1.1: Introduction

Isatin (1-*H*-indole-2,3-dione), **Figure1.1,** is a well-known natural product found in plants of genus Isatis and in Couropita guianancis aubl (Bergman *et al.* 1985;Da Silva *et al.* 2001). It has also been isolated as a metabolic derivative of adrenaline in humans (Erdmann 1840;Laurent 1840). It was first obtained by Erdmannand Laurent as an oxidation product of indigo in the early 19th century, and its current structure was proposed by Kekule (Kekulé 1869). Isatin and its derivatives possess a broad range of biological and pharmacological properties and are widely used as starting materials for the synthesis of a broad range of heterocyclic compounds and as substrates for drug synthesis.

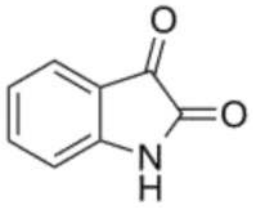
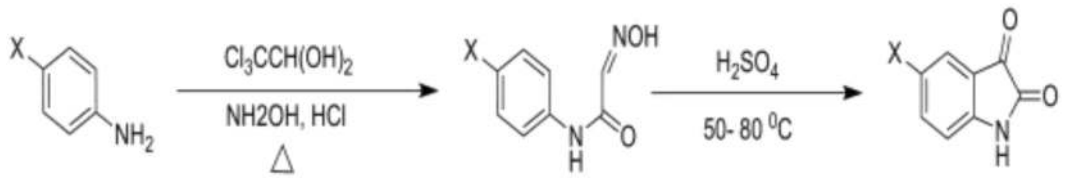


Figure 1.1: Isatin

Formerly, the study of isatin derivatives was connected with dye synthesis, but more recently these heterocycles have been shown to demonstrate antiprotozoal, antibacterial, antifungal, antiviral, anti-HIV, anticonvulsant, antitumoral, anti-inflammatory and antihelminthic activities. It also influence neurodegenerative diseases, participate in metabolism, acetylcholinesterase inhibitors, and stimulate the growth of plants (Da Silva *et al.* 2001). Drugs containing the isatin skeleton are used to treat diseases such as epilepsy (Pandeya *et al.* 2002b),tuberculosis (Pandeya *et al.* 2001), and bulimia (Brewerton *et al.* 1995). Therefore the need to create novel isatin derivatives for emerging drug targets is an active area in medicinal chemistry.

1.2: Synthesis of Isatin

Isatin was first synthesized by Sandmeyer (Al Maamari 2013;Alam *et al.* 1989;Jnaneshwara *et al.* 1999) by the reaction of substituted aniline derivatives with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate through isonitrosoacetanilide intermediate **(Scheme1.2.1).**



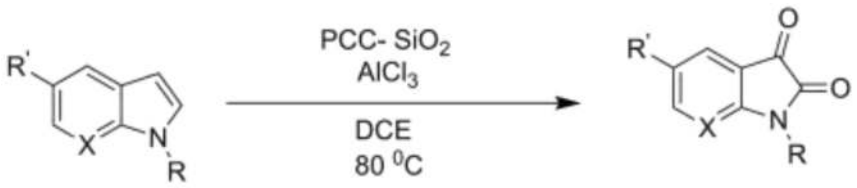
Scheme 1.2.1

In Stolle method, *N*-substituted anilines are allowed to react with oxalyl chloride to form an intermediate chlorooxalylanilide which can be cyclized in the presence of Lewis acids (Fukuda *et al.* 1994;Stolle *et al.* 1922). This method has been used for the synthesis of 1-arylisatin (Bryant III *et al.* 1993;Hashiba *et al.*) and polycyclic isatins derived from phenoxazine, phenothiazine and dibenzoazepineas well as indoline (Welstead Jr *et al.* 1979).

Raj et al, (Raj *et al.* 2010) demonstrates that H-β zeolite is superior catalyst as compared to homogeneous Lewis acid catalysts like $SnCl_4$ and $BF_3.Et_2O$. The procedure requires simple filtration of the catalyst and evaporation of the solvent to obtain good yields of isatins. Klein (Klein and Tufano 2013) used the Stole's procedure for the synthesis of isatin but in a different way. In this method "(E)-2-((benzyloxy) imino) acetyl chloride" was first synthesized by treatment of benzyloximinoacetic acid with oxalyl chloride. This on reaction with aniline in the presence of bases such as triethylamine or diisopropylethylamine in common organic solvents (dichloromethane, tetrahydrofuran) followed by heating in methanesulfonic acid results isatin in good yield.

Synthesis of isatin by Gassman (Gassman *et al.* 1977;Gassman and Van Bergen 1974) involves conversion of substituted anilines into 3-methylthiooxindoles, which upon subsequent oxidation give the corresponding substituted isatins.

Recently, a simple and efficient method was described for the oxidation of 7-azaindoles and indoles to 7-azaisatins and isatins using pyridinium chlorochromate-silica gel (PCC-SiO_2) with the aid of $AlCl_3$ in dichloroethane in good yields (**Scheme 1.2.2**) (Sriram *et al.* 2012).



Scheme 1.2.2

Besides these well known methods, some other methods are also reported for the synthesis of isatin (BCG 2008;Hewawasam and Meanwell 1994;Khan *et al.* 2000;Mattsson *et al.* 2012;Parrick *et al.* 1984;Söderberg *et al.* 2009;Tang *et al.* 2010).

1.3: Chemical reactivity of isatin

The cumulative efforts carried out in the area of isatin chemistry have culminated in the publication of a number of reviews (Ball-Jones *et al.* 2012;Borad *et al.* 2014a;b;Da Silva *et al.* 2001;Flores *et al.* 2013;Khanna *et al.* 2014;Lashgari and Ziarani 2012;Liu *et al.* 2013;Pakravan *et al.* 2013;Popp 1975;Singh and Desta 2012;Sumpter 1944;Xia and Ma 2014;Ziarani *et al.* 2016). These reviews have nicely discussed the versatility of isatin in organic synthesis. Some general trends of isatin reactions are described as follows.

Isatin mainly reacts at three different sites, *N*-alkylation, aromatic substitution at benzene ring, and carbonyl group reactions (**Figure 1.3.1).**

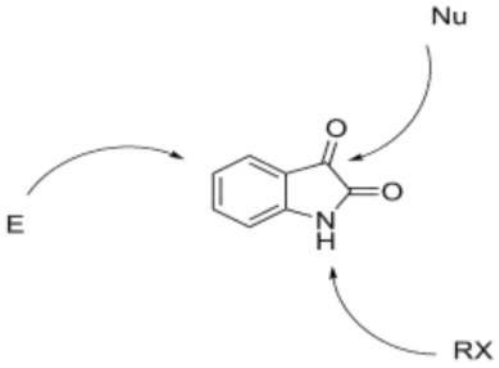


Figure 1.3.1: Chemical reactivity of isatin

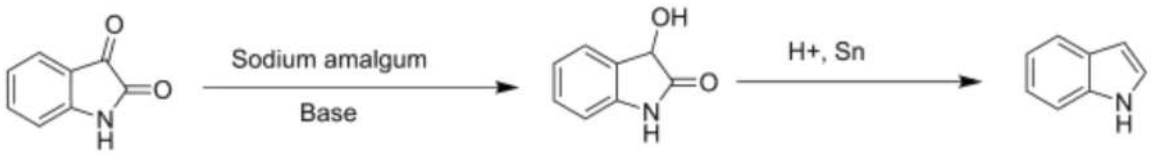
Isatin also undergoes reduction and oxidation recations and results indole and isatoic anhydride respectively. All these types of rections are discussed below in more detail.

1.3.1: Reduction

The reduction of isatins with lithium aluminum hydride in pyridine gives indoles in moderate yields. However, the use of THF as a solvent under an inert atmosphere give greater yields and this procedure is applied to the synthesis of substituted ellipticine derivatives (Menicagli *et al.* 1977).

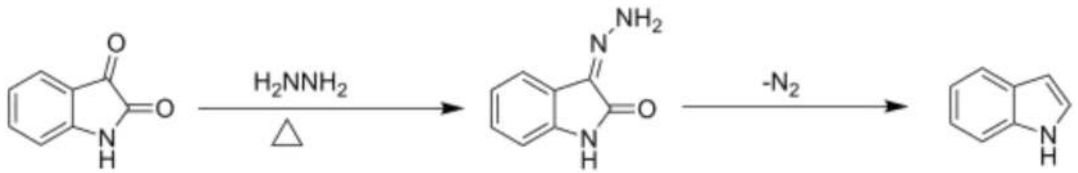
N-Acetylisatins (Pinto *et al.* 1994) were suitable substrates for the synthesis of *N*-alkylindoles under mild reaction conditions. Indoles have also been prepared in good yield from *N*-substituted-5-nitroisatin using the $ZnCl_4/NaBH_4$ system in DME at room temperature. But the direct reduction of 5-nitro-isatin produces the desired 5-nitroindole in only 30% yield (Torisawa *et al.* 2001).

Dioxindoles are obtained from isatins by reduction or by carbanion addition at the C-3 carbonyl functionality. The reduction of isatin to dioxindoles are carried out by $Zn/HgCl_2$ in refluxing benzene and Fe/HCl in aqueous ethanol (Al Maamari 2013) as well as electrochemical and photochemical (Tatsugi *et al.* 1996) reduction. *N*-Methylisatin is reduced to the corresponding dioxindole in quantitative yield by reaction with potassium tetracarbonylhydridoferrate [$KHFe(CO)_4$] (Brunet *et al.* 1994). Oxindoles can be prepared by the reduction of either dioxindoles or isatins. The reductions have been performed by using red phosphorous & iodic acid (Al Maamari 2013), H_2S in a pyridine/co-solvent mixture or by the Wolf-Kishner reaction (Kuo *et al.* 1999) in presence of ethanol or iso-propanol, lead to high yields of the desired product. The first reported synthesis of oxindole was by Baeyer (von Baeyer *et al.* 1905) and involved the reduction of isatin in a two step process using sodium amalgam and base to initially form an intermediate 3-hydroxy-indolinone. This hydroxyl indolinone was then further reduced under acidic conditions in the presence of tin to afford oxindole **(Scheme 1.3.1.1)**.



Scheme 1.3.1.1

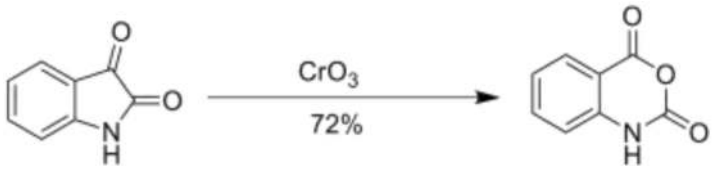
Hydrazones of α-dicarbonyl compounds may be decomposed under relatively mild conditions. Crestini (Crestini and Saladino 1994) devised a one-pot Wolff-Kishner reduction of isatins by refluxing the isatins in 98% hydrazine hydrate for 15-30 min without isolation of the intermediate hydrazones **(Scheme1.3.1.2)**.



Scheme 1.3.1.2

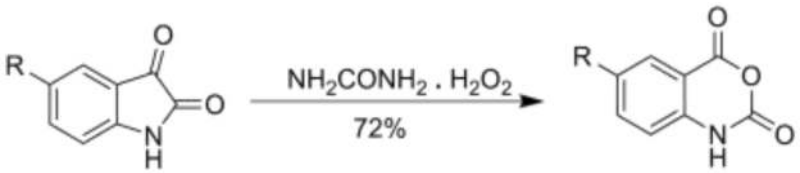
1.3.2: Oxidation

Oxidation of isatin to isatoic anhydride, the oxidizing agent selected should be able to introduce an oxygen atom between the two adjacent carbonyl groups without substantial decomposition of the ring system. Several reagents have been successfully used in the process, mainly peracids, and have been reviewed in the oxidation of isatins (Coppola 1980;Da Silva *et al.* 2001)**(Scheme 1.3.2.1)**.



Scheme 1.3.2.1

A novel, cheap and environmentally friendly synthetic procedure for the oxidation of isatin derivatives has been developed by the use of the urea–hydrogen peroxide complex (Taliansky 2005) **(Scheme 1.3.2.2).**



Scheme 1.3.2.2

1.3.3: Electrophilic Aromatic Substitution of Isatin

Nitration of isatin at the C-5 position with fuming nitric acid in concentrated sulfuric acid (Calvery *et al.* 1925) was reported in 1925. However, a more

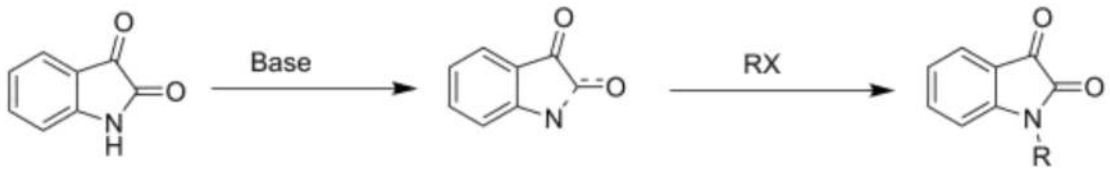
convenient method to synthesize 5-nitroisatin involves the dropwise addition of a solution of isatin in sulfuric acid to a solution of potassium nitrate dissolved in concentrated sulfuric acid at 0-4ºC. The isatin so obtained was isolated, as bright yellow/orange crystals with a melting point of 252-254 ºC (Vine *et al.* 2007).

The chlorination of isatin at the C-5 position has been described using *N*-chloroamides, *N*-chloroimides, *N*-chlorosaccharins in a heterogenous medium (SiO_2/CH_2Cl_2) (de Souza *et al.* 2003) and also using the relatively stable reagent trichloroisocyanuric acid (TICA). Isomeric 7-chloroisatin was detected in the crude reaction product by HRGC (high-resolution gas chromatography). It is believed that the strongly acid medium promotes the formation of a super electrophilic species wherein TICA being either polyprotonated or protosolvated causes the "Cl^+" transfer to isatin more efficiently due to the charge-charge repulsion relief.

Mono-halogenation (-Cl, -I, -Br) of isatin can be achieved by reacting *N*-halosaccharins with isatin in the presence of SiO_2 at room temprature to produce the *5*-halo derivatives (de Souza *et al.* 2003). This method is an alternative to the use of highly toxic and corrosive Cl_2 and Br_2, which lead to other products such as 5,7-dibromo-3,3-dialkoxyoxindole when the bromination of isatin is attempted in alcoholic media (Lindwall *et al.* 1931).

1.3.4: *N*- substitution at isatin

Many methods have been developed for the *N*-substitution of isatins. *N*- alkyl isatin derivatives are commonly synthesized from the reaction of the sodium salt of isatin with alkyl halides or sulphates.Various methods have been used for the preparation of *N*-alkyl isatins which can be successfully achieved using alkyl iodides, bromides and chlorides as well as reactive allyl-, benzyl-, and propargyl halides with any variety of base such as Na_2CO_3 , K_2CO_3, Cs_2CO_3, LiH , NaH , CaH_2, TEA , LiOH, NaOEt and solvent (DMF, DMA, HMPT, MeCN, DMSO, NMP, EtOH, MeOH, Me_2CO) (Bridges *et al.* 2009;Majumdar *et al.* 1996;Rekhter 2005;Shmidt *et al.* 2008)(**Scheme 1.3.4.1**).



Scheme 1.3.4.1

N-Arylisatin can be obtained from isatin in quantitative yields by reaction with Ph3Bi(OAc)$_2$ and Cu (0) under an inert atmosphere (Da Silva *et al.* 2001) or from aryl bromides and cupric oxide (Coppola 1987). The Mannich reaction is readily applied to isatins. The *N*-aminomethylisatins (Mannich bases), can be obtained from the *N*- hydroxymethyl derivatives by reaction with an amine or by reaction with acetyl chloride to yield *N*-chloromethylisatin which can be further treated with potassium phthalimide or an alcohol to give the corresponding *N*-phthalimidomethyl or *N*-alkoxymethyl isatins. The Mannich reaction can be performed with isatin derivatives, such as isatin-3- hydrazones (Varma *et al.* 1985) and isatin-3-thiosemicarbazones (Gupta and Narayana 1997).

The synthesis of *N*-acylisatins under a variety of conditions has been described using acyl chlorides or anhydrides under reflux. The reaction may be performed without additives (Pinto *et al.* 1994) or by using perchloric acid in benzene, triethylamine in benzene (Tomchin *et al.* 1986), pyridine in benzene (Black *et al.* 1994), or triethylamine in chloroform (Da Silva *et al.* 2001) as catalysts; or by conversion of isatin to sodium isatide using NaH in toluene under reflux and subsequent reaction with acyl chlorides (Radul *et al.* 1983).

N- Sulfonylisatins are obtained from the reaction of isatin and sulfonyl chlorides by applying the same methodologies as used for obtaining 1-acylisatins. For example, 1-tosylisatin is formed in 71-74% yield by mixing tosyl chloride with isatin in the presence of Et_3N or with the sodium salt of isatin (Tomchin and Krylova 1986).

The treatment of isatin with sodium hypochlorite in acetic acid leads to 1-chloroisatin, an effective mild oxidizing agent for the conversion of alcohols to aldehydes and ketones (Berti and Greci 1981) and of indoles to 3-chloroindoles without formation of by-products (Berti *et al.* 1982). *N*-[phenyliodine (III)] *bis*-

isatin can be obtained from the sodium salt of isatin and phenyliodine (III) *bis*-trifluoroacetate in excellent yield.

1.3.5: Reactivity due to the carbonyl group of isatin

Isatins and its derivatives can undergo nucleophilic attack at positions C-2 and/or C-3 carbonyl group. The chemoselectivity of these reactions depends on the nature of the nucleophile as well as the nature of the substituents attached to the isatin nucleus and especially of those bonded to the nitrogen atom, as well as upon the solvent and temperature employed. The initial products obtained can suffer further reaction in the presence of a second nucleophilic group in order to give cyclization products.

1.3.5.1: Reactivity of C-3 carbonyl group of isatin

The most attractive application of isatin and its derivatives in organic synthesis is due to the highly reactive C-3 carbonyl group that is a prochiral center as well. The reactions at C-3 carbonyl group of isatins, mostly by nucleophilic additions or spiroannulation transform it into 2-oxindole derivatives (**Figure 1.3.5.1.1**).

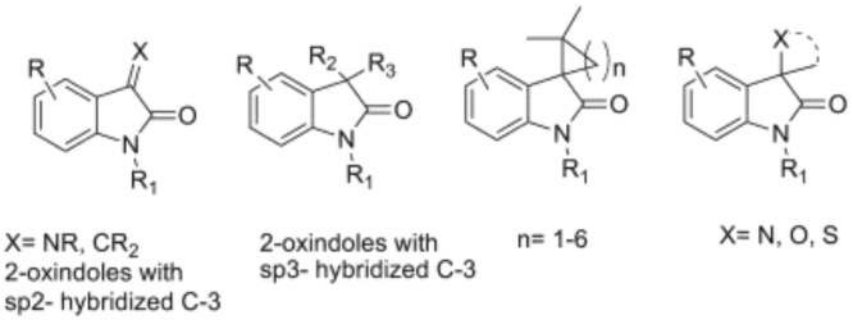
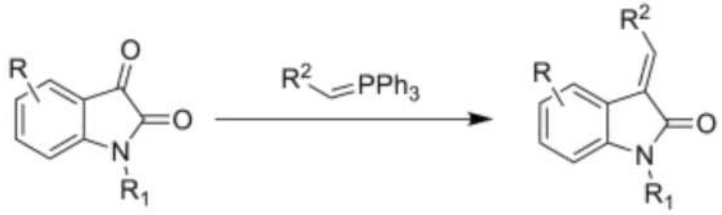


Figure 1.3.5.1.1: 2-oxindole derivatives of isatin

2-Oxindoles, especially those which are spiro-fused to other cyclic frameworks (**Figure 1.3.5.1.1**), have drawn remarkable interest of scientists and researchers in the area of synthetic organic chemistry and medicinal chemistry worldwide because they occur in many natural products and have been reported to possess various types of bioactivity (Badillo *et al.* 2010) such as progesterone receptor modulators (Fensome *et al.* 2008), anti-HIV (Kumari *et al.* 2011), anticancer

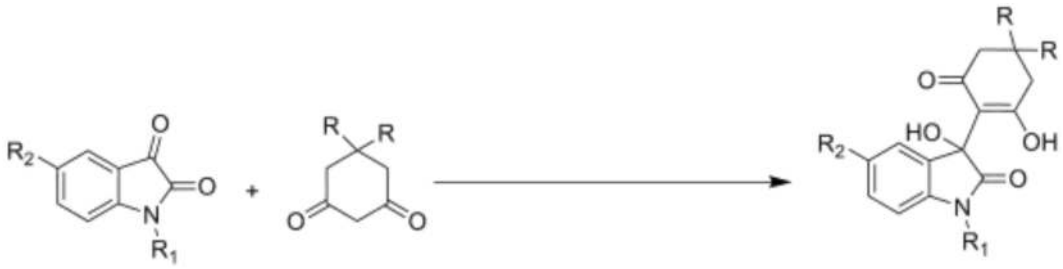
(Ding *et al.* 2005;Lo *et al.* 2004), antitubercular (Vintonyak *et al.* 2010), antimalarial (Rottmann *et al.* 2010;Yeung *et al.* 2010;Zhang 2008), and MDM2 inhibitor (Ding *et al.* 2006). The synthetic endeavors to C-3 functionalized 2-oxindoles from isatins exploit the reactivity of the C-3 carbonyl group in isatins with nucleophiles. Some of the well-known reactions include the condensation reactions of the ketone carbonyl group with nitrogen nucleophiles such as amines, hydrazines, semicarbazides, and thiosemicarbazides forming the imines (Khan *et al.* 2008;Piceirilli and Popp 1973), hydrazones (Sridhar *et al.* 2002), semicarbazones (Pandeya *et al.* 2002a), and thiosemicarbazones (Pervez *et al.* 2007) respectively even in the absence of any catalyst either at room temperature or by heating for few hours. Isatin-3-imines and isatin-3-hydrazones are reported to furnish quaternary 3-aminooxindoles by allylation and propargylation under the influence of indium and zinc catalysts respectively in aqueous media (Alcaide *et al.* 2010).

The addition of alkynes to *N*-tert-butylsulfinylimine of isatins is reported through dialkylzinc (Yan *et al.* 2012). The Mannich reaction of *N*-protected isatin-3-imines with hydroxyacetone in the presence of a chiral primary amino acid catalyst is reported to yield 3- amino-2-oxindoles (Guo *et al.* 2012;Shi *et al.* 2012). The carbon analogs of the 3-azomethine-2-oxindoles, 3-alkylidene-2-oxindoles are synthesized by Witting reaction of isatins with an appropriate Wittig reagent (**Scheme 1.3.5.1.1**) and reactions of isatins with active methylene compounds.



Scheme 1.3.5.1.1

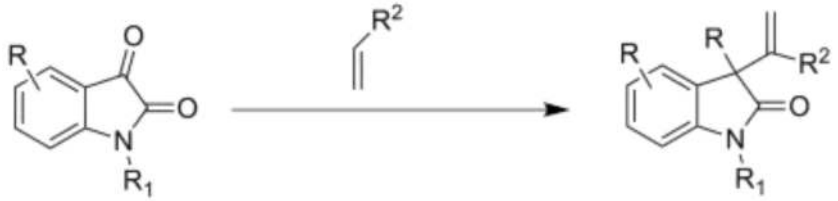
The aldol reactions of isatins with cyclic 1, 3-diketones either chemically or electrochemically afford 3-substituted 3-hydroxy-2-oxindoles (Aikawa *et al.* 2011;Elinson *et al.* 2010;Liu *et al.* 2011) **(Scheme 1.3.5.1.2).**



Scheme 1.3.5.1.2

The aldol reactions of isatins have stereochemical implications because they transform C-3 carbonyl carbon into a chiral center, and hence efforts have been made to carry out the reaction enantioselectively. There are many examples of enantioselective organocatalytic aldol reaction of isatins with in activated carbonyl compounds (Allu *et al.* 2011;Chen *et al.* 2010b;Feng *et al.* 2012;Peng *et al.* 2011). Isatins undergo the nitro-aldol reaction with nitromethane in the presence of diethylamine as a catalyst to form 3-hydroxy-3-nitromethyl-2- oxindoles (Chen *et al.* 2010a).

Isatins have been used as electrophilic components for the Morita-Baylis-Hillman reaction as well (Basavaiah *et al.* 2003). Isatin itself as well as *N*-substituted isatins react with activated alkenes in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to yield an adduct (**Scheme 1.3.5.1.3**) (Basavaiah and Rao 2003;Chung *et al.* 2002;Garden and Skakle 2002).



Scheme 1.3.5.1.3

A palladium-catalyzed asymmetric allylation of isatins using allyl alcohols has been reported in the presence of a new class of phosphorimidite ligand (Qiao *et al.* 2009). The reaction, applicable to differently substituted isatins and allyl alcohols, afforded products in excellent yields but moderate enantioselectivity. An Iridium-catalyzed transfer hydrogenation approach for allylation, crotylation, and reverse prenylation reactions of isatins is reported using allyl acetate reagents or 1,1-

dimethylallene as precursors for transient allyl-metal intermediates (Itoh *et al.* 2009). The reverse prenylation of isatins with 1, 1-dimethylallene afforded products in good yields and with good enantioselectivity (**Scheme 1.3.5.1.4**). This method does not necessarily require stoichiometric quantities of allyl metal reagents, but some complex mixtures of additives are required.

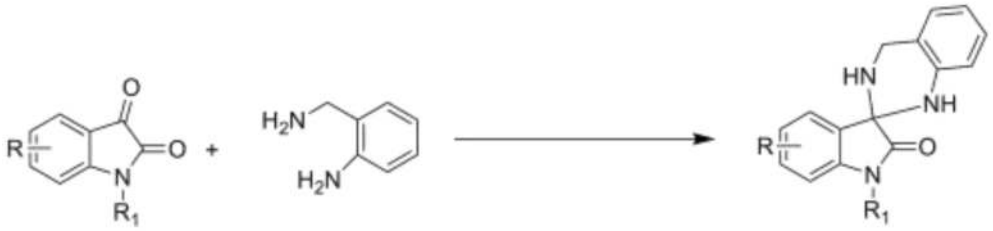
Scheme 1.3.5.1.4

1.3.5.2: Synthesis of isatin based spiro-fused heterocyclic scaffolds

Isatins and its C-3 derivatives have been employed in the synthesis of different types of spiro-heterocyclic moieties bearing 2-oxindoles. In many cases, such compounds are synthesized directly from isatins either by cyclocondensation or cycloaddition reactions with other reagents. Recently, multicomponent cascade reactions of isatins have been employed which lead to an easy and convenient one-pot synthesis of spiro-heterocyclic frameworks. In many instances, the synthesis of the target spiro-heterocycle, however, is accomplished via a simple C-3 derivative of isatins such as alkylideneisatins, isatinimines, isatin hydrazones, Baylis-Hillman adducts of isatins, aldol-adducts of isatins etc. Novel asymmetric synthesis using chiral metal-complexes, chiral organocatalysts, and chiral auxiliaries furnishing complex molecules in an enantioselective manner have been developed.

The reactions of ammonia, 1,2-diamines, and 1,3-diamines with isatins have been reported to furnish the five- or six-membered spiro-azaheterocycles (Wang and Wu 2011). The reaction of isatin with *N,N*-dimethylethylenediamine in water afforded the spiro-*N,N*-dimethylimidazolidine-oxindole (Bergman *et al.* 1997). The reaction of isatins with 2-aminobenzylamine in methanol at room temperature

led to the formation of spiro-tetrahydroquinazoline-oxindoles products (**Scheme 1.3.5.2.1**) (Bergman *et al.* 2003).



Scheme 1.3.5.2.1

It has been reported that the condensation of isatins with 2-aminobenzylamine afforded a good yield of spiro-fused 2-oxindole in acetic acid and only trace amounts in refluxing methanol (Cui *et al.* 1996a;b;Niume *et al.* 1982). However spiro-dihydroimidazole-oxindoles was reported by the reactions of *N*-acylisatins with *o*-phenylenediamine and 2,3-diaminopyridine in acetic acid and ethanol (Joshi *et al.* 1984).The cyclocondensation of isatin with a heterocyclic 1, 2-diamine and 3, 4-diaminofurazane on refluxing in acetonitrile afforded the spiro-1, 2, -oxadiazoloimidazolidine-oxindole (Leong *et al.* 2014). The reaction of isatins with 2-nitrobenzamides in the presence of tin(II) chloride is reported to afford the spiroquinazolinone-oxindoles (Hu *et al.* 2011). While these products were reported earlier by a three-component reaction of isatins, amines and isatoic anhydride (Mohammadi *et al.* 2009).There action of isatin with ethylene glycols has been reported to form the spiro-dioxolane-oxindoles under both homogeneous and heterogeneous catalysis employing the strongly acidic resin Dowex 50X-X2 (Ribeiro *et al.* 2007). The solvent-free preparations of spiro-dioxolaneoxindoles in high yields from isatin and 5-chloroisatin using the Keggin's heteropolyacids, namely, heteropolyphosphotungsticacid (HPW), HPW/SiO_2, and Cs_2.2HPW are reported (dos Santos *et al.* 2008).

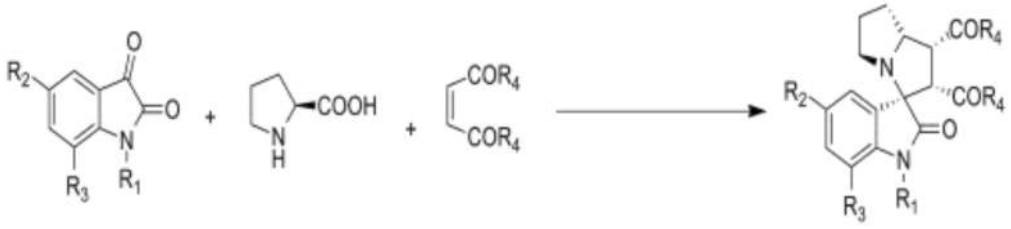
The reactions of isatins with 2-aminothiophenol have been observed to afford the spiro-benzothazoline-oxindoles in varying yields depending on the substituent at the nitrogen atom of isatin ring and reaction conditions (Dandia *et al.* 1990).

The condensation of β-arylethylamines such as tryptamine with aldehydes under acidic conditions followed by cyclization to afford the β-tetrahydrocarbolines is

well-known as the Pictet-Spengler reaction (Pictet and Spengler 1911;Whaley and Govindachari 1951). Furthermore, an increase in amine chain length allows access to seven- and eight-membered spiroazaheterocycles such as spiro-tetrahydroazepine-oxindoles and spiro-hexahydroazocene-oxindoles though in diminished yields. For example, the reaction of 5-chloroisatin with 4-indol-(3-yl)-1-butanamine affords the spiro-hexahydroazoceneoxindole in 8% yield.

Condensation reaction between isatin and α- amino acid derivatives in the presence of methanol and water to form azomethine ylides followed by the 1,3-dipolar addition of the dipolarophiles yields the pyrrolidine-2-spiro-3-(2-oxindole) (Rehn *et al.* 2004).

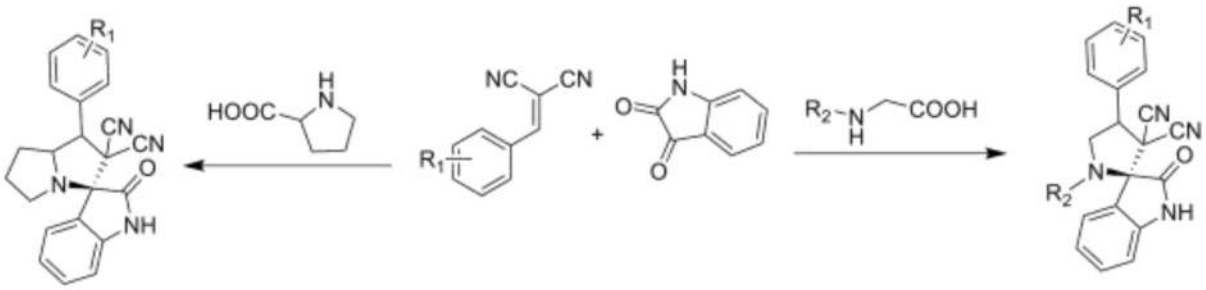
Two ester groups or two amide groups containing spiropyrrolizidine oxindoles have been synthesized and reported by using Maleates or maleamides as dipolarophiles (**Scheme 1.3.5.2.2**) (Xie *et al.* 2011).



Scheme 1.3.5.2.2

The stereoselective reaction between oxindole, aldehyde in the presence of modified proline catalyst and benzoic acid, resulting in the final spiro compound in very good yields with excellent stereoselectivities (Companyó *et al.* 2010). Chen and coworkers testified their new findings in the 1, 3-dipolar cycloaddition reactions of isatin, α-amino acids, and (E)-b-nitro-styrene, which showed different regioselectivity (Chen *et al.* 2012).

The reaction of various arylidenemalononitrile Knoevenagel adducts with non stabilized azomethine ylides, which were produced from isatin and α-aminoacids, resulting in novel dicyano-functionalized spiropyrrolidine and spiropyrrolizidine, was carried out using conventional heating as well as ultrasonic irradiation conditions (**Scheme 1.3.5.2.3**) (Rezaei *et al.* 2011).



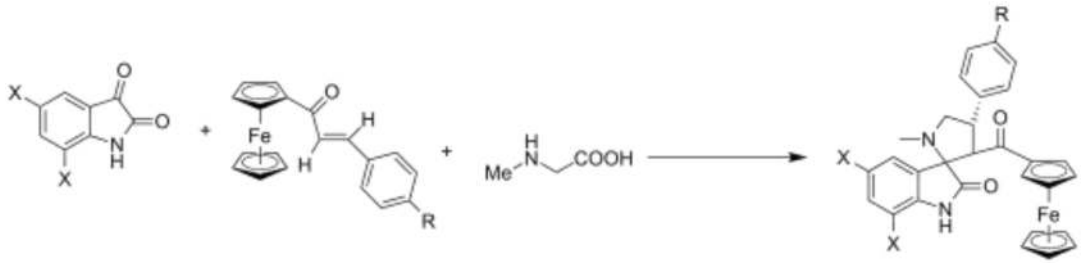
Scheme 1.3.5.2.3

The Knoevenagel condensation reaction between isatin derivatives and active methylene formed 3-cyanomethylidene oxindole derivatives in very good yields by utilizing 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) catalyst. Further DBU-promoted Michael addition reaction of 3-cyanomethylidene oxindolederivatives with azaenamine yields spiro cyclic 2-oxindole derivatives of 6-amino-4*H*-pyridazine and fused derivatives via [3+3] atom combination reaction (Abdelhamid *et al.* 2009).

A well-organized method for the synthesis of some fused spiro[4*H*pyran-oxindole] heterocycles by means of multicomponent one-pot reactions(MCR) of isatin, malononitrile or ethyl cyano-acetate and 1, 3-dicarbonylcompounds was reported by making use of [BMIm]BF4 as an ionic liquid catalyst (Rad-Moghadam and Youseftabar-Miri 2011).

The synthesis of 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 have been developed via one-pot, three-component (MCR) approach involving substituted isatins, active methylene and 2-thioxo-4-thiazolidinone under conventional heating as well as microwave irradiation using NIO nanoparticle as a catalyst (Sachdeva *et al.* 2012).

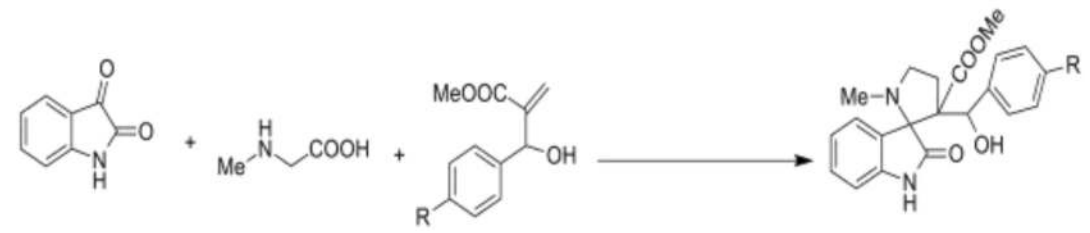
[3+2]-Cycloaddition reaction of several azomethine ylide derived from various derivatives of isatins and α-amino acid (proline, sarcosine) with various unusual ferrocene derivatives as dipolarophilic partners resulted in the formation of novel ferrocenylmonospirooxindolo pyrrolidines in good yield (**Scheme 1.3.5.2.4**) (Babu *et al.* 2012;Babu and Raghunathan 2008;Babu *et al.* 2009).



Scheme 1.3.5.2.4

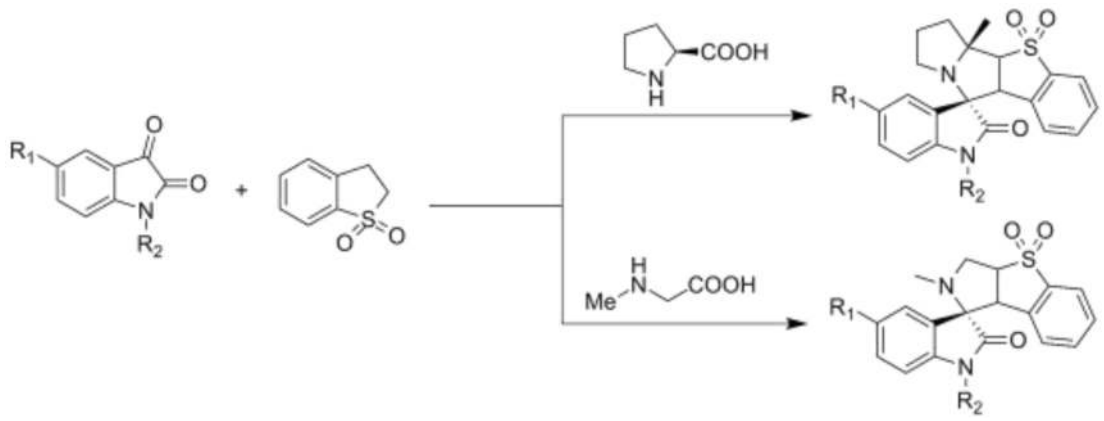
A multicomponent [3+2] cycloaddition reaction of isatin, amino acids, aldehydes, and 3-cyanoacetyl indoles was also reported (Zhao *et al.* 2010). Fluorinated spiro[3*H*-indole-3,2'-tetrahydro-1,3-thiazine]-2,4'(1*H*)-diones and fluorinated spiro[3*H*-indole-3,2'-thiazolidine]-2,4' (1*H*)-diones was synthesized in good yield by one-pot ecologically friendly microwave irradiation using bronsted acidic ionic liquid such as 1-methylimidazolium, 1-butyl-3-methylimidazolium and BF_4, PF_6, and PTSA as catalysts (Arya *et al.* 2012a). Spiro[3*H*-indole-3,2'-[4*H*]pyrido[3,2-e]-1,3-thiazine]-2,4'(1*H*) diones can be prepared by treatment of *in situ* generated 3-indolylimine derivatives with 2-mercaptonicotinic acid under ultrasonication in the presence of a zeolite- supported Brønsted acid catalyst (Arya *et al.* 2012b).

A novel, simple, and efficient synthetic procedure has been developed for the synthesis of spiro[indoline-3,4'-pyrazolo[3,4-e][1,4]thiazepine]diones by using bioglycerol-based sulfonic acid functionalized carbon as a recyclable catalyst from isatin, 5-amino-3-methyl-1-phenyl pyrazole, and 2-mercapto acetic acid in MeCN as a model reaction (Karnakar *et al.* 2012). In a related study, Chen and Shi synthesized the same spiro compound without use of catalyst (Chen and Shi 2011).The synthesis of indole derivative based spiro compound by reaction of indole-2,3-diones and *o*-aminothiophenol using tetrabutylammonium (TBAB) under aqueous micellar media is an effective, simplistic, and straightforward green procedure (Jain *et al.* 2012a). The cycloaddition reaction of isatin and sarcosine with the olefinic bond of Baylis–Hillman adducts gave the corresponding cycloadducts as single regioisomers (**Scheme 1.3.5.2.5**) (Jayashankaran *et al.* 2006).



Scheme 1.3.5.2.5

In another study multicomponent (MCR) 1,3-dipolar cycloaddition reaction of isatin 1, 1-benzothiophene1,1-dioxide, and sarcosine or L-proline resulted in a series of spirooxindoles containing tri- and tetracyclic fused pyrrolo-benzothiophene1,1-dioxide derivatives and regioselectively (**Scheme 1.3.5.2.6**) (Lakshmi *et al.* 2010).



Scheme 1.3.5.2.6

The synthesis of novel spiro[1,4,2-dioxazole-5,3'-indolin]-2'-one derivatives and was also done by the 1, 3-dipolar cycloaddition reaction of isatin derivatives with the nitrile oxide generated in situ from 4-methoxybenzaldoxime and sodium hypochlorite (Bouhfid *et al.* 2011).

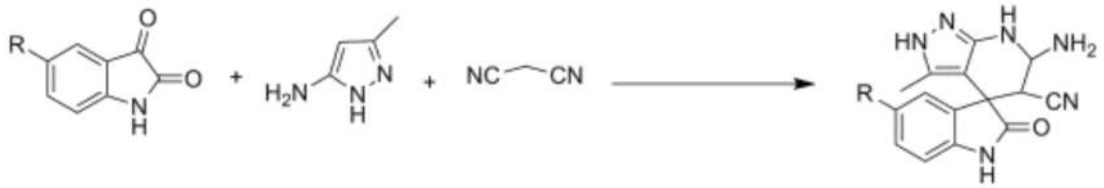
Reaction between α-diazo ketones and isatin in the presence of $Rh_2(OAc)_4$ created a novel spiro dioxa-bridged indole derivatives as a mixture of diastereomers (Muthusamy *et al.* 2003). Isatin with 5-aminoindazole and mercaptoacetic acid gave the desired spiro systems containing three heterocyclic moieties, namely indole, thiazolidine, and indazole (Jain *et al.* 2006). Yavari et al. have designed a very useful one-pot route to spiro[1,3]oxazino[2,3-a] *N*-heterocyclic derivatives in outstanding yields from *N*-heterocycles (isoquinoline, quinolone, orpyridine) and

dialkyl acetylene dicarboxylates(DMAD) in the presence of *N*-alkylisatins or ninhydrin (Yavari *et al.* 2007). While, Nair and coworkers used 1, 2- and 1, 4-benzoquinones instead of *N*-alkyl isatin or ninhydrin (Nair *et al.* 2003). A favorable Huisgen dipolar addition involving isatin, amines, and DMAD to afford spiro lactones was discussed. In a similar study, Kiruthika and coworkers have reported a facile strategy for the synthesis of functionalized spiro lactones and dispirodihydrofuranyl oxindoles in good yield (Kiruthika *et al.* 2012). A well-organized, simple, an atom-efficient and high-yielding preparation of a series of spirodihydropyridines via one-pot, four-component reaction have also been reported (Kiruthika *et al.* 2012).

An efficient procedures were developed for the stereoselective 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, acetylenedicarboxylate, and isatin under different conditions (Han *et al.* 2012b). A green, simple, efficient, one-pot, three-component method for the diversity-oriented synthesis of spiro[indoline-3,4'-thiopyrano[2,3-b]indole] derivatives has been developed by the domino reaction of indoline-2-thione, isatin, and ethyl cyanoacetate or malononitrile in ethanol at 80 ^{0}C for only 20 min (Majumdar *et al.* 2012).

A modern synthesis of some novel unsymmetrical bis-indol-2, 3-diones has been achieved by Jain et al. through 1-(6-bromohexyl)-1*H*-indol-2, 3-diones. These compounds have been further used for the synthesis of novel bis-spiroindoles through hitherto unknown bis Schiff bases (Jain *et al.* 2008).

A direct and creative method for the preparation of therapeutically favorablepyrazolopyridinyl spirooxindoles has been developed through a progressiveone-pot, novel regio- and diastereoselective three-component reaction of isatin, α-cyanoacetic ester or malononitrile, and 5-amino-3-methylpyrazole catalyzed by sodium chloride as green catalyst and water as an ecologically benign reaction medium (**Scheme 1.3.5.2.7**) (Dandia *et al.* 2012).



Scheme 1.3.5.2.7

A facile, one-pot, three-component method for the synthesis of spiro[benzo[h]pyrazolo[3,4-b][1,6]naphthyridine-7,3'-indoline]-2',6(5*H*)-diones and spiro[chromeno[4,3-b]pyrazolo[4,3-e]pyridine-7,3'-indoline]-diones in water was reported with good yield (Ahadi *et al.* 2009).

An efficient, ecofriendly strategy and diversity-oriented three-component synthesis of spiro[pyranopyrazolopyridine-indoline]diones was reported from the condensation of isatin with 4-hydroxy-1,3-dimethyl-1*H*-pyrazolo[3,4-b] pyridine-6(7*H*)-one and malononitrile in the presence of piperidine and water at 30 ^{0}C (Jayarajan and Vasuki 2012).

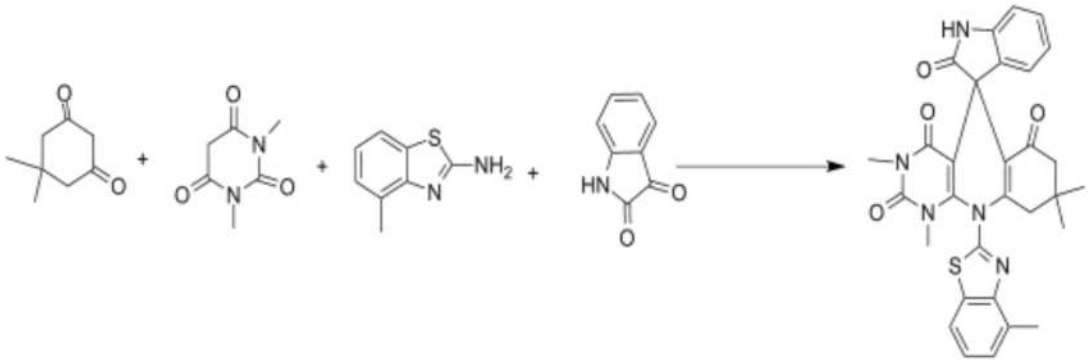
A innovative and efficient one-pot reaction of isatin, 1, 5-amino-3-methylpyrazole and 1, 3-dicarbonyl compounds in aqueous medium has afforded spiro[indoline-3,4'pyrazolo[3,4-b]quinoline]dione, spiro[furo[3,4-e]pyrazolo[3,4-b]pyridine-4,3'-indoline]dione and spiro[indeno[2,1-e]pyrazolo[3,4-b]pyridine-4,3'-indoline]dione derivatives under mild reaction condition (Chen and Shi 2010).

A new ecofriendly four-component domino reaction for the synthesis of spiro[indoline-3,4'-pyrazolo[3,4-b]pyridines covering up to five rings in good to excellent yield was developed from the reactions of phenyl hydrazine, 3-aminocrotononitrile, isatin/ acenaphthylene-1,2-dione, and cyclic 1,3-dicarbonylcompounds in the presence of cellulose sulfuric acid (CSA) in aqueous medium (Balamurugan *et al.* 2011).

A novel, green, one-pot, efficient, three-component condensation reaction of isatin, isoxazole, and barbituric acid in water gives spirooxindoles in good yield at 70 ^{0}C using a catalytic amount of *p*-toluene sulfonic acid (Rahmati and Khalesi 2012).

Ghahremanzadeh and coworkers have invented a one-pot, pseudomulticomponent procedure for the synthesis of spiro[diindenopyridine-indoline]trionesand spiro[acenaphthylene-diindenopyridine]triones through the reaction of 1, 3-indandione, aromatic amines, and isatin or acenaphthylene-1, 2-dione using a‘‘grindstone chemistry’’ method (Ghahremanzadeh *et al.* 2010). While Sun et al. reported a similar reaction using acetone instead of 1,3-indandione (Sun *et al.* 2012).

An efficient and eco-compatible synthetic methodology was developed for the synthesis of structurally diverse spiroheterocycles with fused heterosystems in excellent yield using a halogen-free SO_3H functionalized ionic liquid/ water as recyclable medium under mild reaction conditions (**Scheme 1.3.5.2.8**) (Kumar *et al.* 2012).



Scheme 1.3.5.2.8

An extremely efficient and solvent free method for the synthesis of novel spiro[dibenzo[a,i]-xanthene-14,3’-indoline]-2’,8,13-triones and spironaphtha pyrano[2,3-d]pyrimidine-5,3’-indolines was reported via a one-pot, three component condensation reaction using [Hmim][HSO_4] as an efficient and reusable catalyst (Yang *et al.* 2012).

The reaction of isatin, barbituric acid, and cyclohexane-1, 3-dione derivatives in the presence of K-10 as catalyst for 30 min was found to be a suitable and efficient method for the synthesis of spiro[chromeno[2,3 d]pyrimidine-5,3’-indoline]-tetraones in the presence of ionic liquid media (Moghaddam *et al.* 2010). In a related study, the same reactions have been done by Jadidi et al. by using water in the presence of *p*-TSA (Jadidi *et al.* 2009a).

Deng and coworkers have readily prepared dodecyl benzene sulfonic acid functionalized silica-coated magnetic nanoparticles and identified an efficient catalyst for the synthesis of a library of spirooxindole-pyrimidine derivatives by three-component condensation reaction of barbituric acids, isatin, and cyclohexane1, 3-diones (Deng *et al.* 2012).

An efficient and simple method for the preparation of spiro[pyrimido[4,5-b]quinoline-5,5,-pyrrolo[2,3-d]pyrimidine] and spiro[indolinepyrido[2,3-d:6,5-d']dipyrimidine] derivatives were developed through a cyclocondensation reaction of 2, 6-diaminopyrimidin-4(3*H*)-one and isatin in refluxing ethanol (Jadidi *et al.* 2009b). An efficient, clean, and simple method for the preparation of spiro[indoline-3,4'-pyridine]-3'-carboxylate derivatives using readily available starting materials has been reported (Alizadeh and Mokhtari 2011).

A very efficient synthesis of spirodihydrofuran oxindole derivatives via a [3+2] oxidative cycloaddition reaction was reported (Savitha *et al.* 2007). The [4+2]/ [2+2] cycloaddition reaction of *N*-protected isatin-3-arylimine with acyl ketene derived from a-diazocarbonyl compounds by rhodium (II) catalysis has attained for the first time for the preparation of a novel class of spiro(oxindolyl)oxazinone and spiro(oxindolyl)- β -lactam derivatives (Reddy *et al.* 2012).

The new GAP (group-assisted-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 (Zou *et al.* 2011).

A suitable, efficient, and environmentally friendly synthesis of novel dispiropyrrolidine-bisoxindole derivatives has been accomplished by three-component, 1, 3-dipolar cycloaddition methodology using ionic liquid (Jain *et al.* 2012b). A similar reaction was reported by using methanol and Et_3N (Liu *et al.* 2012).

A method for highly efficient and diastereoselective reaction between 3-isothiocyanatooxindoles and isatins/isatinimines has been developed to afford structurally varied dispiro[oxazolidine-2-thione]bisoxindoles and

dispiro[imidazolidine-2-thione]bisoxindoles in excellent results under mild conditions (Han *et al.* 2012a). The synthesis of novel dispiropyrrolidine bisoxindole derivatives via condensation of azomethine ylides with the Knoevenagel adduct, prepared by the reaction of isatin with malononitrile was reported (Liu *et al.* 2010).

Novel dispiropyrrolidines were synthesized by a tandem Knoevenagel 1, 3-dipolar cycloaddition reaction sequence of isatin, sarcosine, 1, 3-indanedione, and an aldehydein the absence of catalyst (Li *et al.* 2008). Li and coworkers investigated the synthesis of novel dispiropyrrolidines via azomethine ylide cycloaddition to 1-benzyl-3,5-diarylmethylidene-4-piperidinone and subsequent cycloaddition with nitrile oxide to obtain novel tri-spiro heterocycles (Li *et al.* 2010a).

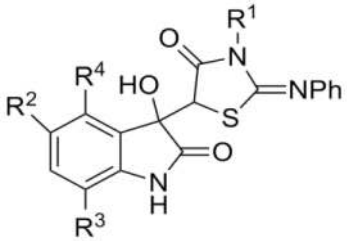
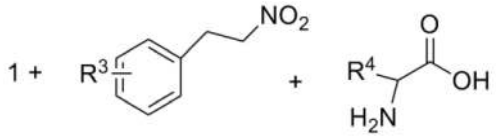
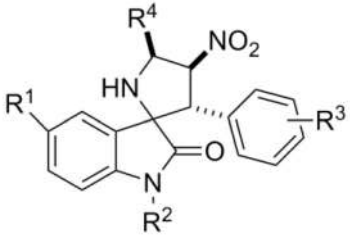
2, 5-Bis (arylmethylidene)-cyclopentanones as dipolarophiles have been used for the synthesis of novel dispiro oxindole/pyrrolidines in moderate yield. Further cycloaddition of compound with nitrile oxide afforded with high region and stereoselectivity (Li *et al.* 2010b). The facile synthesis of tetraspiro-bisoxindolopyrrolidine derivatives in a highly regio- and stereoselective manner through 1, 3-dipolar cycloaddition of bis-dipolarophiles with the 1,3-dipole generated from isatin and sarcosine has also been reported (Rajesh and Raghunathan 2010).

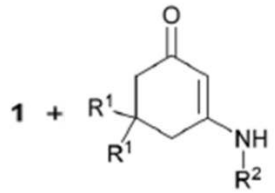
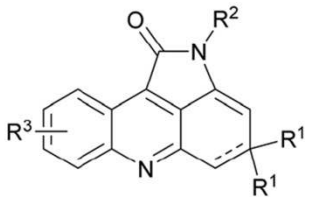
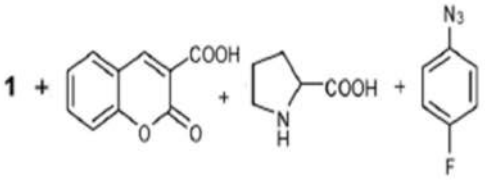
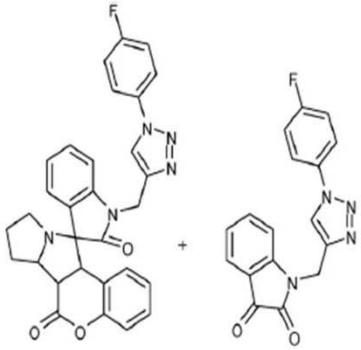
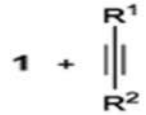
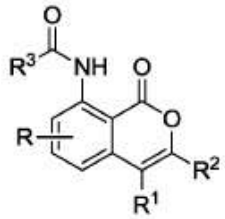
1.4: Recent synthetic developments

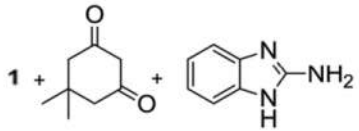
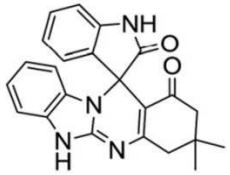
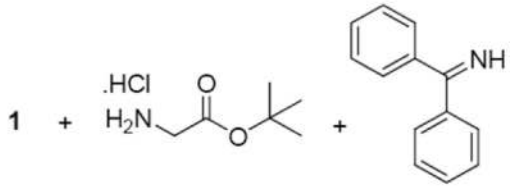
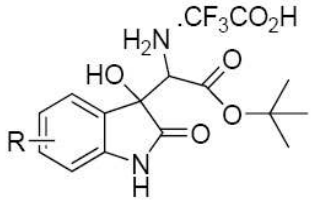
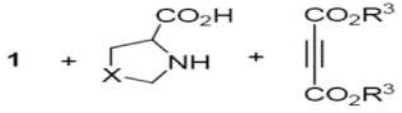
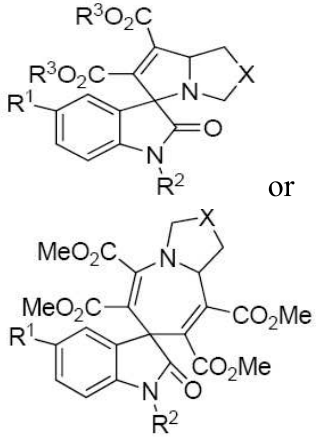
Recent progress in the area of isatin chemistry has been so rapid that it is rather impossible to cover the subject adequately here. Indeed, some of the developments which are of synthetic nature and pertinent to the present dissertation have been selected for special mention (**Table 1.4.1**). The literature is covered from year 2013 and the cut off point is 2016.

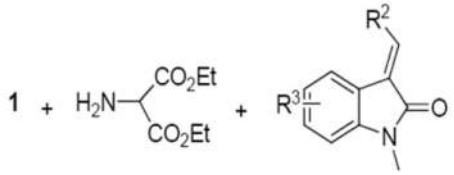
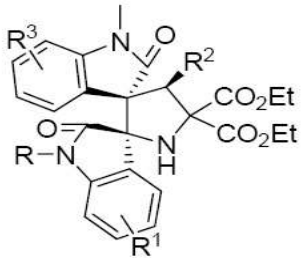
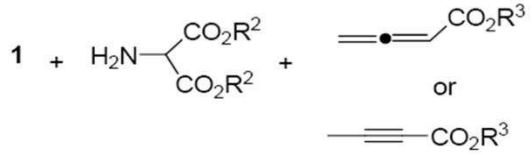
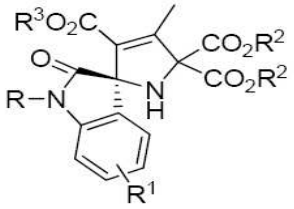
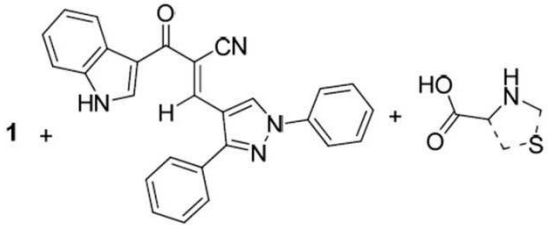
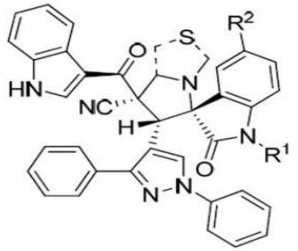
With a view to explore the synthetic applicability of isatin moiety and in order to synthesis some novel derivative of isatin, the studies described in the subsequent chapters **2-5** undertaken.

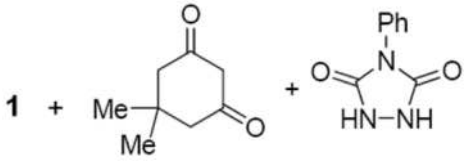
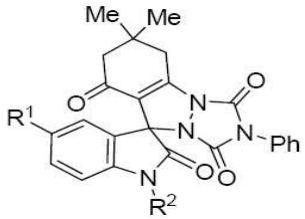
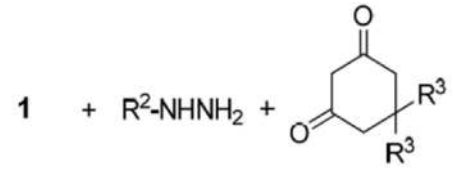
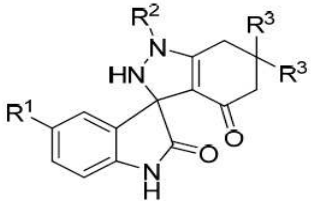
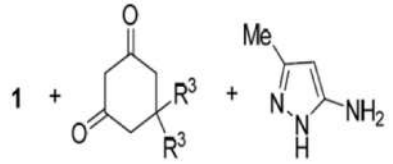
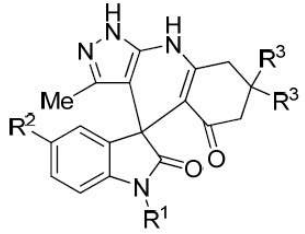
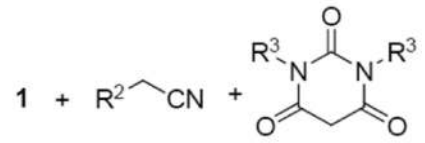
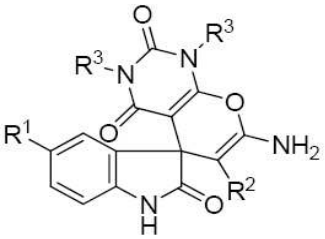
Table 1.5.1: Recent synthetic developments in the field of isatin chemistry

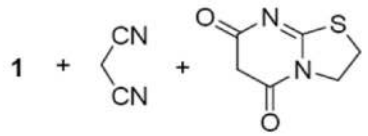
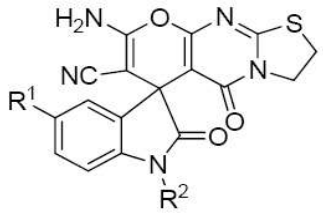
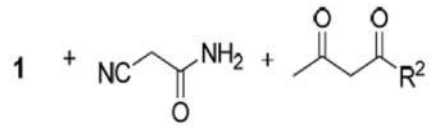
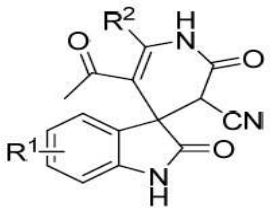
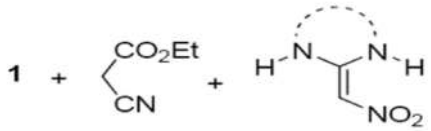
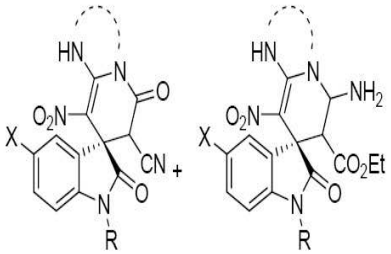
Entry	Substrate(s)	Product(s)	Key reagents and Remarks	Year	Ref. No.
1			DABCO H_2O 70 ^{0}C, 30 min	2016	(Bejjam *et al.* 2016)
2			MW, H_2O 100^{0}C, 10 min	2016	(Mali *et al.* 2016)

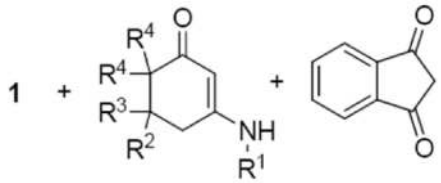
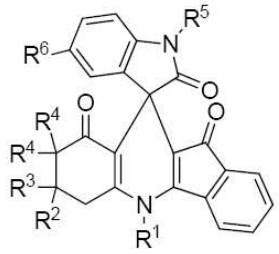
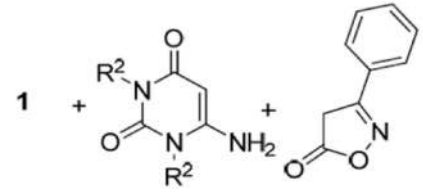
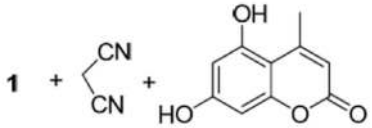
3			$C\text{-}SO_3H$ H_2O 80^0C, 10 min	2016	(Li and Zhang 2016)
4			$CaSO_4.5H_2O$ Sodium Ascorbate Glacial acetic acid 60 ^0C, 35-40 min	2016	(Rajeswari *et al.* 2016)
5			R^3COOH [{$RuCl_2$(*p*-cymene)}$_2$, CsOAc, DCE/H_2O 80 ^0C, 36 h	2016	(Kaishap *et al.* 2016)

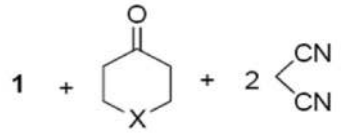
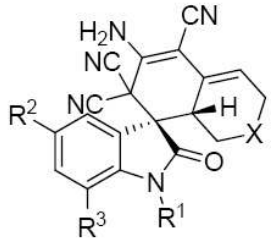
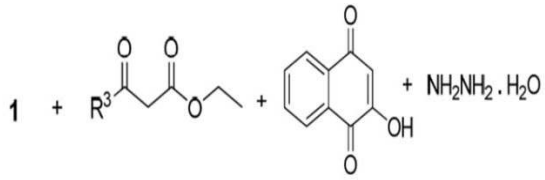
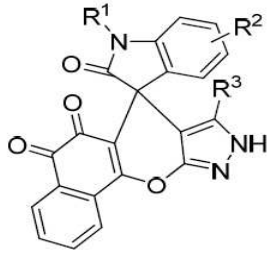
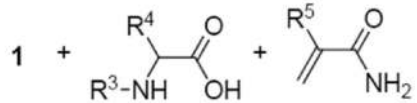
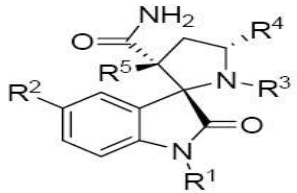
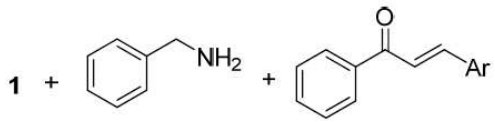
6			MW 60 ^{0}C, 35-40 min	2016	(Maloo *et al.* 2016)
7			1, 4- Dioxane, EA/TFA, 3 h	2015	(Huang *et al.* 2015)
8			MeOH, 24 h	2015	(Yang *et al.* 2015)

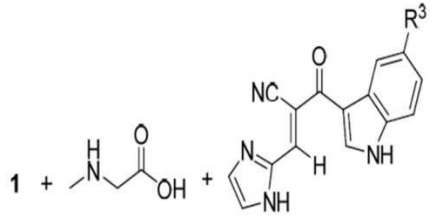
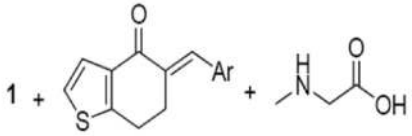
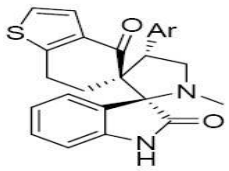
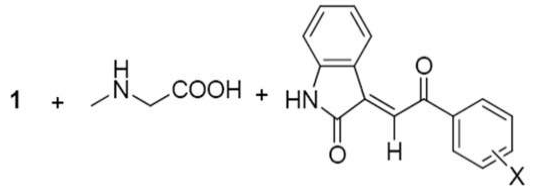
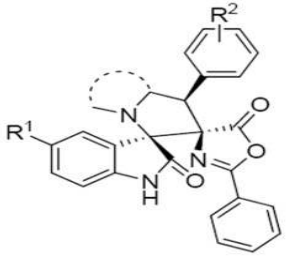
9			Bis- PA 3 A MS, $CHCl_3$ 50 ^{0}C, 36 h	2015	(Dai *et al.* 2015)
10			Bis- PA 3 A MS, Toluene 25 ^{0}C, 36 h	2015	(Wang *et al.* 2014)
11			MeOH Reflux, 2- 3 h	2015	(Kathirvelan *et al.* 2015)

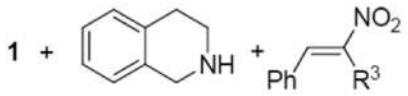
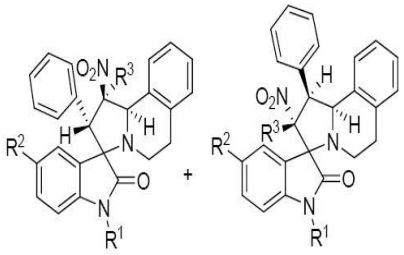
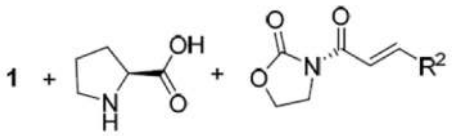
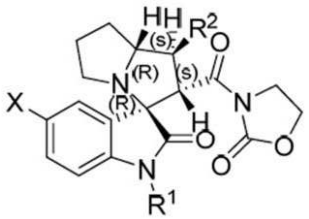
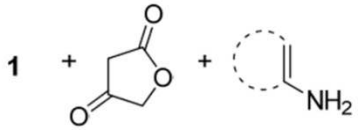
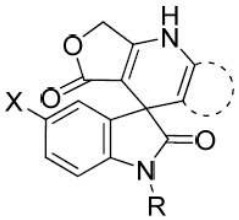
12			Camphor Sulphonic acid Water, EtOH Reflux, 3- 4.5 h	2015	(Chandam *et al.* 2015)
13			Glycerol: water (4:1) 75 ^{0}C, 2.5- 4 h	2015	(Singh *et al.* 2016)
14			H_2O/EtOH (5:1) Alumino silicate NP Reflux, 4 h	2015	(De *et al.* 2015)
15			SBA-Pr-SO_3H Solvent Free Heat, 25- 110 min	2015	(Ziarani *et al.* 2014a)

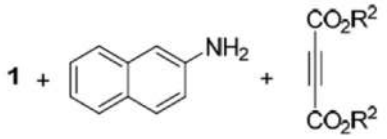
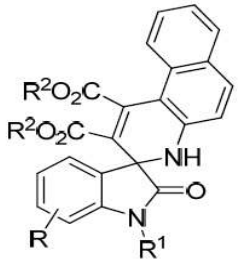
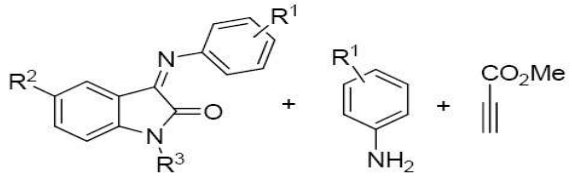
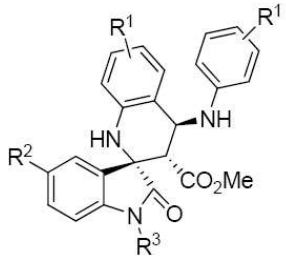
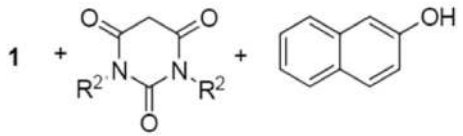
16			DIEA EtOH Reflux, 14- 40 min	2015	(Esmaeili *et al.* 2015)
17			Acylase Amano ethylene glycol 50 0C, 24 h	2015	(Liang *et al.* 2015)
18			NaCl H_2O Reflux, 3- 8 h	2015	(Alizadeh and Moafi 2015)

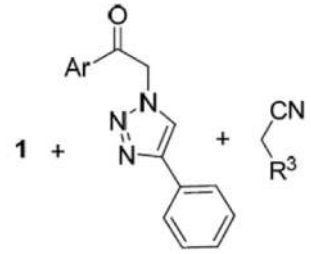
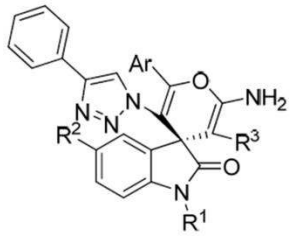
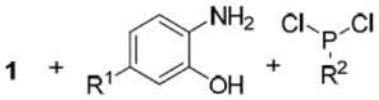
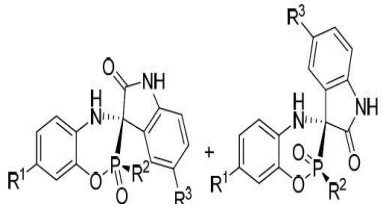
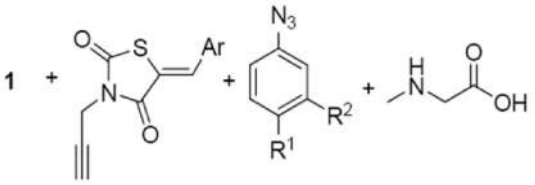
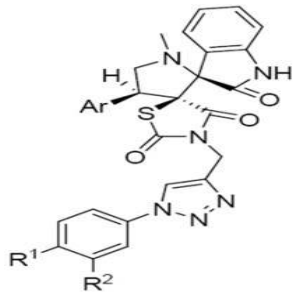
19			$FeCl_3$ CH_2Cl_2 2- 6 h	2015	(Mondal and Mukhopadhyay 2015)
20			*P*- TSA. H_2O H_2O Reflux, 3- 5 h	2015	(Poomathi *et al.* 2015)
21			Piperidine MeOH Reflux, 1- 8 h	2015	(Pal *et al.* 2015)

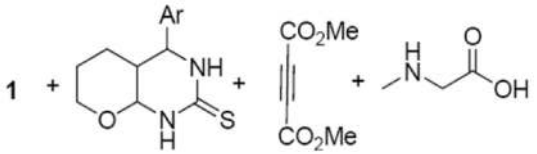
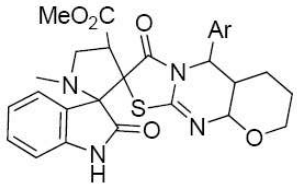
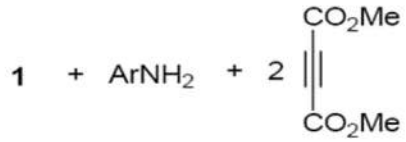
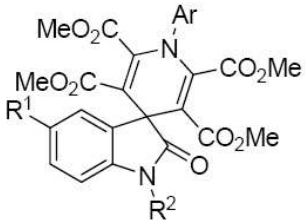
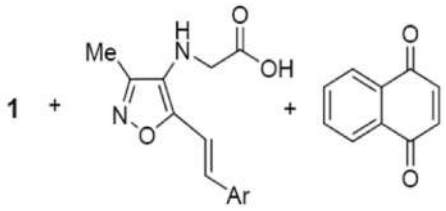
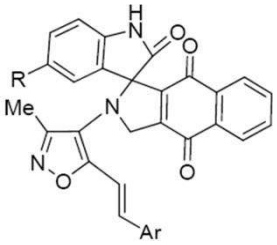
22			NEt_3 EtOH 20 ^{0}C, 1.5- 2 h	2015	(Elinson *et al.* 2015)
23			$MgCl_2$ EtOH 78 ^{0}C, 4- 7 h	2015	(Shen *et al.* 2015)
24			MeOH/ H_2O (3:1) Reflux, 40 min- 7 h	2014	(Pavlovskaya *et al.* 2014)
25			MeOH Reflux	2014	(Sarrafi *et al.* 2012)

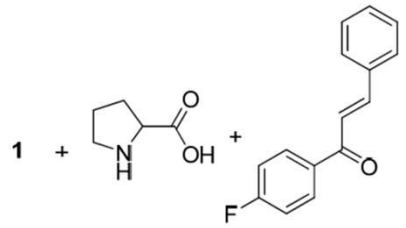
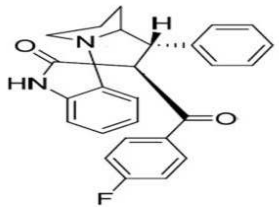
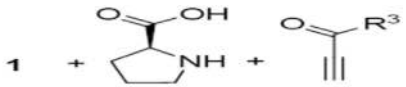
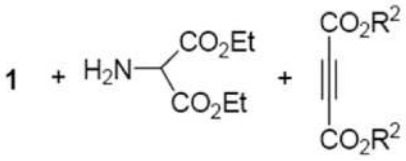
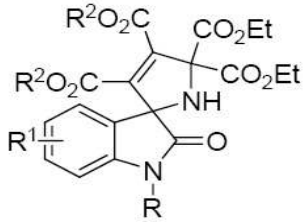
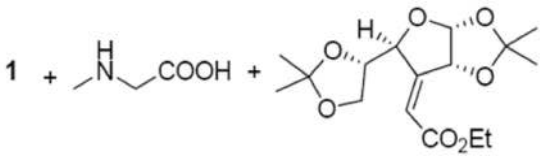
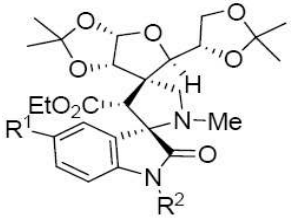
26			EtOH Reflux, 90- 120 min	2014	(Arun *et al.* 2014)
27			MeOH Reflux, 36 h	2014	(Yan 2014)
28			EtOH Reflux, 2- 5 h	2014	(Yang *et al.* 2014)

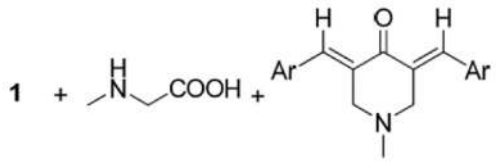
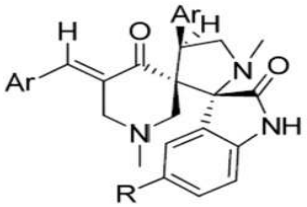
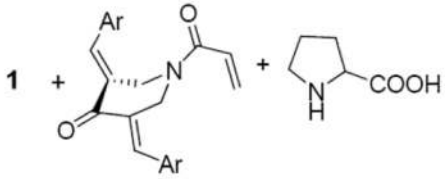
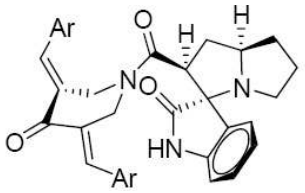
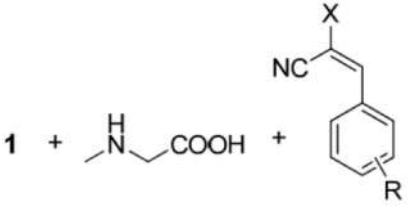
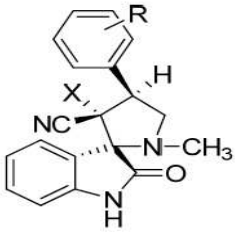
29			EtOH Reflux, 2- 3 h	2014	(Alimohammadi *et al.* 2014)
30			$Cu(OTf)_2$ CH_2Cl_2/ EtOH 22 h	2014	(Salahi *et al.* 2014)
31			Nano $MnFe_2O_4$ H_2O Reflux, 6 h	2014	(Rahmati and Eskandari-Vashareh 2014)

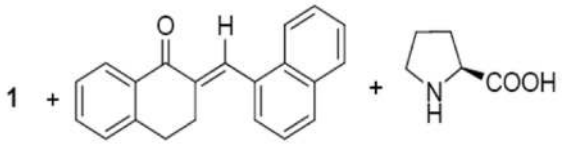
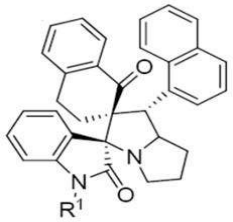
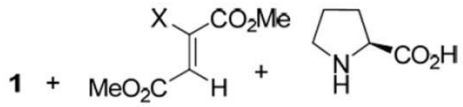
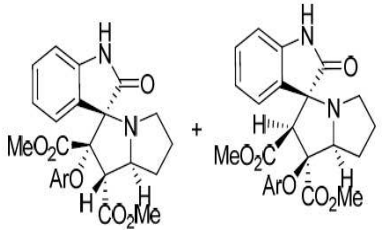
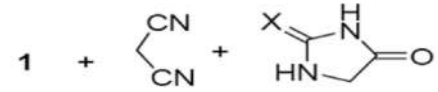
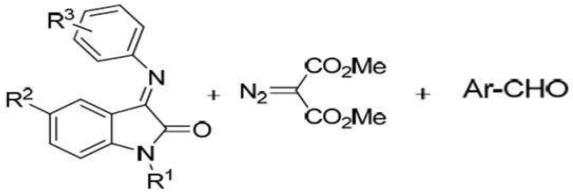
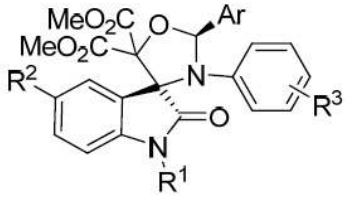
32			$SbCl_3$ CH_3CN Argon atm. 80 ^{0}C, 5-8 h	2014	(Karmakar *et al.* 2014)
33			*p*- TsOH EtOH, 12 h	2014	(Gao *et al.* 2014b)
34			SBA-Pr-SO_3H Solvent Free 140 ^{0}C, 15- 50 min	2014	(Ziarani *et al.* 2014b)

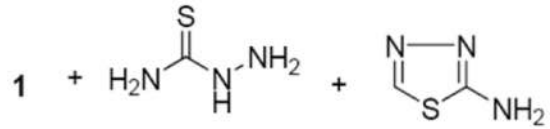
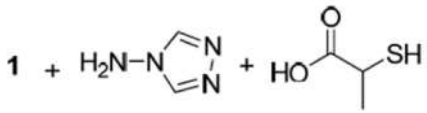
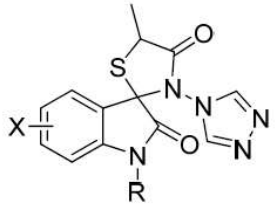
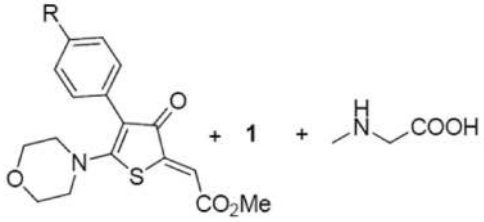
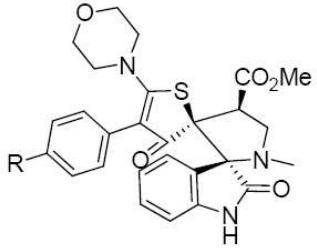
35			$InCl_3$ Solvent free 100 ^{0}C, 1- 2 h	2014	(Kamalraja *et al.* 2014)
36			THF Reflux, 8 h	2014	(Liu *et al.* 2014)
37			$CuSO_4.5H_2O$ Sodium ascorbate PEG- 400, 130 ^{0}C, 10- 12 h	2014	(Sindhu *et al.* 2014)

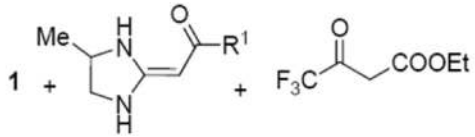
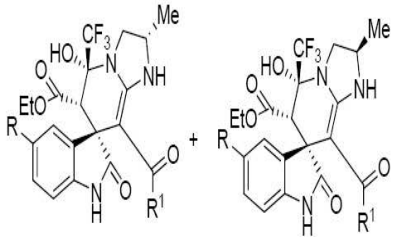
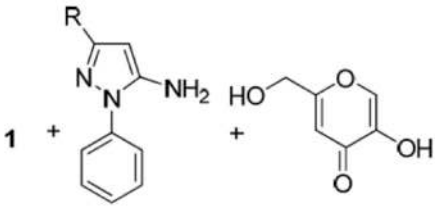
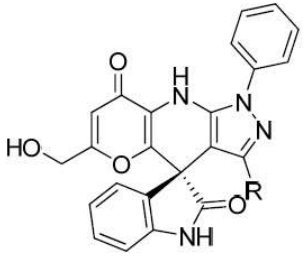
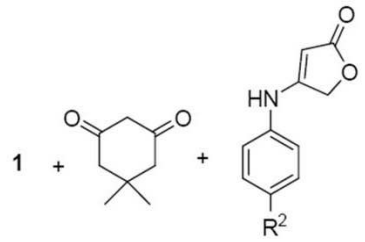
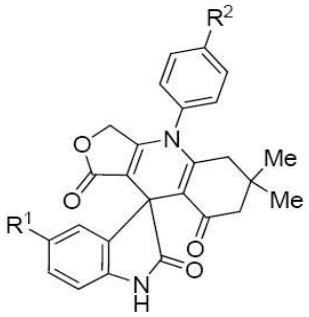
38			MeOH Reflux, 15h	2014	(Li *et al.* 2014)
39			BF_3OEt_2 CH_2Cl_2 Reflux, 24 h	2014	(Gao *et al.* 2014a;c)
40			CAN ETOH, O_2 (air), 30 min	2013	(Rajanarendar, Ramakrishna et al. 2013

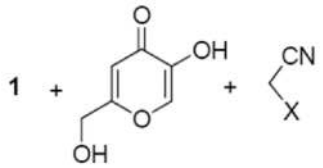
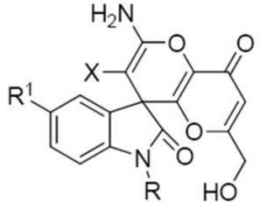
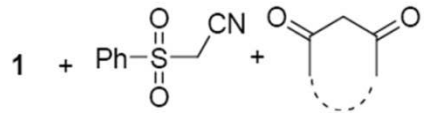
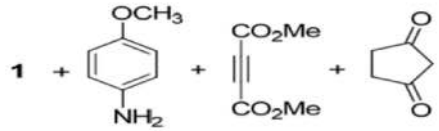
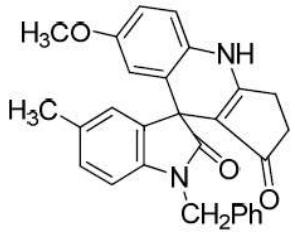
41			EtOH Reflux, 24 h	2013	(Sapnakumari *et al.* 2013)
42			CuI, MeCN 80 ^{0}C, 2- 3 h	2013	(Singh *et al.* 2013)
43			CF_3COOH $ClCH_2CH_2Cl$ 3A MS, 36 h	2013	(Tan *et al.* 2013)
44			Toluene Reflux, 11- 14 h	2013	(Barman *et al.* 2013)

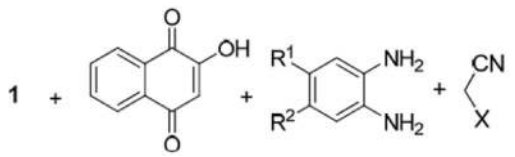
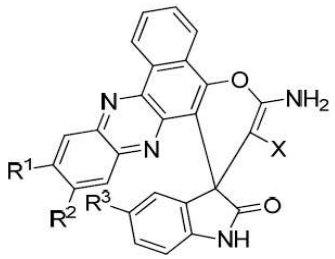
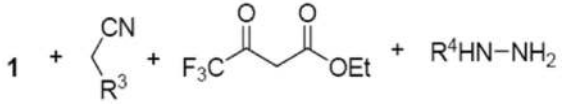
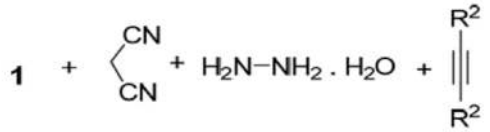
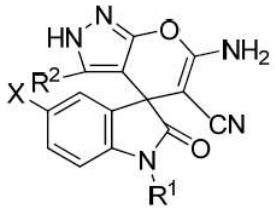
45			EtOH Reflux, 20- 30 min	2013	(Dandia *et al.* 2013a)
46			MeOH Reflux, 5h	2013	(Kia *et al.* 2013)
47			Aq. MeOH Reflux, 6- 8 h	2013	(Dandia *et al.* 2013b)

48			MeOH Reflux, 6- 7 h	2013	(Saravanan *et al.* 2013)
49			EtOH Reflux, 5 min	2013	(Sarrafi *et al.* 2013)
50			Et_3N, H_2O 70 ^{0}C, 7- 10 h	2013	(NasimáKhan 2013)
51			$Rh_2(OAc)_4$ Benzene 80 ^{0}C, 20 min.	2013	(Rajasekaran *et al.* 2013)

52			AcOH Reflux, 2 h	2013	(Hamama *et al.* 2013)
53			[bmim]PF_6 120 ^{0}C, 4- 6 h	2013	(Jain *et al.* 2013)
54			MeOH Reflux, 3 h	2013	(Moghaddam *et al.* 2013)

55			Piperidine EtOH Reflux, 2 h	2013	(Yu *et al.* 2013)
56			$Zn(OTf)_2$ Solvent free, 120 ^0C 1 h	2013	(Safaei *et al.* 2013)
57			$MnFe_3O_4$ H_2O, 80 ^0C	2013	(Ghahremanzadeh *et al.* 2013)

58			$Cu(OTf)_2$ $(CH_2)_2$ Cl_2 Reflux, 20- 45 min	2013	(Parthasarathy *et al.* 2013)
59			HEAA, EtOH 80 ^{0}C, 2-5 h	2013	(Jin *et al.* 2013)
60			AcOH Room Temprature 24 h	2013	(Sun *et al.* 2013)

61			EtOH Reflux, 10- 15 min	2013	(Mahdavinia *et al.* 2013)
62			Piperidine EtOH Reflux, 4- 10 h	2013	(Liu *et al.* 2013)
63			H_2O: EtOH (8:2) Room Temprature 0.25- 4 min	2013	(Pore *et al.* 2013)

*Isatin/ Substituted isatin derivative

1.5: References

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