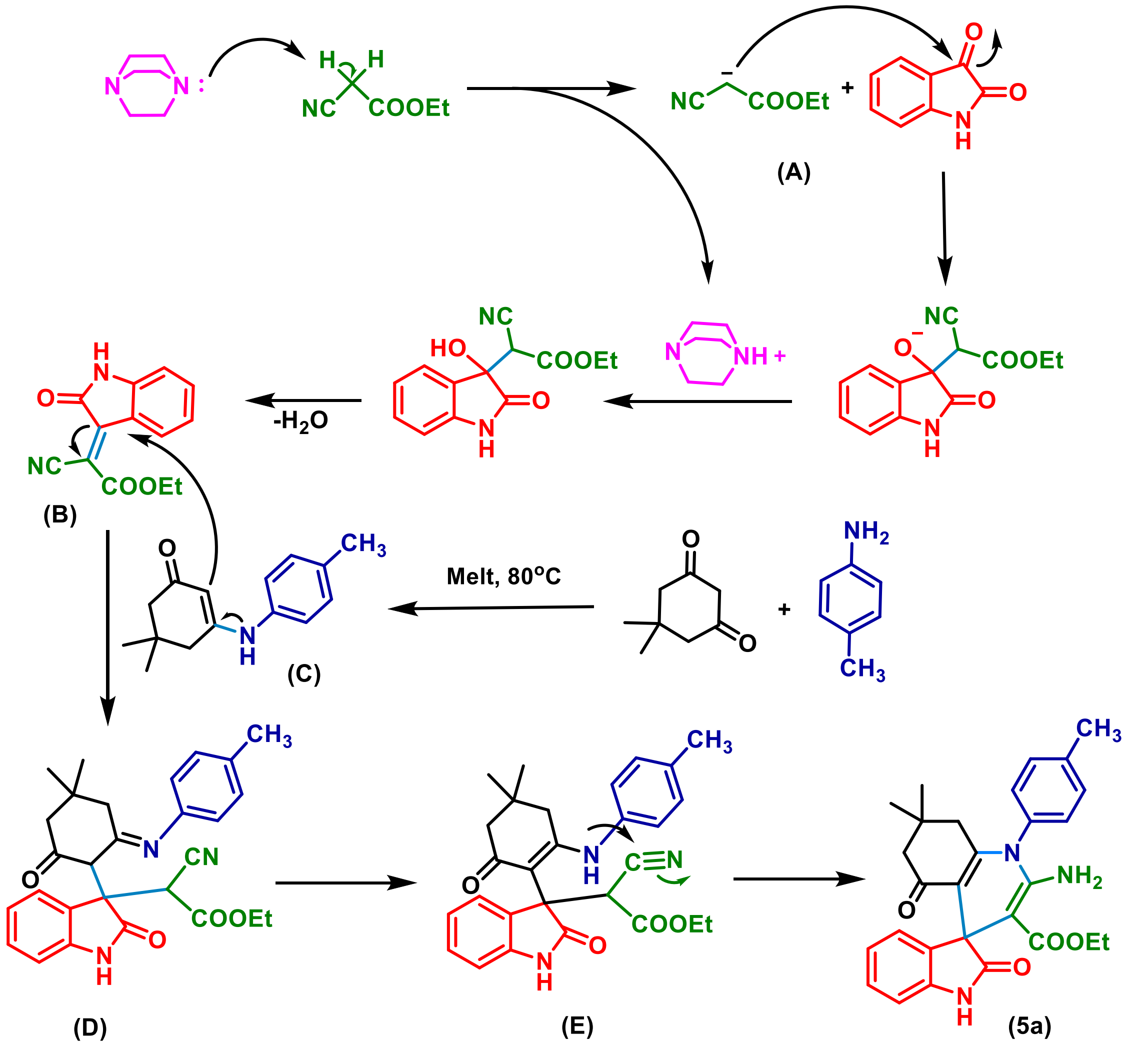
[b]Isolated yields, [c] NA- no reaction



Scheme 5.2 Synthesis of Indoloindole pyrimidine derivatives

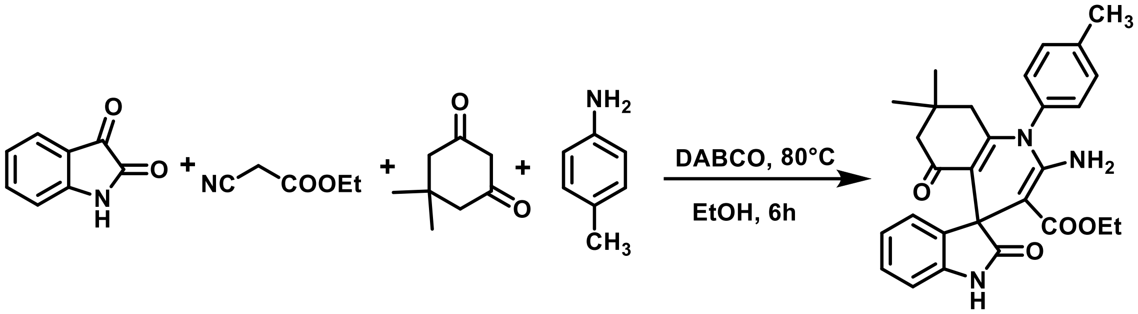
A probable mechanism (**Scheme 5.3**) of the reaction is projected based on product isolation in the presence of DABCO, represented in Scheme 5.3. Firstly, DABCO reacts with ethyl cyanoacetate, takes the acidic proton of the active methylene group, and gives the intermediate **A**. Then intermediate A reacts with isatin experienced Knoevenagel condensation in a solution to provide a cyanoolefin intermediate **B** with the elimination of water. The enaminone **C** (formed in situ from aniline and dimedone) reacts with intermediate

B through Micheal addition and provides **D**. Further, the intermediate **D** isomerizes to furnish **E**. The final product **5a** was formed by intramolecular cyclization (by the attack of nitrogen of **E** towards its cyano moieties).



Scheme 5.3 A plausible mechanism for the synthesis of Spiro [Indoline-3, 4'-Quinoline] **(5a)**

In addition, the practicality was confirmed by performing the model reaction on a gram scale (Figure 5). The mixture of isatin **1** (10 mmol), ethyl cyanoacetate **2** (10 mmol), dimedone **3** (10 mmol), aniline **4** (10 mmol), and DABCO catalyst was added to ethanol (50 ml) and stirred at 80°C for 6h. After completing the reaction (monitored by thin-layer chromatography), the solid product was obtained, which was filtered and washed with ethanol. The product was recrystallized with hot ethanol to give the desired product in good yield (**Scheme 5.4**).



1 (10 mmol) **2** (10 mmol) **3** (10 mmol) **4** (10 mmol)

5a
3.34 g, 71%

Scheme 5.4 Synthesis of Spiro [Indoline-3, 4’-Quinoline] in gram scale.

5.3 Conclusion

In summary, we have established a simple, green, and efficient one-pot four-component strategy of isatin, ethyl cyanoacetate, dimedone, and aniline to synthesize spiro[Indoline-3,4'-quinoline] employing DABCO as a catalyst under ethanol as a solvent. The current approach produces good to excellent yields in a short reaction time. This approach works for gram-scale reactions as well.

5.4 Experimental section

5.4.1 General procedure for the synthesis of Spiro [Indoline-3, 4’-Quinoline] (5)

To the mixture of isatin **1** (1.0 mmol), ethyl cyanoacetate **2** (1.0 mmol), dimedone **3** (1.0 mmol) aniline **4** (1.0 mmol) and DABCO catalyst (20 mol %) was added to ethanol (5 ml) and stirred at 80°C for 2h. After completing the reaction (monitored by thin-layer chromatography), the solid product was obtained, which was filtered and washed with ethanol. The product was recrystallized with hot ethanol to give the desired product in good yield.

5.4.2 Analytical Data

Ethyl 2'-amino-7',7'-dimethyl-2,5'-dioxo-1'-(p-tolyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5a)

White solid, m.p. >300 °C, yield: 0.435 g, 93%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.09 (s, 1H), 7.44 (m, *J* = 8.4 Hz, 4H), 7.12 (d, *J* = 7.4 Hz, 1H), 7.06 (m, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 3.79 – 3.64 (m, 2H), 2.43 (s, 3H), 2.06 (m, 2H), 1.86 (m, 2H), 0.84 (m, 6H), 0.77 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.19, 181.97, 169.00, 153.31, 151.48, 143.36, 140.48, 139.94, 133.78, 130.31, 129.42, 126.93, 124.59, 123.12, 112.46, 111.53, 109.24, 78.67, 58.98, 50.52, 49.68, 42.37, 32.10, 28.48, 27.18, 21.34, 13.63. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{30}N_3O_4$, 472.2236; found, 472.2231.

Ethyl 2'-amino-5-chloro-7',7'-dimethyl-2,5'-dioxo-1'-(p-tolyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5b)

White solid, m.p. >300 °C, yield: 0.455 g, 90%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 9.93 (s, 1H), 7.42 (t, *J* = 7.6 Hz, 4H), 7.11 – 6.97 (m, 3H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 3.79 – 3.61 (m, 2H), 2.43 (s, 3H), 2.10 (m, 2H), 1.81 (m, 2H), 0.88 – 0.80 (m, 6H), 0.74 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 193.99, 182.23, 169.13, 153.21, 150.98, 144.07, 139.90, 138.21, 133.97, 127.18, 123.09, 120.64, 113.17, 108.06, 79.50, 58.87, 50.65, 49.16, 42.35, 32.07, 28.88, 26.76, 21.33, 13.61. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{29}ClN_3O_4$, 506.1846; found, 506.1844.

2'-Amino-7',7'-dimethyl-2,5'-dioxo-1'-(p-tolyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5c)

White solid, m.p. >300 °C, yield: 0.402 g, 95%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.23 (s, 1H), 7.39 (m, *J* = 7.4Hz, 4H), 7.14 (m, *J* = 8.2 Hz, 2H), 6.95 – 6.89 (m, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 5.34 (s, 2H), 2.42 (s, 3H), 2.12 (m, 2H), 1.89 (m, 2H), 0.89 (s, 3H), 0.82 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.35, 179.98, 152.53, 151.68, 141.90, 140.03, 137.19, 133.75,131.25, 128.13, 123.63, 121.86, 119.46, 110.75, 109.30, 61.20, 56.50, 49.78, 48.94, 41.81, 32.57, 28.74, 27.08, 21.31 . **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{25}N_4O_2$, 425.1977; found, 425.1974.

2'-Amino-5-chloro-7',7'-dimethyl-2,5'-dioxo-1'-(p-tolyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5d)

White solid, m.p. >300 °C, yield: 0.435 g, 95%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.37 (s, 1H), 7.57 – 7.24 (m, 5H), 7.17 (m, *J* = 8.2 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.43 (s, 2H), 2.42 (s, 3H), 2.07 (m, 2H), 1.95 (m, 2H), 0.89 (s, 3H), 0.85 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.55, 179.80, 153.07, 151.78, 141.00, 140.07, 139.24, 133.54, 131.22, 130.21, 127.99, 125.88, 123.79, 119.30, 110.65, 110.00, 60.31, 49.65, 49.48, 41.83, 32.61, 28.31, 27.59, 21.32. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{24}ClN_4O_2$, 459.1587; found, 459.1582.

Ethyl 2'-amino-1'-(4-fluorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5e)

White solid, m.p. >300 °C, yield: 0.389 g, 82%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 9.94 (s, 1H), 8.01 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.2 Hz, 3H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 3.70 (s, 2H), 2.17 – 2.06 (m, 2H), 1.79 (m, 2H), 0.87 – 0.80 (m, 6H), 0.75 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.06, 182.08, 169.18, 152.91, 150.13, 144.12, 138.08, 131.93, 130.67, 130.42, 127.95, 127.26, 123.18, 120.65, 113.51, 108.12, 79.79, 58.97, 50.67, 49.19, 42.35, 32.16, 28.80, 26.71, 13.59. **^{19}F NMR (471 MHz, DMSO-d^6) δ** -111.35. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{27}FN_3O_4$, 476.1985; found, 476.1987.

Ethyl 2'-amino-7',7'-dimethyl-1'-(3-nitrophenyl)-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5f)

White solid, m.p. >300 °C, yield: 0.421 g, 84%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 9.96 (s, 1H), 8.46 (d, *J* = 7.2 Hz, 2H), 8.01 – 7.85 (m, 2H), 7.38 – 7.13 (m, 3H), 7.03 (m, *J* = 7.6, Hz, 1H), 6.85 – 6.76 (m, 1H), 6.65 (t, *J* = 7.9 Hz, 1H), 3.74 – 3.67 (m, 2H), 2.17 – 2.00 (m, 2H), 1.81 (m, 2H), 0.85 (d, 3H), 0.82 (d, 3H), 0.75 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.16, 182.11, 169.23, 153.00, 150.25, 144.09, 137.70, 132.07, 127.25, 126.40, 125.36, 120.64, 113.46, 108.06, 79.81, 59.32, 59.00, 56.50, 50.68, 49.19, 42.38, 32.20, 28.84, 26.71, 13.59. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{27}N_4O_6$, 503.1930; found, 503.1934.

Ethyl 2'-amino-5-chloro-7',7'-dimethyl-1'-(3-nitrophenyl)-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5g)

White solid, m.p. >300 °C, yield: 0.428 g, 80%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.12 (s, 1H), 8.45 (m, *J* = 8.6 Hz, 1H), 7.90 (t, *J* = 8.0 Hz, 2H), 7.46 – 6.87 (m, 5H), 6.65 (t, *J* = 7.8 Hz, 1H), 3.71 (m, 2H), 2.07 (m, 2H), 1.98 – 1.80 (m, 2H), 0.84 (s, 6H), 0.78 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.35, 181.88, 169.11, 153.12, 150.74, 143.61, 143.36, 137.70, 137.53, 132.92, 131.99, 126.97, 125.41, 124.71, 111.53, 109.20, 78.94, 59.09, 50.56, 49.69, 42.43, 32.21, 28.49, 27.13, 13.61. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{26}ClN_4O_6$, 537.1540; found, 537.1543.

Ethyl 2'-amino-7',7'-dimethyl-1'-(4-nitrophenyl)-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5h)

White solid, m.p. >300 °C, yield: 0.426 g, 85%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 9.95 (s, 1H), 8.46 (d, *J* = 8.2 Hz, 2H), 7.84 (d, *J* = 7.6 Hz, 2H), 7.26 – 7.10 (m, 3H), 7.03 (m, *J* = 7.6 Hz, 1H), 6.79 (m, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 3.70 (t, 2H), 2.12 – 2.07 (m, 2H), 1.81 (m, 2H), 0.84 (m, 6H), 0.75 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.07, 182.24, 169.19, 152.76, 149.95, 144.08, 142.73, 138.12, 132.64, 127.30, 125.99, 123.33, 121.52, 120.65, 113.47, 108.13, 79.89, 59.01, 50.71, 48.97, 42.22, 32.21, 28.82, 26.67, 13.59. **HRMS** (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{27}H_{27}N_4O_6$, 503.1930; found, 503.1929.

2'-Amino-7',7'-dimethyl-1'-(4-nitrophenyl)-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5i)

White solid, m.p. >300 °C, yield: 0.400 g, 88%,**^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.23 (s, 1H), 8.42 (m, *J* = 7.8 Hz, 2H), 7.80 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.16 – 7.11 (m, 1H), 6.93 (m, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 7.2 Hz, 1H), 5.67 (s, 2H), 2.22 – 2.11 (m, 2H), 1.89 (m, 2H), 0.89 (s, 3H), 0.82 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.41, 179.82, 151.28, 148.58, 142.39, 141.97, 137.00, 132.51, 128.20, 126.37, 125.88, 123.73, 121.84, 119.23, 111.13, 109.33, 61.61, 49.86, 49.02, 41.82, 32.70, 28.69, 26.99. **HRMS** (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{25}H_{22}N_5O_4$, 456.1671; found, 456.1669.

2'-Amino-5-bromo-7',7'-dimethyl-1'-(4-nitrophenyl)-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5j)

White solid, m.p. >300 °C, yield: 0.459 g, 86%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.55 (s, 1H), 7.59 – 6.60 (m, 9H), 2.21 – 2.06 (m, 4H), 1.03 (s, 6H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 195.56, 178.14, 165.09, 159.36, 141.94, 137.28, 134.79, 131.40, 120.15, 119.68, 117.68, 111.66, 110.67, 108.19, 62.43, 57.21, 50.48, 47.53, 45.49, 44.31, 32.46, 28.05, 27.65. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}BrN_5O_4$, 534.0776; found, 534.0772.

Ethyl 2'-amino-1'-(3-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5k)

White solid, m.p. >300 °C, yield: 0.407 g, 83%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 9.94 (s, 1H), 7.77 – 7.63 (m, 3H), 7.49 (s, 1H), 7.16 (s, 2H), 7.02 (m, *J* = 7.6 Hz, 1H), 6.81 – 6.75 (m, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 3.74 – 3.64 (m, 2H), 2.19 – 2.05 (m, 2H), 1.80 (m, 2H), 0.84 (m, 6H), 0.75 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.08, 182.15, 169.18, 152.99, 150.39, 145.62, 144.67, 144.05, 138.07, 138.01, 132.22, 130.86, 130.67, 127.22, 120.64, 108.04, 75.07, 58.94, 50.65, 49.14, 42.29, 32.14, 28.87, 26.75, 13.60. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{27}ClN_3O_4$, 492.1690; found, 492.1688.

Ethyl 2'-amino-5-chloro-1'-(3-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5l)

White solid, m.p. >300 °C, yield: 0.431 g, 82%,**^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.10 (s, 1H), 8.02 – 7.59 (m, 4H), 7.36 (d, *J* = 8.6 Hz, 3H), 7.12 – 7.03 (m, 1H), 6.64 (t, *J* = 7.6 Hz, 1H), 3.84 – 3.59 (m, 2H), 2.15 – 2.01 (m,2H), 1.94 – 1.76 (m, 2H), 0.88 – 0.85 (m, 3H), 0.85 – 0.81 (m, 3H), 0.79 (d, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.28, 181.92, 169.05, 153.09, 150.87, 143.34, 140.35, 137.80, 132.13, 130.99, 130.70, 129.73, 126.97, 124.69, 109.20, 78.76, 59.04, 50.53, 49.67, 42.31, 32.16, 28.48, 27.22, 13.61. **HRMS** (ESI-TOF) m/z: [M + H]+ calcd for C27H26Cl2N3O4, 526.1300; found, 526.1299.

2'-Amino-5-chloro-1'-(3-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro [indoline-3,4'-quinoline]-3'-carbonitrile (5m)

White solid, m.p. >300 ºC, yield: 0.390 g, 83%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.36 (s, 1H), 7.70 – 7.56 (m, 3H), 7.42 (s, 2H), 7.17 (m, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.68 (s, 2H), 2.14 – 1.82 (m, 4H), 0.90 (s, 3H), 0.85 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.62, 179.79, 152.57, 151.60, 140.98, 139.15, 137.59, 131.99, 130.95, 130.69, 129.63, 128.00, 125.93, 119.28, 110.59, 60.39, 49.67, 49.52, 41.78, 32.66, 28.31, 27.59. **HRMS** (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{25}H_{21}Cl_2N_4O_2$, 479.1041; found, 479.1039.

2'-Amino-5-bromo-1'-(3-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5n)

White solid, m.p. >300 ºC, yield: 0.443 g, 85%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.38 (s, 1H), 7.96 – 7.27 (m, 6H), 6.73 (d, *J* = 7.6 Hz, 1H), 5.68 (s, 2H), 2.14 – 1.84 (m, 4H), 0.90 (s, 3H), 0.86 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.65, 179.67, 152.59, 151.66, 141.41, 139.53, 137.57, 134.74, 132.00, 130.94, 130.87, 130.70, 129.63, 119.28, 113.71, 111.18, 60.38, 49.66, 49.50, 41.79, 32.67, 28.26, 27.61. **HRMS** (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{25}H_{21}BrClN_4O_2$, 523.0536; found, 523.0532.

2'-Amino-5-chloro-7',7'-dimethyl-2,5'-dioxo-1'-(4-(trifluoromethyl)phenyl)-5',6',7',8'-tetrahydro-1' H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5o)

White solid, m.p. >300 °C, yield: 0.450 g, 88%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.36 (s, 1H), 7.97 (d, *J* = 8.2 Hz, 4H), 7.31 (s, 1H), 7.17 (m, *J* = 8.0, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 5.68 (s, 2H), 2.31 – 1.72 (m, 4H), 0.87 (d, 6H). **^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 194.62, 179.73, 152.35, 151.54, 141.04, 140.01, 139.12, 131.91, 128.03, 127.79, 125.91, 123.90, 119.19, 110.67, 110.29, 60.55, 49.69, 49.54, 41.83, 32.68, 28.27, 27.51. **^{19}F NMR (471 MHz, DMSO-d^{6}) δ** -111.41. **HRMS** (ESI-TOF) m/z: [M + H]+ calcd for $C_{26}H_{21}ClF_{3}N_{4}O_{2}$, 513.1305; found, 513.1303.

2'-Amino-5-bromo-7',7'-dimethyl-2,5'-dioxo-1'-(4-(trifluoromethyl)phenyl)-5',6',7',8'-tetrahydro-1' H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5p)

White solid, m.p. >300 °C, yield: 0.490 g, 88%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.37 (s, 1H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.6Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.30 (m, *J* = 8.2 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 5.69 (s, 2H), 2.05 (m, 4H), 0.89 (s, 3H), 0.84 (d, 3H). **^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 194.62, 179.58, 152.35, 151.53, 141.48, 140.00, 139.51, 131.92, 130.89, 127.79, 126.57, 119.20, 113.65, 111.24, 110.29, 108.42, 60.56, 49.69, 49.53, 41.83, 32.70, 28.24, 27.55. **^{19}F NMR (471 MHz, DMSO-d^{6}) δ** -111.43. **HRMS** (ESI-TOF) m/z: $[M + H]^{+}$ calcd for $C_{26}H_{21}BrF_{3}N_{4}O_{2}$, 557.0799; found, 557.0797.

2'-Amino-7',7'-dimethyl-2,5'-dioxo-1'-(4-(trifluoromethyl)phenyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile(5q)

White solid, m.p. >300 °C, yield: 0.420 g, 88%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.20 (s, 1H), 7.44 (t, *J* = 8.3 Hz, 4H), 7.23 – 7.10 (m, 2H), 6.91 (m, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 5.51 (s, 2H), 2.10 (m, 2H), 1.89 (d, 2H), 0.90 (s, 3H), 0.82 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.36, 179.94, 152.43, 151.75, 141.93, 137.16, 134.71, 133.82, 132.96, 129.97, 128.13, 123.68, 123.59, 121.82, 110.91, 109.28, 60.15, 49.79, 48.94, 41.83, 32.56, 28.74, 27.06. **^{19}F NMR (471 MHz, DMSO-d^6) δ** -111.42. **HRMS** (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{26}H_{22}F_3N_4O_2$, 479.1694; found, 479.1696.

2'-Amino-1'-(4-methoxyphenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5r)

White solid, m.p. >300 °C, yield: 0.436 g, 92%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.21 (s, 1H), 7.38 (m, *J* = 7.6 Hz, 1H), 7.18 – 7.10 (m, 4H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 5.38 (s, 2H), 3.85 (s, 3H), 2.12 (m, 2H), 1.89 (m, 2H), 0.89 (s, 3H), 0.82 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.37, 180.03, 160.28, 152.86, 151.90, 141.89, 137.24, 128.65, 128.11, 123.64, 121.84, 119.53, 116.08, 112.28, 110.66, 109.28, 60.94, 55.97, 49.75, 48.93, 41.82, 32.54, 28.78, 27.07. **HRMS** (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{26}H_{24}ClN_4O_3$, 475.1536; found, 475.1534.

Ethyl 2'-amino-5-bromo-1'-(4-fluorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5s)

White solid, m.p. >300 °C, yield: 0.464 g, 84%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.09 (s, 1H), 7.57 (m, 5H), 7.32 – 7.16 (m, 3H), 6.60 (d, *J* = 8.1 Hz, 1H), 3.75 – 3.64 (m, 2H), 2.10 – 2.02 (m, 2H), 1.86 (m, 2H), 0.92 – 0.73 (m, 9H).). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.32, 181.91, 168.83, 153.31, 151.55, 143.36, 140.48, 139.94, 133.78, 130.31, 129.42, 126.93, 124.59, 123.12, 112.46, 111.53, 109.24, 78.38, 58.98, 50.52, 49.68, 42.37, 32.03, 28.48, 27.09, 13.32. **^{19}F NMR (471 MHz, DMSO-d^6) δ** -111.36.

2'-Amino-1'-(3-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5t)

White solid, m.p. >300 °C, yield: 0.381 g, 86%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.22 (s, 1H), 7.80 – 7.58 (m, 3H), 7.46 (s, 1H), 7.31 – 7.09 (m, 2H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 5.59 (s, 2H), 2.10 (t, 2H), 1.87 (m, 2H), 0.90 (s, 3H), 0.82 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.19, 179.69, 152.48, 151.68, 141.90, 140.03, 137.19, 133.75, 131.25, 128.13, 123.63, 121.86, 119.46, 110.75, 109.30, 106.29, 90.39, 61.20, 56.50, 49.78, 48.94, 41.81, 32.57, 28.74, 27.22.

Ethyl 2'-amino-5-bromo-1'-(3-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7', 8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5u)

White solid, m.p. >300 °C, yield: 0.490g, 86%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.12 (s, 1H), 7.70 – 7.17 (m, 7H), 6.60 (d, J = 8.1 Hz, 2H), 3.70 (m, 2H), 2.12 – 2.00 (m, 2H), 1.95 – 1.78 (m, 2H), 0.87 (s, 3H), 0.83 (t, 3H), 0.79 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ**

194.30, 181.60, 169.19, 153.12, 150.74, 143.61, 143.36, 137.70, 137.53, 132.92, 131.99, 126.97, 125.41, 124.71, 111.53, 109.20, 78.67, 59.09, 50.56, 49.69, 42.43, 32.05, 28.49, 27.08, 13.32.

5-((5aR,10bR)-5a-Hydroxy-3,3-dimethyl-1-oxo-5-(p-tolyl)-1,3,4,5,5a,6-hexahydroindolo[2,3-b]indol-10b(2H)-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (7)

White solid, m.p. 225 °C, yield: 86%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.53 (s, 1H), 10.12 (s, 2H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.85 – 7.68 (m, 1H), 7.66 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.32 (m, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 2H), 5.97 (s, 1H), 3.02 (d, 3H), 2.43 – 2.06 (m, 4H), 1.13 (s, 6H). 5.98 (s, 1H), 3.35 (br, 1H), 3.03 (d, 3H), 2.43 – 2.08 (m, 4H), 1.14 (s, 6H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 166.52, 159.72, 151.19, 150.05, 147.77, 145.81, 143.58, 135.59, 130.47, 129.29, 128.57, 127.85, 126.94, 125.40, 124.98, 124.55, 119.41, 52.27, 47.51, 32.86, 28.11.

Ethyl (Z)-2-cyano-2-(2-oxoindolin-3-ylidene) acetate (B)

Red solid, m.p. 222 °C, yield: 86%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 11.10 (s, 1H), 8.10 (d, *J* = 7.7 Hz, 1H), 7.48 – 7.45 (m, 1H), 7.03 – 6.98 (m, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 4.41 (d, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 166.33, 161.66, 146.51, 145.69, 138.82, 136.53, 129.59, 122.37, 118.96, 111.33, 105.11, 63.37, 14.10.

5.4.3 Spectral data of Product ethyl 2'-amino-7',7'-dimethyl-2,5'-dioxo-1'-(p-tolyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5a)

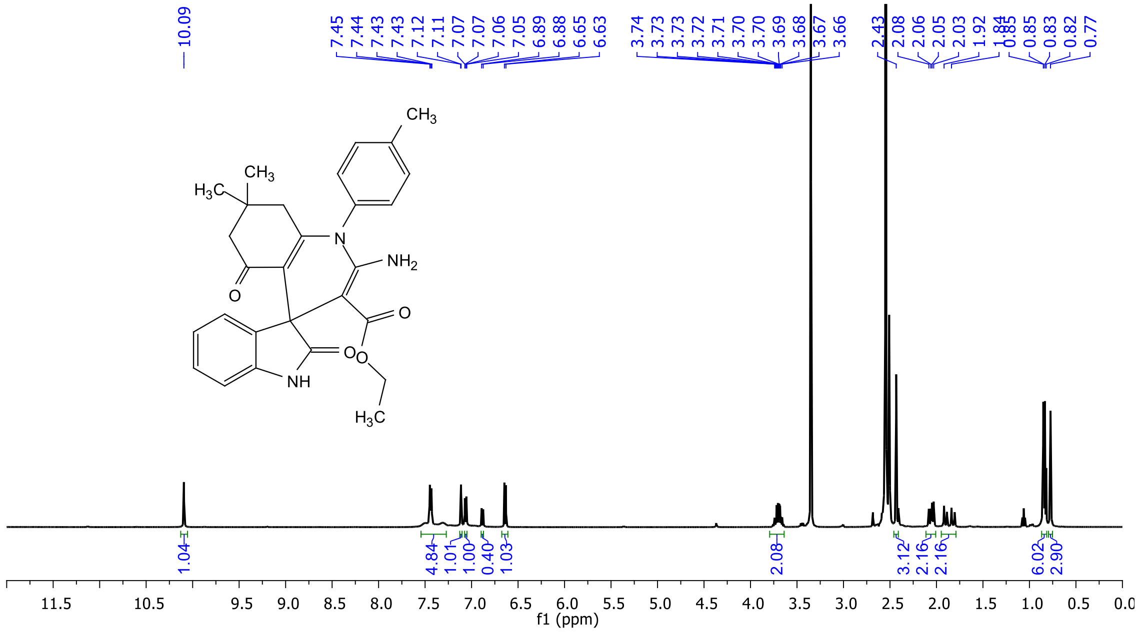


Figure 5.1 ^{1}H NMR **(500 MHz, DMSO-d^6) δ** of ethyl 2'-amino-7',7'-dimethyl-2,5'-dioxo-1'-(p-tolyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate **(5a)**

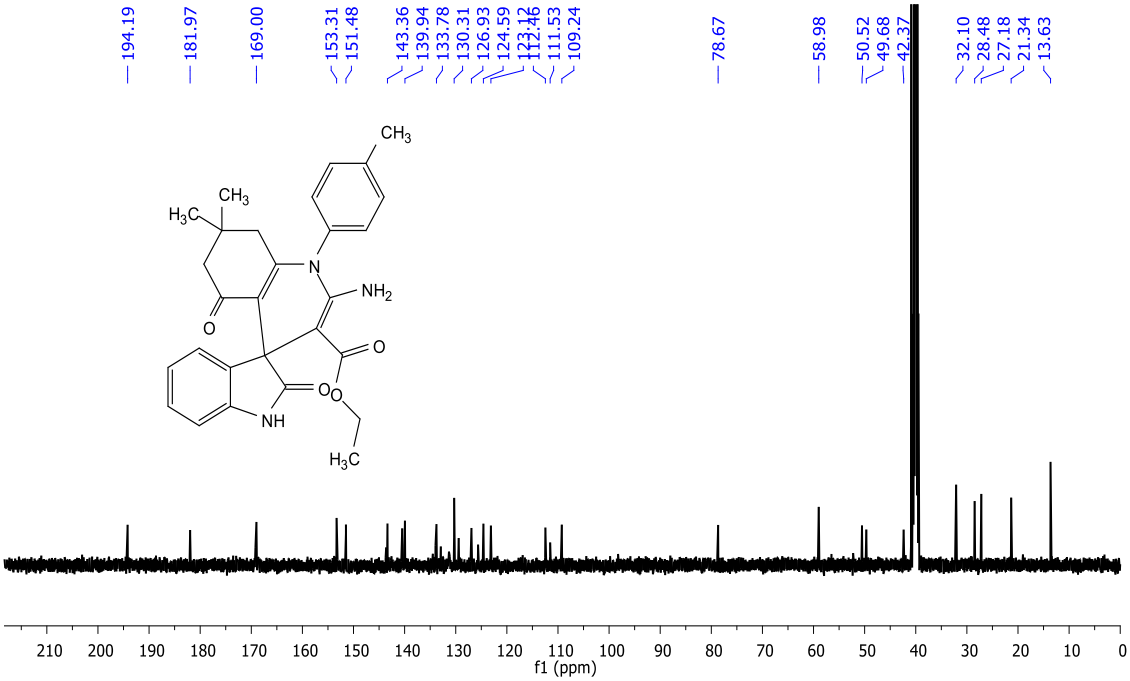


Figure 5.2 ^{13}C NMR of ethyl 2'-amino-7',7'-dimethyl-2,5'-dioxo-1'-(p-tolyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate **(5a)**

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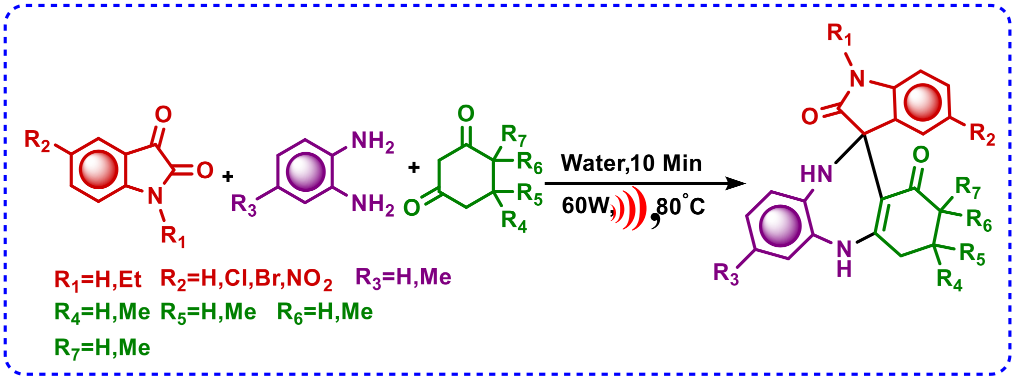
SUMMARY AND CONCLUSION

Summary and Conclusion

The thesis entitled "**A new avenue for the synthesis of some biologically active Isatin derivatives**" described the effective synthesis of biologically active isatin derivatives. The contents of the thesis have been divided into six chapters.

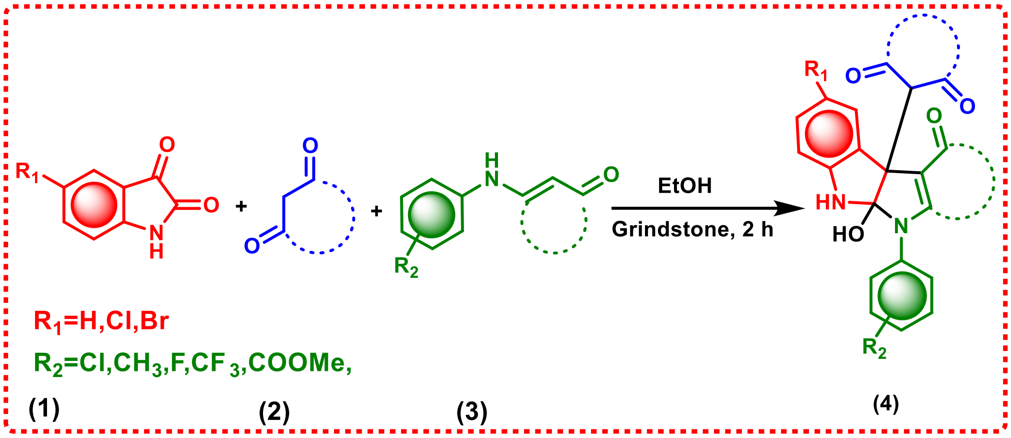
Chapter 1 Provide a general introduction to isatins, such as the synthesis of isatin, biological importance, and physical and chemical properties, and also adds the various synthetic application of isatin, i.e., N- substitution at isatin, the reactivity of carbonyl group of isatin, oxidation, reduction, the electrophilic aromatic substitution of isatin.

Chapter 2 described a facile and efficient multicomponent synthesis of a benzodiazepine ring via the reaction of isatin, diphenylamine, and 1,3-diketone under ultrasound irradiation in water. This method was successfully achieved by the condensation reaction of 1, 2-phenylenediamine with 1, 3-diketone in water, followed by intramolecular cyclization of isatin. This developed method offers advantages in terms of excellent yield, easy work-up procedure without column chromatography, short reaction time, and also validate without catalyst **(Scheme A)**.



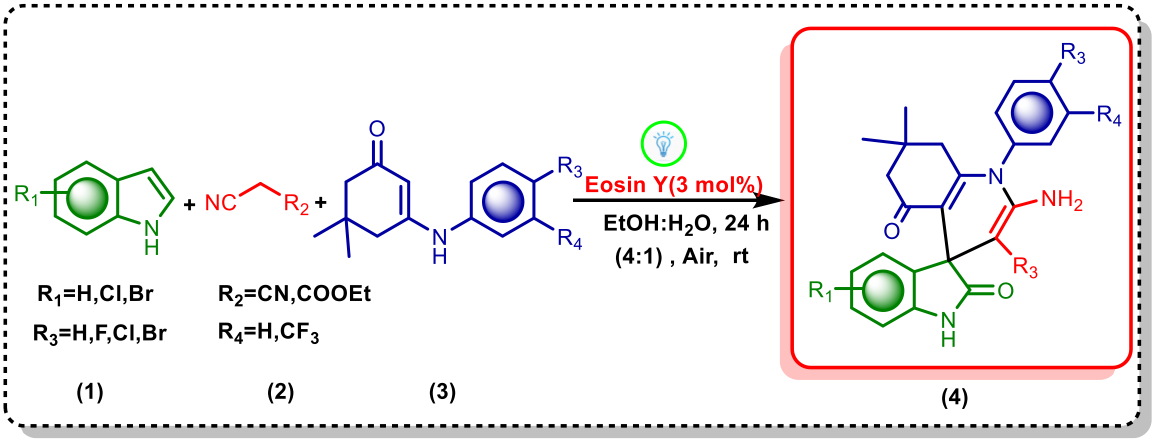
Scheme A Synthesis of benzodiazepine ring

Chapter 3 explained a grinding-induced catalyst-free, multicomponent synthesis of indoloindole pyrimidine from isatin, barbituric acid, and enaminone under ethanol as a solvent at room temperature. The grinding methodology has been exploited as a simple experimental setup, energy-efficient, economical, ecologically favorable procedure, and easy work-up without column chromatography. The present methodology includes isolating the product by a simple crystallization method **(Scheme B**).



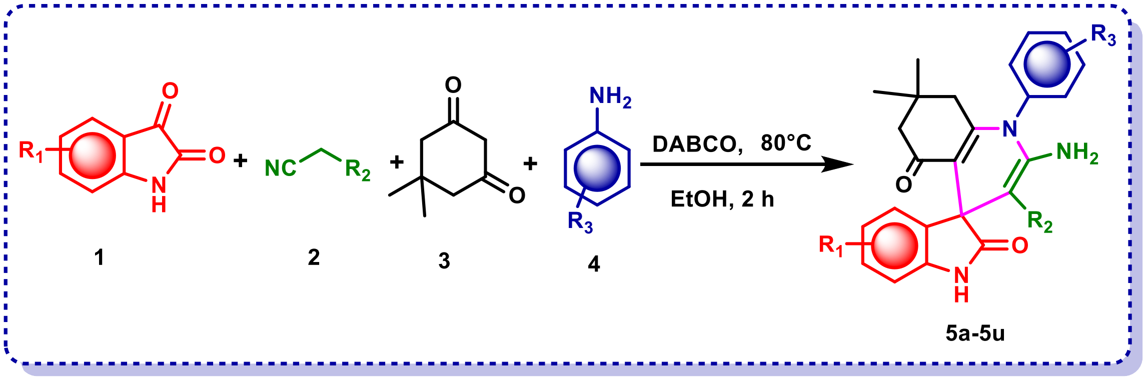
Scheme B Synthesis of indoloindole pyrimidine derivatives

Chapter 4 explores a facile and ecologically friendly one-pot multicomponent synthesis of biologically active spiro [indoline-3, 4'-quinoline] derivatives via oxidative coupling of indole with enaminone and malononitrile under EtOH: H2O (4:1) as a solvent. The reaction proceeded under eosin Y as a photocatalyst to form the product in good to excellent yields with a range of substrate scopes. Visible light has been exploited as an environment-friendly energy source, inexpensive and green, and yield of the product was obtained with high yields without any chromatographic purification **(Scheme C)**.



Scheme C Synthesis of biologically active spiro [indoline-3, 4'-quinoline] derivatives

Chapter 5 illustrated a facile, efficient and environment-friendly, easy work, short reaction time approach for the synthesis of Spiro[Indoline-3,4'-Quinoline] via one pot, four-component reaction of amine, dimedone, isatin, and malononitrile using DABCO in the presence of ethanol at 80 ^{0}C. This methodology used for the transformation of C-C and C-N bond formation takes place under mild reaction conditions (**Scheme D**).



Scheme D Synthesis of spiro [indoline-3, 4’-quinoline] derivatives

Conclusions

Various novel isatin derivatives were synthesized using environmentally benign methods such as ultrasound-assisted organic synthesis, grinding-induced organic synthesis, visible light-mediated organic synthesis, DABCO-catalyzed organic synthesis, and TBHP-mediated organic synthesis. Synthetic methodologies developed for the synthesis of isatin derivatives have many advantages, such as high yield, and mild reaction conditions, and the products can be isolated very easily without the use of column chromatography. The simplicity of the presented protocols makes it an interesting alternative to other approaches. Synthesized isatin derivatives can be attractive entities for biological investigations.

Scope for Future work

1. The synthesized compounds benzodiazepine ring , Indoloindolpyrimidine, spiro[indoline-3,4'-quinoline] derivative may be used for biological activities such as anti inflammatory,antimicrobial,antiviral ,antibacterial etc.
2. Further, explore the indole as a surrogate for the construction of some privileged heterocycles.
3. Development of different methodologies like metal-free, ultrasound assisted, grinding induced, and visible light irradiation to synthesize heterocyclic scaffold and biologically active compounds.

LIST OF
RESEARCH PUBLICATIONS

List of Publications: Suresh Kumar

1 Visible light triggered synthesis of spiro[indoline-3,4'-quinoline] via oxidative coupling of indole with enaminone and malononitrile

Suresh Kumar Maury, Ambuj Kumar Kushwaha, Arsala Kamal, Himanshu Kumar Singh and Sundaram singh

Journal of Molecular Structure, (2022) https://doi.org/10.1016/j.molstruc.2022.134452

2 A New Avenue to One-Pot Four-Component Synthesis of Spiro[Indoline-3,4'-Quinoline] Derivative Using DABCO As A Green Catalyst

Suresh Kumar Maury and Sundaram Singh

Synthesis,(2022), DOI: 10.1055/a-1948-2677

3 Visible Light Initiated Oxidative Coupling of Indole and Active Methylene Compounds Using Eosin Y as a Photocatalyst.

Ambuj Kumar Kushwaha, **Suresh Kumar Maury**, Arsala Kamal, Himanshu Kumar Singh and Sundaram Singh

Synthesis,(2022), DOI: 10.1055/a-1894-830

4 Visible Light-Driven Synthesis of Amine–Sulfonate Salt Derivatives: A Step towards Green Approach

Arsala Kamal, Himanshu Kumar Singh, **Suresh Kumar Maury**, Savita Kumari, Ambuj Kumar Kushwaha, Vandana Srivastava, and Sundaram Singh

Journal of Molecular Structure, 1257(1):132523,(2022)

5 TBAI-catalyzed C–N bond formation through oxidative coupling of benzyl bromides with amines: a new avenue to the synthesis of amides

Dhirendra Kumar, **Suresh Kumar Maury**, Savita Kumari, Arsala Kamal, Himanshu Kumar Singh, Sundaram Singh &Vandana Srivastava

Synthetic communication, Volume 52, 2022 - Issue 3,2022

6 Visible Light Mediated, Photocatalyst-Free Condensation of Barbituric Acid with Carbonyl Compounds

Savita Kumari, **Suresh Kumar Maury**, Dhirendra Kumar, Arsala Kamal, Himanshu Kumar Singh, Sundaram Singh

Chemistry Select, 6(12), Pages 2980-2987(2021)

7 Visible-Light-Promoted Synthesis of Fusesd Imidazoheterocycle by Eosin Y under Metal-Free and Solvent-Free Conditions

Himanshu Kumar Singh, Arsala Kamal, Savita Kumari, **Suresh Kumar Maury**, Ambuj Kumar Kushwaha, Vandana Srivastava, Sundaram Singh

Chemistry Select, 6(48),13982-13991(2021)

8 Visible Light-Induced Cu-Catalyzed Synthesis of Schiff's Base of 2- Amino Benzonitrile Derivatives and Acetophenones

Arsala Kamal, Himanshu Kumar Singh, Dhirendra Kumar, **Suresh Kumar Maury**, Savita Kumari, Sundaram Singh

Chemistry Select 6.1:52-58(2021)

9 Grinding induced catalyst free, multicomponent synthesis of Indoloindole pyrimidine

Suresh Kumar Maury, Savita Kumari, Ambuj Kumar Kushwaha, Arsala Kamal, Himanshu Kumar Singh, Dhirendra Kumar, Sundaram Singh

Tetrahedron Letter 61 (2020) 152383

10 Eosin Y-Catalyzed Synthesis of 3-Aminoimidazo [1,2-a] Pyridines via the HAT Process under Visible Light through Formation of the C−N Bond

Himanshu Kumar Singh, Arsala Kamal, Savita Kumari, **Suresh Kumar Maury**, Dhirendra Kumar, Sundaram Singh

ACS Omega 5, 46, 29854–29863(2020)

11 A facile and efficient multicomponent ultrasound-assisted “on water” synthesis of Benzodiazepine ring

Suresh Kumar Maury, Dhirendra Kumar, Arsala Kamal, Himanshu Kumar Singh, Savita Kumari, Sundaram Singh

Molecular Diversity, (2020) DOI: 10.1007/s11030-019-10031-y