Chapter 1

Introduction
Organic chemistry plays an important role as it is the origin in the study of natural products. Many of organic compounds available from natural sources which have significant importance to living organisms. Many compounds having carbon atom are mostly isolated from plant and animal sources; while most of them are to be synthesized. The organic compounds are constructed by carbon framework and hydrogen, oxygen and other heteroatoms are to be attached to it. Carbon atoms can particularly join with one another and their ends of the chain are joined together to form a ring referred as carbocyclic compounds or cyclic compounds. In the molecule of carbocyclic compounds, substitution of one or more of the ring carbon atoms by a heteroatom such as N, S, O etc. provides a heterocyclic compound. Heterocyclic compounds have shielded the largest areas of research in the field of organic chemistry in vogue. They contribute to the development of society through a pharmaceutical and industrial point of view by drug designing. They also have played an important role in biochemical processes. They are one of the parts of side groups of crucial constituents of living cells such as DNA and RNA.

1.1 Spiro Heterocyclic Compounds: An Overview

The synthesis of the privileged classes of heterocyclic compounds has become one of the major areas of research in the field not only synthetic but also medicinal chemistry as the most biologically active compounds. But, recently growing efforts with spiro heterocyclic compounds have been made to synthesize, characterize and investigate the biological activities. A spiro compound, or spirane, from the Latin spīra, meaning a twist or coil, is a chemical compound, typically an organic compound represents a twisted structure of two or more rings are linked together by one common atom. A spiro compound is a bicyclic organic compound with rings connected through just one atom. The rings can be different in nature or identical. The connecting atom is also called the spiro atom, most often a quaternary carbon ‘spiro carbon’ or ‘chiral carbon’ making them analogous to any simple chiral compound. Some of the spiro compound displays central chirality rather than axial chirality resulting from the twist. Spiroatoms can be the origin of chirality even when they lack of four different substituents normally observed in chirality because of axial chirality. One which ring systems having two or more rings linked by one common atom is known as ‘spiro’ compounds. Spiro compounds are considered even if the
common atom is O, S, N, Si, etc. Nomenclature$^1$ of spiro scaffold can be done as mentioned below (Figure 1.1). When two rings are identical the priority is determined by CIP system.

![Figure 1.1 Common Nomenclature of Spiro Scaffold](image)

1.1.1 Spiro in Natural Source

Natural products have been an irreplaceable source of medicines and other resources in history. The sterically constrained spiro structure is present in many natural products.

![Figure 1.2 Natural Products containing Spirocycles](image)

The structures of natural products from a variety of sources contain spirocycles have various biological properties, e.g., the neurotoxic properties of the poison-dart frog’s Histrionicotoxin$^2$ has been shown to arise from both the chiral nature of the central spiro carbon atom and from two six membered rings of spiro system. Other closely related spiro perhydro compounds exhibit these neurotoxic properties. Ginkgo biloba, ginkgo or
the maidenhair tree, has various uses in traditional medicine and as a source of food found in fossils dating back 270 million years. The sesquiterpene and halogenated carbocyclic spiro compound present in red algae,\(^3\) the Brazilian *Laurencia dendroidea*. Acorus calamus also called sweet flag used medicinally and to make fragrances. The dried powder rhizome has been used as a substitute for ginger, cinnamon and nutmeg.

1.1.2 Biology

A Function of an antimicrobial agent\(^4\) is to inhibit their growth or to kill the microorganisms. Use of substances with antimicrobial properties is known to have been common practice for as a minimum 2000 years. A various microorganisms were clarified to cause infectious diseases. Antimicrobial chemotherapy made notable advances during the 20\(^{th}\) century, resulting in the overly optimistic view that infectious diseases would be dominated in the near future. Yet, in reply to the improvement of antimicrobial agents, microorganisms have acquired resistance to drugs by a variety of mechanisms have developed and continue to plague human beings. Infectious diseases caused by drug resistant bacteria are one of the most important problems in daily life. In the current condition, where multidrug-resistant bacteria have feast extensively and selections for treatment with antimicrobial agents are limited. As drug-resistant bacteria have been designated by the use of antimicrobial drugs, the proper use of antimicrobial drugs, in addition to efforts to minimize the transmission and spread of resistant bacteria through suitable infection control would be the first step in resolving the issue of resistant organisms. Since several decades, human has been struggling with a variety of diseases like neurological disorders, mycobacterial, opportunistic bacterial, cancer, fungal infections and AIDS. People living in the developing countries are more influenced with such kind of illnesses because of limited resources of healthcare systems. The fundamental pharmaceutical and biochemical properties of spirocycles evaluated the usefulness in drug discovery.\(^5\) This structural superfamily comprises many interesting representatives showing biological activities relevant to the drug discovery and medicinal chemistry fields.\(^6,7\)

1.1.3 Some Spiro Drugs

Medicinal chemistry is rich with an example of both naturally occurring and laboratory synthesized compounds in which spiro type structures have become drug candidate.
• Spironolactone
• Buspirone
• Rifabutin
• 1-[1’-(3-phenylacryloyl)spiro[1-benzofuran-3,4’-piperidin]-5-yl]methanamine
• 1-(1’-{[3-(methylsulfanyl)-2-benzothiophen-1-yl]carbonyl}spiro[1-benzofuran-3,4’-piperidin]-5-yl) methanamine
• (5-aminomethyl)-2H-spiro[benzofuran-3,4’-piperidine]-1’-yl)(5-(phenylethynyl)furan-2-yl)methanone
• 8,9,10-Trihydroxy-7-hydroxymethyl-2-thioxo-6-oxa-1,3-Diaza-spiro[4.5]decan-4-One
• (C8-S)-hydantocidin 5’-phosphate
• 9,10-deepithio-9,10-didehydroacanthifolicin

1.1.4 Spiro Compound Applications
Spiro compounds are used in leuco dye (transformation between leuco form and colored form induced by UV radiation), Spiro[fluorene-7,9’-benzofluorene]-type compounds are used in Blue OLEDs as Hosts and Dopants.

1.2 Isatin: A Versatile Scaffold to form Spiroheterocycles
The structural design of a spiro-cyclic framework has always been a thought-provoking is colour for synthetic organic chemists by reason of it often requires synthetic design based on specific strategies. Due to steric strain, the presence of a spiro carbon in the heterocycles causes structural rigidity and has conformational restrictions, considerably influences the biological activities. Under such a complex scenario, isatin constitute has been employed extensively, either directly or via 3-substituted 2-oxindoles, in the design and synthesis of spiro-cyclic frameworks. A wide investigation of this aspect of isatin chemistry during the past decade has led to effective design and synthesis of miscellaneous types of heterocyclic and carbocyclic compounds with a spiro-fused 2-oxindole ring containing one or more stereo centers. From many heterocyclic compounds, indole moiety has attracted special attention of synthetic chemists since they are a fertile source of biologically active molecules. Isatin is one of the versatile compounds containing indole moiety. Isatin is generally known as Indoline-2,3-dione or indole-1H-2,3-dione (Figure 1.3). Since 1840, Isatin was firstly synthesized by Erdman.\(^8\)
and Laurent from the oxidation of indigo by chromic acid and/or nitric acid and its present structure was proposed by Kekule.  

![Figure 1.3 Structure of Isatin and Isatin-derived Spiro 2-oxindoles](image)

### 1.2.1 Chemistry of Isatin

The chemistry of isatins was studied for the first time by Sumpter and later updated by Popp and by Silva et al. An extensive investigation on the synthesis and reactivity of isatins, possessing an indole motif with a ketone and a γ-lactam moiety, has unfolded many interesting aspects of organic reactions and mechanisms. The exclusive potential of isatin to be used not only as an electrophile but also as a nucleophile and their easy availability have made them valuable building blocks in organic synthesis. The most captivating application of isatin in organic synthesis is unquestionably due to the highly reactive C-3 carbonyl group that is a prochiral center. The reactions of the C-3 carbonyl group of isatin, mostly by nucleophilic additions or spiro annulation, transform it into 2-oxindole derivatives. It undergoes electrophilic aromatic substitution at positions C-5 and C-7 of the phenyl ring, N-substitutions, nucleophilic additions onto the C-3 carbonyl group, chemo selective reductions, oxidations, ring-expansions, and spiro annulations, etc. Synthesis of several heterocyclic frameworks of biological significance such as pyrrolidines, uinolones, indoles, β-lactams and 2-oxindoles, etc. have been developed using isatin as substrates. 2-Oxindoles or spirooxindole particularly those which are spiro-fused to other cyclic frameworks (Figure 1.4), have drawn great interest to researchers in the area of synthetic organic chemistry as well as medicinal chemistry worldwide.

-5-
Introduction

1.2.2 Isatin in Nature

Isatin and its derivatives are naturally found in some plants such as genus Isatis, Calanthe iscolour LINDL and Couroupita guianensis Aubl. It has also been isolated as a metabolic derivative of adrenaline in humans. They are present in many natural products such as elacomine, rhynchophylline, spirotryprostatins, horsfiline, gelseverine, and, gelsemine etc.

1.2.3 Biological Properties of Isatin

Biological properties of isatin contain a wide range of actions in the brain and offer protection against certain types of infections. From current literature survey, spirooxindole showed various biological activities such as anti-HIV,
anticancer, progesterone receptor modulators, antitubercular, antimalarial, MDM2 inhibitor, anticonvulsant, anxiogenic, antiviral, antifungal, antidepressant, diuretic, antidepressant, antioxidant, H1-anti-histaminic, anti-inflammatory etc.

It is also known to possess CNSMAO inhibition. DNA Binding is deliberated as a mechanism to explain the numerous anti-cancer activities of various derivatives of isatin. Additionally, some of isatin Mannich bases are effective compounds in contradiction of variola and vaccinia viruses. Recently, some reviews for the synthesis of spiro compounds have been reported through asymmetric synthesis using asymmetric catalysis, by transition metal-mediated cyclization of anilides, through enantioselective reaction and methodologies.
In 2013-14, we have published two reviews articles\textsuperscript{6,7} for a brief outline of isatin chemistry in the design and synthesis of different types of compounds containing spiro-fused heterocycles followed by their applications in the field of both organic synthetic chemistry as well as medicinal chemistry. Encouraged by the previous studies and in continuation of our efforts towards the synthesis of spiro heterocycles, the present synthetic schemes are included to emphasize the reactivity of isatin for the synthesis of diverse spirooxindole derivatives by using various catalysts via conventional or microwave methods.

1.3 Review of Literature

There are four types of spiroheterocycles (mono, di, tri and tetra) designed in (Figure 1.7). Different types of work has been done is mentioned with schemes below.

1.3.1 Synthesis of Monospiroheterocycles

A favourable Huisgen dipolar addition involving isatin, amines and DMAD to afford spiro lactones was discussed. In likewise study, Perumal and co-workers have given a facile strategy for the synthesis of functionalized spiro lactones and dispirodihydrofuranyl oxindoles from same material which offers several advantages like high yield, readily available starting materials and involves less hazardous chemical techniques (Scheme 1).\textsuperscript{25}

![Scheme 1](image-url)
Introduction

Development of an efficient procedures for the stereo selective synthesis of two kinds of the functionalized spiro[indoline-3,5-pyrroline]-2,2'-diones via acid-catalyzed (p-TsOH) three component reactions of aryl amine, acetylene dicarboxylate and isatin under different conditions (Scheme 2).  

\[
\begin{align*}
\text{Scheme 2}
\end{align*}
\]
A direct and creative method for the preparation of therapeutically favourable pyrazolopyridinyl spirooxindoles has been developed through a progressive one-pot, novel regio- and diastereoselective three-component reaction of isatin, α-cyanoacetic ester or malononitrile, and 5-amino-3-methylpyrazole catalysed by sodium chloride as green catalyst and water as an ecologically benign reaction medium (Scheme 3).\(^{27}\)

Scheme 3

The three-component synthesis of spiro[pyrano(pyrazolopyridine-indoline]diones have been invented by Vasuki and et al. which derived from the condensation of isatin with 4-hydroxy-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-6(7H)-one and malononitrile in the presence of piperidine and water at 30 °C. This procedure can be considered as an efficient and eco-friendly strategy for diversity oriented synthesis (Scheme 4).\(^{28}\)

Scheme 4

An innovative and efficient one-pot reaction of isatin, 5-amino-3-methylpyrazole and 1,3-dicarbonyl compounds in aqueous medium have afforded spiro[indoline-3,4′]pyrazolo[3,4-b]quinoline]dione, spiro[furo[3,4-e]pyrazolo[3,4-b]pyridine-4,3′-indoline]dione and spiro[indeno[2,1-e]pyrazolo[3,4-b]pyridine-4,3′-indoline]dione derivatives. The advantages of this method include high efficiency, mild reaction conditions, convenient operation, and environmentally benign conditions (Scheme 5).\(^{29}\)

Scheme 5
A novel, green, and one pot efficient three-component condensation reaction of an isatin, isoxazole and barbituric acid in water to give spirooxindoles in high yield at 70 °C temperature, using a catalytic amount of p-toluene sulfonic acid have reported by Rehmati and et al. (Scheme 6).  

Scheme 6
Mahendra and et al. have developed an efficient and eco-compatible synthetic methodology for the synthesis of structurally diverse spiroheterocycles with fused heterosystems in excellent yield using a halogen free -SO$_3$H functionalized ionic liquid/water as recyclable medium which gives some benefit like mild reaction conditions, shorter reaction time, easy work-up, excellent yield, and recycled and reusable solvent/catalyst etc. (Scheme 7).

Scheme 7
Liqiang Wu and co-workers have developed an extremely efficient method for the synthesis of novel spiro[dibenzo[a,i]-xanthene-14,3'-indoline]-2',8,13-triones and spiro naphthopyrano[2,3-d]pyrimidine-5,3'-indolines via a one-pot three component condensation reaction using [Hmim][HSO$_4$] as an efficient and reusable catalyst. This method give with several unique merits, such as high conversions, simplicity in operation, cost efficiency, use of solvent-free and mild conditions, simple work-up, high yield and usage in the synthesis of complex molecules (Scheme 8).
Shou-Xin Liu and co-workers have readily prepared dodecyl benzene sulfonyl acid functionalized silica-coated magnetic nanoparticles and identified as an efficient catalyst for the synthesis of a library of spirooxindole-pyrimidine derivatives by three-component condensation reaction of barbituric acids, isatin and cyclohexane 1,3-diones (Scheme 9).\textsuperscript{33}

The [4+2]/[2+2] cycloaddition reaction of N-protected isatin-3-arylimine with acyl ketene derived from α-diazocarbonyl compounds a rhodium(II) catalyzed has attained for the first time for the preparation of a novel class of spiro (oxindolyl)oxazinone and spiro(oxindolyl)-β-lactam derivatives (Scheme 10).\textsuperscript{34}
The new GAP (Group-Assistant-Purification chemistry) synthesis of spiro[indoline-3,4′-pyrano[2,3-c]pyrazole] derivatives has been achieved by four-component reaction of hydrazine, β-keto esters, isatin and malononitrile or ethyl cyanoacetate at room temperature by ultrasound irradiation (Scheme 11).\textsuperscript{35}

An efficient asymmetric diastereo- and enantioselectivities [3+2] cycloaddition reaction of Morita-Baylis-Hillman carbonates of isatin with N-phenylmaleimide has been developed a spirocyclopentaneoxindoles under a Me-DuPhos (Scheme 12).\textsuperscript{36}

An efficient, novel and one-pot synthesis of 5H-spiro[benzo[7,8]chromeno[2,3-c]pyrazole-7,3′-indoline]-2′,5,6-(9H)-trione derivatives have been synthesized by Shen and co-workers.\textsuperscript{37} A four-component reaction of hydrazine hydrate, β-keto esters, isatins and 2-hydroxynaphthalene-1,4-dione were catalyzed by MgCl\textsubscript{2} (10 mol\%) refluxing in ethanol. The structure was confirmed by the X-ray single crystal diffraction analysis. This
reaction provides the advantages of excellent yields, environmental friendliness solvent, shorter reaction time and simple work-up procedure (Scheme 13).

**Scheme 13**
The synthesis of (E)-8'-arylidene-5',6',7',8'-tetrahydrospiro[oxindole-3,4'-pyrano[3,2-c]pyridin] derivatives were synthesized by Wang et al.\(^{38}\) an efficient and mild cyclization procedure was achieved via one-pot three-component condensation of isatins, malononitrile and (E)-3-arylidene-1-methylpiperidin-4-ones using piperidine as an effective catalyst and ethanol as a solvent. These compounds were evaluated for their *in vitro* antitumor activity in human cervical carcinoma cell line (Hela), human liver hepatocellular carcinoma cell line (HepG2), and human breast carcinoma cell line (MDA-MB-231) (Scheme 14).

**Scheme 14**
An easiest, fastest and eco-efficient protocol has been explored for the synthesis of spirotetrahydroquinoline derivatives through hetero Diels-Alder methodology by using arylamines, isatin and maleic anhydride was catalyzed by InCl\(_3\) in PEG 400 as a green solvent under ultrasonication. The feasibility of this reaction is established in terms of shorter reaction time, good yield and waste minimization. Use of green solvent PEG 400 and ultrasonication makes this approach very attractive pathway to achieve complex molecules. The coupling of two biologically active moieties indole and tetrahydroquinoline where there is a C-3 spirooxindole bridge in the product molecules encouraged for evaluating their anti-microbial and analgesic activities. Some of the compounds showed favorable results for future application in drug discovery (Scheme 15).\(^{39}\)
In continuation of their work, Kianfar and coworkers developed new catalysts for organic transformations, using isatin and its derivatives as a precursor. Therefore, we can raise the biocidal activity with the entity of two or more various heterocyclic moieties in one molecule. They have reported the preparation of spirooxindole derivatives using isatin, malononitrile and 5,5-bis-substituted-1,3-cyclohexanedione. In this method, recyclable catalysts used are silica-bonded N-propyl diethyl enetriamine and silica-bonded N-propyl diethyl enetriamine sulfamic acid. This method has many advantages like as simple work-up, clean and facile procedure, and environmental friendly circumstance (Scheme 16).

Kumari and et al. discovered a mild and efficient protocol for synthesis of spiro[indoline-3,4′-pyrazolo[3,4-b]quinoline]diones via a one pot three component condensation of isatins, 1,3-dicarboxyls and 5-amino-1-phenyl-3-methylpyrazole using [NMP]H$_2$PO$_4$ catalyst in binary mixture of EtOH: H$_2$O. The catalyst could be recycled and reused four times without significant loss of activity. Spiro[indoline-3,4′-pyrazolo[3,4-b]quinoline]diones with stabilized zwitter ionic resonance structures showed viable application as new fluorescent probes and pH indicators. These chemo sensors have good wavelength shift and showed outstanding sensitivity in the pH range of 11-13 (Scheme 17).
Scheme 17

Shinde and his coworkers explored a novel silica sodium carbonate assisted convenient strategy for the synthesis of spiro[chromene-4,3'-indoline]-3-carbonitriles derivatives in solvent-free media. The reactions can be performed at low catalyst loadings with excellent functional group tolerance. The catalyst can be easily recovered for three runs without any significant loss of the yields, low amount, and safe, cheap, environmentally benign, make the protocol attractive, sustainable, and economic (Scheme 18).

Scheme 18

Withaferin-A (WA) is very interesting structure and have various biological activities and also the biological importance of pyrrolidine-2-spiro-3-oxindole ring system, Bharitkar and et al. Synthesized an interested motif involving both the ring systems via the 1,3-dipolar cycloaddition of WA at the second bond of the α,β-unsaturated carbonyl system. They have reported ten compounds of novel spiro-pyrrolizidino-oxindole adducts of withaferin-A, which are facile, atomeconomic synthesis via the intermolecular cycloaddition of azomethine ylides generated in situ from proline and isatins. The reaction is highly chemo, regio, and stereoselective producing the cis fused products. The structures were determined by 1D/2D NMR analysis and by X-ray crystallographic analysis in some cases. They have also reported bio-evaluation of synthesized compounds against six cancer lines (e.g., CHO, HepG2, HeLa, HEK 293, MDCK-II, and Caco-2). Among them, one of the compounds was to be identified promising potential anticancer compounds (Scheme 19).
A convenient, efficient and novel indolin-2-one annulated spirochromanone conjugates were described by Ashok et al. using of ionic liquid 1-n-butyl-3-methylimidazolium tetrachloroferrate, [bmim]Cl·FeCl₃. This approach offers the advantages of reuse of ionic liquid, high yields, convenient operation, easy work-up and environment benign. The synthesized compounds were estimated for their antioxidant activity. Among those compounds, Compound two was found to be IC₅₀ values 1.25 and 1.74 μM, comparable to that of ascorbic acid (IC₅₀ 8.64 μM), a standard antioxidant agent (Scheme 20).44

A one-pot, four-component procedure for the synthesis of a new chiral spiro-oxindolo-pyrrolidines with high regio, diastereo and enantioselectivity (up to 80% ee) was described by Taghizadeh et al. The regio and stereo chemical 1,3-dipolar cycloaddition of azomethine ylides, which were generated in situ during the reaction of isatin derivatives, sarcosine with optically active chiral menthylcinnamate. The reaction was studied on theoretical calculations and on the basis of the assignment of the absolute configuration of the cycloadducts (Scheme 21).45
Shi and co-workers prepared the highly functionalized spiro[indoline-3,4′-pyran-3,2-H[quinolines]] in high yields from three-component reaction of 8-hydroxyquinoline, isatins and malononitrile or ethyl cyanoacetate in the presence of piperidine and ethanol as a solvent at room temperature for about 12 hrs (Scheme 22).

Reddy et al. prepared an inclusive selection of aldehydes undergo smooth cross-coupling with 3-hydroxy-3-(4-hydroxybut-1-en-2-yl)-1-methylindolin-2-one in the presence of 10 mol% BF$_3$·OEt$_2$ in dichloromethane at 0°C to afford 2,3,5,6-tetrahydro-1′H-spiro[pyran-4,4′-quinoline]-2′,3′-dione derivatives in good yields with excellent diastereoselectivity. The synthesis of tetrahydro-1′H-spiro[pyran-4,4′-quinoline]-2′,3′-dione scaffolds were firstly reported through a cascade of Prins/Pinacol reaction (Scheme 23).
The multicomponent and solvent-free reaction between isatins, malononitrile, and dimedone was described by Elinson and coworkers using sodium acetate as a catalyst. The method of grinding in mortar results in faster and efficient formation of substituted spirooxindoles with very good practical (90-99%) yield. The substituted spirooxindoles, the pharmacological perspective substances with diuretic, spasmytic, anticoagulant, anticancer and antianaphylactic activities is beneficial for the diversity oriented large-scale processes. This reaction represents fast, efficient and environmentally benign synthetic concept for multicomponent reactions strategy (Scheme 25).

A synthesis of 1-H-spiro[isoindoline-1,2-quinazoline]-3,4(3H)-diones has been expediently accomplished by Mane and co-workers. The product was synthesized by using isatin(s) or cyclic ketone and anthranilamide in ethanol at room temperature. Admirable yields of the products, shorter reaction time, operational easiness and simple work-up procedure are the gorgeous features of the present protocol. Synthesized compounds were found to be fluorescent with absorption in UV region (302, 362 nm) and emission in the visible region (413-436 nm) with Stokes shift of 44-72 nm (Scheme 26).
Mali and his co-worker accomplished an eco-friendly and one-pot three-component aqueous phase synthesis of functionalized spirooxindole derivatives by the reaction of isatin, β-nitrostyrene and benzyl amine or α-amino acids in water under microwave irradiation. The method displayed easy construction of a series of spirooxindoles in good yields with good diastereo selectivity starting from readily available precursors. In addition, all the synthesized compounds were screened for their antimicrobial activity and majority of the compounds showed significant activity against Escherichia coli (ATCC 10536), Candida tropicalis (ATCC 750), Staphylococcus aureus (ATCC 25923) and Pseudomonas aeruginosa (ATCC 15442) (Scheme 27).

NHC (N-Heterocyclic carbene)-catalyzed asymmetric [4+2] annulation reaction of isatins and α,β-unsaturated carboxylic acids bearing γ-H gave spiro cyclic oxindole-dihydropyranones synthesized by Ling Zhu. This protocol featured, easy availability of raw materials, in situ activation strategy, good yields and excellent enantio selectivities (up to 99% ee) (Scheme 28).
An efficient, four component reaction of isatin, 1,3-indanedione, ethyl acetoacetate and ammonium acetate in binary mixture of ethanol: water (9:1) system provided spiro[4H-indeno[1,2-b]pyridine-4,3’-[3H]indoles] at room temperature. Merits of the method are mild reaction conditions at ambient temperature were accomplished by Dige and co-workers. The synthesized compounds display excellent fluorescence properties (Scheme 29).

Scheme 29
Padvi et al. attempted for a rapid and efficient, one pot synthesis of spirooxindole derivatives by three component reaction of isatin, malononitrile and carbonyl compound possessing a reactive α-methylene group by using specific ionic liquid, 1-butyl-3-methyl imidazolium hydroxide [bmim]OH as a catalyst. The significant features of this methodology are straightforward route in short reaction time at room temperature and avoidance of any hazardous organic solvent, tedious purification step, a toxic catalyst. Stimulatingly, this protocol is not only limited to monosystems but also to the synthesis of the newer bisspirooxindole system. The [bmim]OH catalyst system, reusability of catalyst at five recycles without appreciable loss of activity (Scheme 30).

Scheme 30
A green and convenient method of synthesis of spiro[dibenzo[a,i]-xanthene-14,3’-indoline]-2’,8,13-triones in the presence of a catalytic amount of cellulose sulfuric acid (CSA) as a prompt biopolymer-based catalyst under solvent-free conditions at 100 °C have been reported by Seyyedeh Cobra Azimi and his co-worker. The condensation reactions between β-naphtol, 2-hydroxynaphthalene-1,4-dione with different isatin derivatives to afford the corresponding xanthenes derivatives with good to excellent
yields. They have described the first example of a multicomponent reaction to synthesize the compounds using cellulose sulfuric acid. The approach offers several advantages such as shorter reaction times, simple work-up, and non-toxicity of the catalyst, excellent yields and solvent-free conditions. Likewise, cellulose sulfuric acid is successfully reused for four cycles without significant loss of activity (Scheme 31).

![Scheme 31](image)

**Scheme 31**
One-pot multicomponent reaction between isatin, barbituric acid, and 6-amino-1,3-dimethyl uracil was investigated by Negar and co-workers. The catalyst used was sulfonic acid functionalized nanoporous silica (SBA-Pr-SO3H) and resulted in the formation of spirooxindole dipyrimidines. As like Spirooxindole unit 1,4-dihydropyridines are also found in many natural products and with interesting biological activities such as vasolidator, antitumor, antidiabetic, bronchodilator and anti-atherosclerotic activities. An excellent yield and short reaction times are related to the high efficiency of SBA-Pr-SO3H that the reactions take place easily in its nanopores material. Mild reaction conditions and easy work-up procedures are the advantages of this green method (Scheme 32).

![Scheme 32](image)

**Scheme 32**
A simple, green, efficient and three-component procedure has been established for the synthesis of 4'-phenyl-1'H-spiro[indoline-3,2'-quinazolin]-2-ones by Kamal and et al. The reaction was carried out through 2-aminobenzophenones, isatins and ammonium acetate in excellent yields under catalyst-free conditions using ethanol as solvent. This method provides several advantages such as operational easiness, shorter reaction time and
catalyst-free conditions with eco-friendly as well as economical. All the derivatives were tested for antimicrobial activity against both Gram-positive and Gram negative bacterial strains, including a fungal strain Candida albicans MTCC 3017 (Scheme 33).\(^{57}\)

\[
\begin{align*}
\text{Ph} & \quad \text{NH}_2 \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

\[
\text{R} \quad \text{NH}_2 \quad \text{N} \quad \text{O} \\
\text{H} & \quad \text{N} \quad \text{O} \\
\end{align*}
\]

Scheme 33

Roy and co-workers studied the interaction between Spirooxindole-Annulated Thiopyran derivatives (STP) and Bovine Serum Albumin (BSA) using multi-spectroscopic and docking method. The intrinsic fluorescence of BSA could successfully quenched by STP through dynamic quenching. The suggested by thermodynamic parameters, hydrogen bonds and van der Waals forces played a key role in stabilizing the BSA–STP complexes. According to Forster non radiation energy transfer theory (FRET) the average binding distance of STP-BSA were found to be \(< 7\) nm. Moreover, UV-visible and circular dichroism results specified that in the presence of the STP secondary structure of BSA changed. Theoretical docking study of the interaction of BSA and STP also supported the experimental results (Scheme 34).\(^{58}\)

\[
\begin{align*}
\text{R} & \quad \text{S} \quad \text{N} \quad \text{S} \quad \text{N} \\
\text{R} & \quad \text{CN} \\
\end{align*}
\]

Scheme 34

The first asymmetric, Brønsted acid-catalyzed and Biginelli-like reaction of a ketone has been developed by Stucchi et al. They employed \(N\)-substituted isatins as carbonyl substrates, urea and alkyl acetoacetates as precursor components. The catalyst BINOL-derived phosphoric acid was utilized to achieve the synthesis of a small library of chiral, enantio enriched spiro(indoline-pyrimidine)-diones derivatives. The absolute configuration of the new spiro stereocenter was evaluated on diastereoisomeric derivatives by NMR spectroscopy. The overall molecular conformation in the solid state
Introduction

allowed to disclose by X-Ray diffractometry. To characterize the crystal packing of a Br-substituted Biginelli-like derivative, computational studies on the reaction transition state allowed justifying the stereochemical outcome (Scheme 35).\(^{59}\)

![Scheme 35](image)

**Scheme 35**

A new bifunctional squaramide organocatalyst derived from L-proline mediated the first enantioselective synthesis of dihydrospiro [indoline-3,4′-pyrano[2,3-c]pyrazole] derivatives have been developed reddy and co-workers. The excellent enantioselectivity obtained by reacting pyrazolones with isatylidine β,γ-unsaturated α-ketoester. This new catalyst outperformed widely used thioureas and squaramides in tempting enantioselectivity (Scheme 36).\(^{60}\)

![Scheme 36](image)

**Scheme 36**

An environmental friendly and green synthetic method developed by Rashid et al. For the preparation of silver nanoparticles (AgNPs) using Ferula Latisecta leaf extract acting as a reducing and capping agent. It can reduce silver ions into AgNPs without using any severe conditions. Furthermore, these nanoparticles were found to be an excellent catalytic activity in simple and safe one-pot preparation of spirooxindoles in water. This procedure has many advantages containing operational simplicity, low cost, short reaction times, and green conditions (Scheme 37).\(^{61}\)
Borad et al. have been synthesized a rapid, efficient, one-pot-three-component and microwave-assisted synthesis of spiro[indoline-3,4’-quinoline] derivatives. The Knoevenagel or Michael addition reaction was carried out by conventional as well as microwave methods. The reaction of isatin, malononitrile and amine derivatives was catalyzed by CuCl₂ resulting good yields. The main benefits of this protocol are simple work-up and eco-friendly reaction conditions. Biological characterization of antibacterial screening of synthesized compounds were also evaluated (Scheme 38).

Borad et al. described ZrSiO₂ (10 mol%) mediated one-pot three-component synthesis of diverse spiro[chromene-4,3’-indoline] derivatives of substituted phenols with isatin and malononitrile. The reaction was carried out by microwave radiations at 100 °C, 300 W for 3-7 min to afford 80-90 % of yield. Antibacterial activity of the synthesized compound was to be screened on Nutrient-agar plates by well-diffusion assay against test culture (Scheme 39).

As part of continuous studies, Borad et al. developed a novel series of N-(benzo[d]thiazol-2-yl)-2-((2,4’-dioxospiro[indoline-3,2’-thiazolidin]-3’-yl)amino)
acetamide derivatives by sequencing reaction of 2-aminobenzothiazole with Chloroacetylchloride, Hydrazinehydrate, Isatin and Thioglycolic acid. The compounds were characterized by elemental analyses and various spectroscopic techniques and were tested for their \textit{in vitro} antibacterial activity against two Gram-positive and two Gram-negative bacteria. One of the compounds possessed a broad spectrum of antibacterial activity against the tested microorganisms (Scheme 40).\textsuperscript{64}

\begin{equation}
\text{Scheme 40}
\end{equation}

1.3.2 Synthesis of Dispiroheterocycles

A suitable, efficient and ecologically gentle synthesis of novel dispiropyrrrolidine-bisoxindole derivatives has been accomplished by three-component, 1,3-dipolar cycloaddition reaction using ionic liquid (Scheme 41).\textsuperscript{65} In related study, Xie et al. has done similar reaction by using methanol and Et\textsubscript{3}N.\textsuperscript{66}

\begin{equation}
\text{Scheme 41}
\end{equation}

The 1,3-dipolar cycloaddition of 1-allyl-5-haloisatin derivatives as dipolarophiles with the azomethine ylides produced from \textit{N}-allyl isatin and L-proline to provide novel dispiro-oxindoles has been studied (Scheme 42).\textsuperscript{67}
**Introduction**

**Scheme 42**
A simple, facile and novel reaction for the synthesis of spiro-frameworks containing spiropiperidine rings from cyclic ketones such as isatin, ninhydrin, acenaphthene quinone and indeno[1,2-b]quinoxalin-11-one (Scheme 43).

**Scheme 43**
A method for highly efficient and diastereoselective reaction between 3-isothio cyanato oxindoles and isatins/isatinimines has been developed to afford structurally varied dispiro[oxazolidine-2-thione]bisoxindoles and dispiro[imidazoleidine-2-thione]bisoxindoles in excellent results under mild conditions (Scheme 44).
In additional study, the dipolarophiles, \((E)-2-(arylmethylidene)-3,4\text{-dihydro}-1(2H)\text{-acridinones}\), prepared by the base-catalyzed condensation of 3,4-dihydroacridin-1(2H)-one with substituted benzaldehydes, readily reacted with nonstabilized azomethine ylides to afford dispirooxindolyl-[acridine-2',3-pyrrolidine]-10-ones (Scheme 45).\(^70\)

Catalyst free 1,3-dipolar cycloaddition reactions of azomethine ylides to 5-benzylidenethiazolidine-2,4-dione promoted by ultrasound has been reported.\(^71\) Application of sarcosine and proline in this reaction was also investigated.\(^72\) The synthesized compounds were screened for their anti diabetic activity on male Wistar rats (Scheme 46).\(^73\)

Lu and his co-workers developed an efficient protocol for synthesis of the functionalized dispirocyclopentyl-3,3'-bisoxindoles with two oxindole units at 1,2-positions of the newly formed cyclopentyl ring. The cyclization reaction of two molecules of 3-phenacylideneoxindoles and nitromethane with refluxed ethanol in the presence of DBU.
as base gave 49-86% yield. The advantage of this reaction is that readily available starting materials, operational simplicity, and high diastereo selectivity (Scheme 47).\textsuperscript{74}

\begin{center}
\begin{tikzpicture}
\draw (0,0) node[anchor=base] \includegraphics[width=\textwidth]{scheme47.png};
\end{tikzpicture}
\end{center}

**Scheme 47**

A facile synthesis of dispirooxindolopyrrolidines has been accomplished by Almansour and his coworkers through a one-pot three component 1,3-dipolar cycloaddition reaction. The azomethine ylides generated in situ from L-phenyl alanine and substituted isatins. A series of (E)-2-oxoindolino-3-ylidene acetophenone dipolarophiles in the ionic liquid 1-butyl-3-methylimidazolium bromide [bmim]BF\textsubscript{4}, equipped the cycloadducts in high yields, with the regioisomers were obtained with high selectivity. Additionally, beneficial thing is the recyclability of [bmim]BF\textsubscript{4}, up to five times (Scheme 48).\textsuperscript{75}

\begin{center}
\begin{tikzpicture}
\draw (0,0) node[anchor=base] \includegraphics[width=\textwidth]{scheme48.png};
\end{tikzpicture}
\end{center}

**Scheme 48**

With the aim to develop new potent antitubercular agents, Mhiri and coworkers designed a series of novel dispirooxindolopyrrolidines and dispirooxindolo pyrrolothiazoles. The compounds have been synthesized via a three-component 1,3-dipolar cycloaddition of (Z)-3-arylidenebenzofuran-2-ones, isatin derivatives and α-aminoacids. The stereochemistry of the spiro adducts has been established by an X-ray diffraction analysis. All the targeted compounds were evaluated for their in vitro antitubercular activity against *Mycobacterium tuberculosis* H\textsubscript{37}Rv strain. The most active compounds were subjected to cytotoxicity studies against (RAW 264.7) cell lines. Among them, twelve compounds indicated potent anti-tubercular activity with good MIC values. This is
the first report which demonstrated the benzofuranone oxindole hybrids as potential antimycobacterial agents (Scheme 49).\textsuperscript{76}

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_49.png}
\caption{Scheme 49}
\end{figure}
\end{center}

1.3.3 Synthesis of Trispiroheterocycles

Li and co-workers investigated the synthesis of novel dispiropyrrrolidines via azomethine ylide cycloaddition to 1-benzyl-3,5-diarylmethylidene-4-piperidinone and subsequent cycloaddition with nitrile oxide to obtain novel tri-spiro heterocycles (Scheme 50).\textsuperscript{77}

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_50.png}
\caption{Scheme 50}
\end{figure}
\end{center}

2,5-Bis (arylmethylidene)-cyclopentanones as dipolarophiles have been used for the synthesis of novel dispiro oxindole/pyrrolidines in moderate yields. Further cycloaddition of dispiro with nitrile oxide afforded trispiro with high regio and stereoselectivity (Scheme 51).\textsuperscript{78}

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_51.png}
\caption{Scheme 51}
\end{figure}
\end{center}

1.3.4 Synthesis of Tetraspiroheterocycles

The facile synthesis of tetraspiro-bisoxindolopyrrolidine derivatives in a highly region and stereoselective manner through 1,3-dipolar cycloaddition of bis-dipolaro philes with the 1,3-dipole generated from isatin and sarcosine has been reported (Scheme 52).\textsuperscript{79}
1.4 Aim of Present Work

Many efforts have been focused on the synthesis of spiro heterocyclic compounds as antimicrobial agent. This inspired us to synthesize and to identify the most active spiro heterocyclic compounds. Our continued interest in identifying novel potent and safe antimicrobial agents led us to synthesis a new series of antimicrobial agents. By using computational study, we aim to predict the *in silico* activity of number of synthesized ligands and the chemistry behind receptor-ligand interactions. The compounds thus identified as potent antimicrobial agent can stand as effective drug candidates for further exploration as future drug development.

1.5 References


