



## Synthesis of Spirooxindole Derivatives

Mahmoud Refaee Mahmoud, Mahmoud Fawzy Ismail\*

Chemistry Department, Faculty of Science, Ain Shams University, Abbassia, Cairo, Egypt, post code 11566.

\*E-mail: [fawzy2010@sci.asu.edu.eg](mailto:fawzy2010@sci.asu.edu.eg)

### ABSTRACT

This review summarizes the methods for preparing spirocyclic oxindole derivatives in the past years until 2012 which are divided into several groups according to ring size of the fused spiroindoles.



## Council for Innovative Research

Peer Review Research Publishing System

**Journal:** Journal of Advances in Chemistry

Vol. 7, No. 1

[editor@cirworld.com](mailto:editor@cirworld.com)

[www.cirworld.com](http://www.cirworld.com), [member.cirworld.com](http://member.cirworld.com)

## INTRODUCTION

Spirocyclic system containing one  $sp^3$  carbon atom common to two rings are structurally interesting <sup>[1]</sup>. The a symmetric structure of the molecule due to the chiral spiro carbon atom is one of the important criteria of the biological activities <sup>[2,3]</sup>. The presence of the sterically constrained spiro structure in various natural products also adds to the interest in the investigations of spiro compounds <sup>[4]</sup>. Similarly, functionalized spirocycloalkyl oxoindoles are found in a variety of natural products and bioactive molecules <sup>[5,6]</sup>.

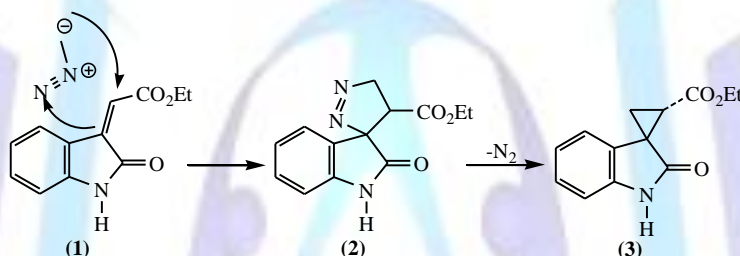
Hence, a number of synthetic methods have been developed for expedition of these structural frame works <sup>[7-25]</sup>.

Moreover, some indolines, spiro-annulated with heterocycles in the position 3, have shown high biological activity <sup>[26-28]</sup>. Therefore, a number of methods have been reported for the preparation of spirooxoindole fused heterocycles <sup>[21,24,29-75]</sup>.

## A) SPIRO[THREE-MEMBERED RING]OXOINDOLES

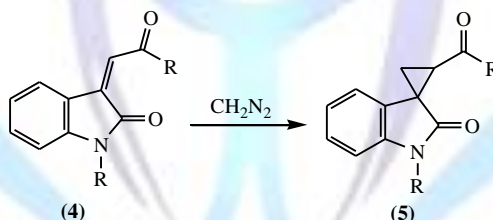
### i. Spirocyclopropane oxoindole derivatives

Oxindolylacrylates **1** react with diazomethane in a regioselective manner, depending on the substituent attached to the carbon atom  $\alpha$  to the ester carbonyl group. In non-substituted acrylates, the 1,3-dipolar cycloaddition occurs furnishing ethyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrazole]-4'-carboxylate **2** which, upon heating, losses  $N_2$  to give a spiro cyclopropane indolinone derivative **3** <sup>[76,77]</sup>. (**Scheme 1**)

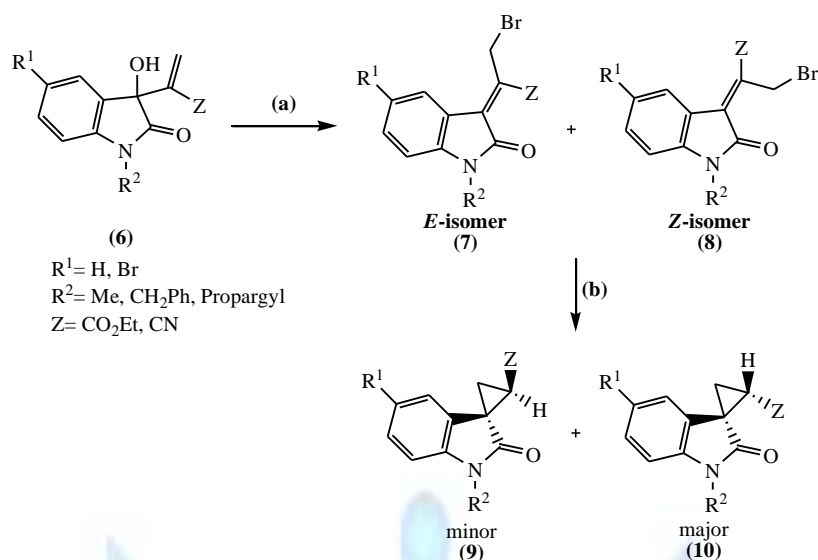


**Scheme 1: synthesis of spirocyclopropane oxoindole derivative 3**

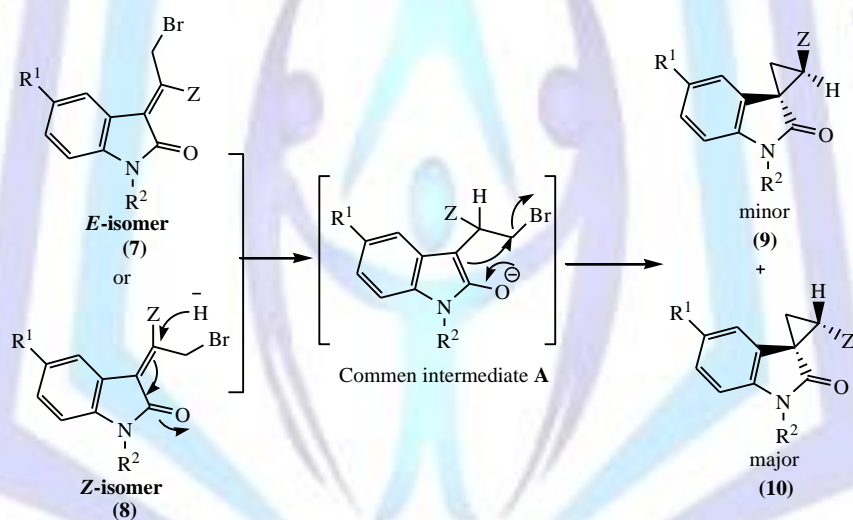
Similarly, *N*-protected isatin derivative **4** when treated with diazomethane afforded the spirocyclopropane indolinone derivative **5** <sup>[76,78,79]</sup>.



A facile, high yield stereoselective synthesis of functionalized diastereomeric 3-spirocyclopropane-2-indolones **9**, **10** from the isomerised bromo derivatives of Baylis-Hillman adducts of isatin **7**, **8** by reductive cyclization with sodium borohydride is reported <sup>[80]</sup>. (**Scheme 2,3**)

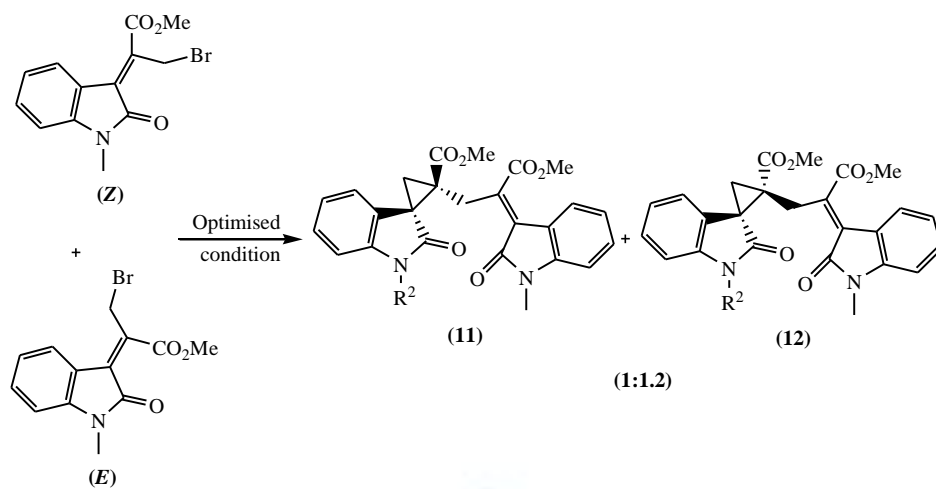


**Scheme 2. Generality of the cyclopropanation.** a) 4 equiv. 46% HBr, silica gel,  $\mu\text{w}$ , 750 W, 3 min; b) 2 equiv.  $\text{NaBH}_4$ , THF, 0.5 h.

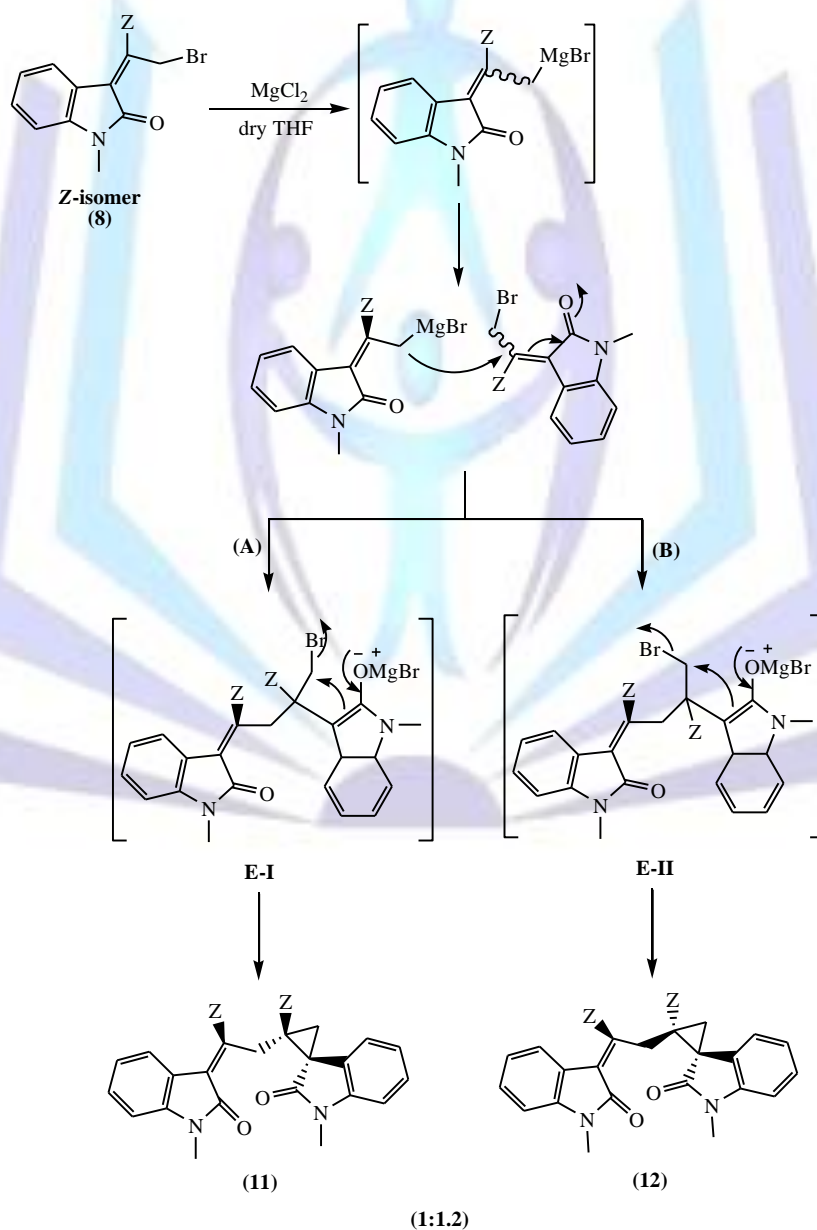


**Scheme 3. A plausible mechanism for cyclopropanation.**

A novel magnesium iodide mediated unusual dimerization-spirocyclopropanation of bromo isomerised Morita-Baylis-Hillman adducts of isatin afforded highly functionalized 3-spirocyclopropane-2-oxindole derivatives **11**, **12** as regioisomers in good combined yield. It has been observed that the regioselectivity is dependent on the nature of electron withdrawing group at the activated position. A plausible mechanism involving organomagnesium reagent has been proposed<sup>[81]</sup>. (**Scheme 4, 5**)



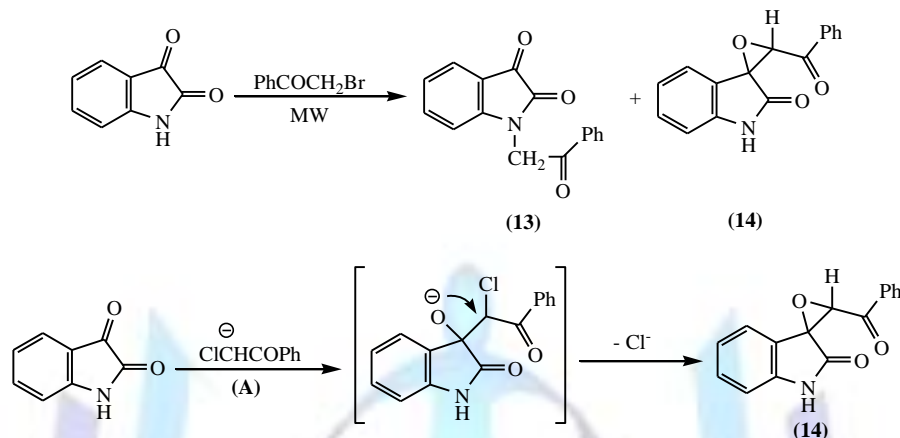
**Scheme 4.** Synthesis of spirocyclopropane derivatives of oxindole 11 and 12 from *Z* and *E* isomers.



**Scheme 5.** Proposed mechanism for the formation of 11 and 12.

## ii. Spirooxirane oxindole derivatives

Reaction of isatin with phenacyl bromide, either under conventional heating or in the MW promoted reaction, leads to *N*-substituted derivative **13** in acceptable yields, although the MW procedure provided the best results. Variable amounts of spirooxirane oxindole **14**, resulting from addition of the halomethylketone anion **A** onto the isatin  $\beta$ -carbonyl and further cyclization were obtained as a side product <sup>[82]</sup>. (**Scheme 6**)



**Scheme 6. Probable mechanism for the synthesis of epoxide.**

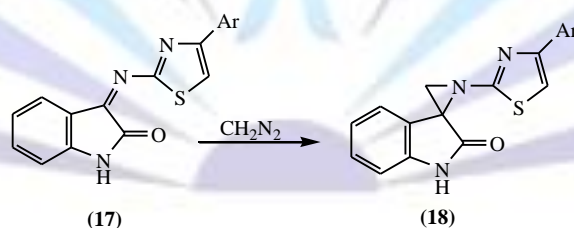
The *o*-methylether of isatin **15** reacts with diazomethane to furnish a quinoline derivative as the major product, together with a spirooxirane derivative **16** <sup>[83]</sup>. (**Scheme 7**)



**Scheme 7**

## iii. Spiroaziridine oxindoles

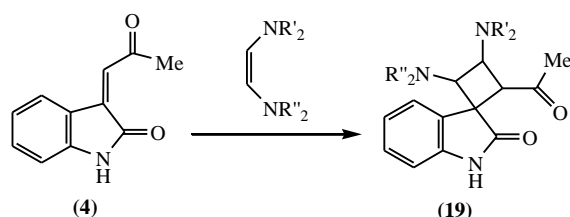
1-(4-Aryl thiazol-2-yl)spiro aziridine-2,3'-indolin-2'-one **18** was synthesized from the reaction of 3-(4-aryl thiazol-2-yl imino)indolin-2-one **17** with diazomethane <sup>[84]</sup>.



## B) SPIRO[FOUR-MEMBERED RING]OXINDOLES

### i. Spirocyclobutane oxindole derivative

Spiro cyclobutane oxindole **19** was obtained by treatment of 1-methyl-3-(2-oxopropylidene)indolin-2-one **4** with ethylene diamine derivative <sup>[85]</sup> (40-97%).

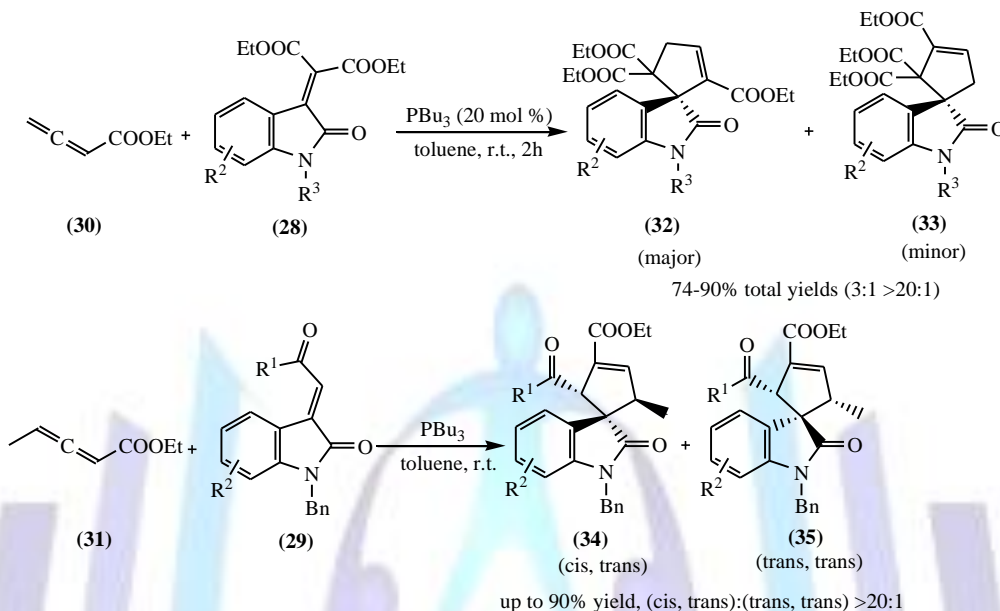




## C) SPIRO[FIVE-MEMBERED RING]OXOINDOLES

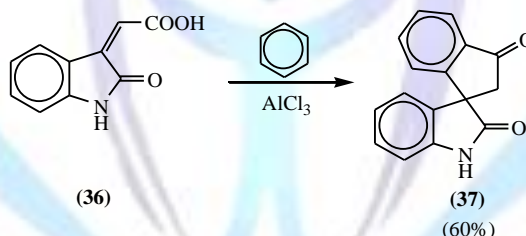
### i. Spirocyclobutane oxindole derivative

Recently, <sup>[110,111]</sup> it was reported a novel phosphorus-containing lewis base catalyzed highly geometric selective [3+2] annulation of isatin derived  $\alpha,\beta$ -unsaturated diesters **28**, **29** with  $\alpha$ -allenic ester **30**, **31** affording functionalized spiro cyclopentane indolinone derivatives **32-35**. (**Scheme 10**)



**Scheme 10**

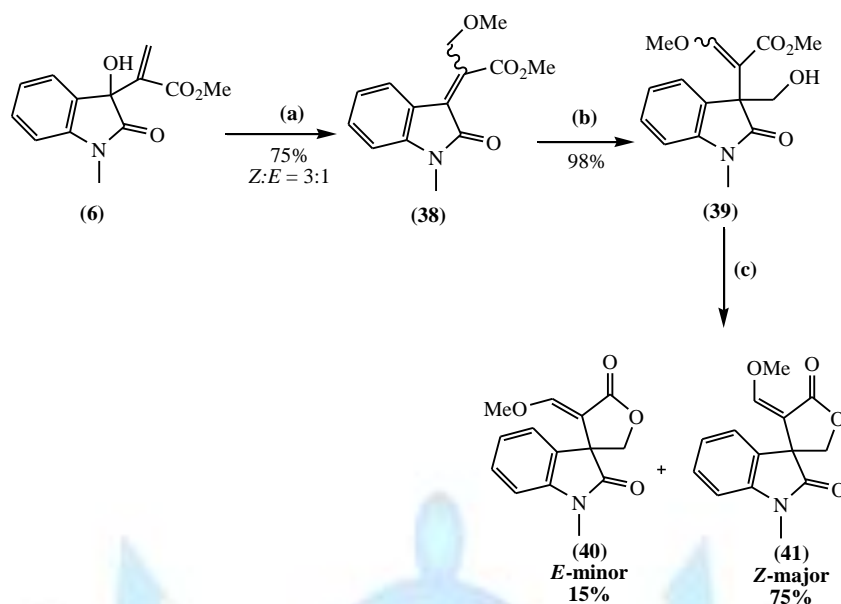
2-(2-Oxindolin-3-ylidene)acetic acid **36** under Friedel-Craft's conditions with benzene in anhydrous aluminium chloride afforded spiro[indene-1,3'-indoline]-2',3-(2*H*)dione **37** <sup>[112]</sup>.



### ii. Spirofurane oxindole

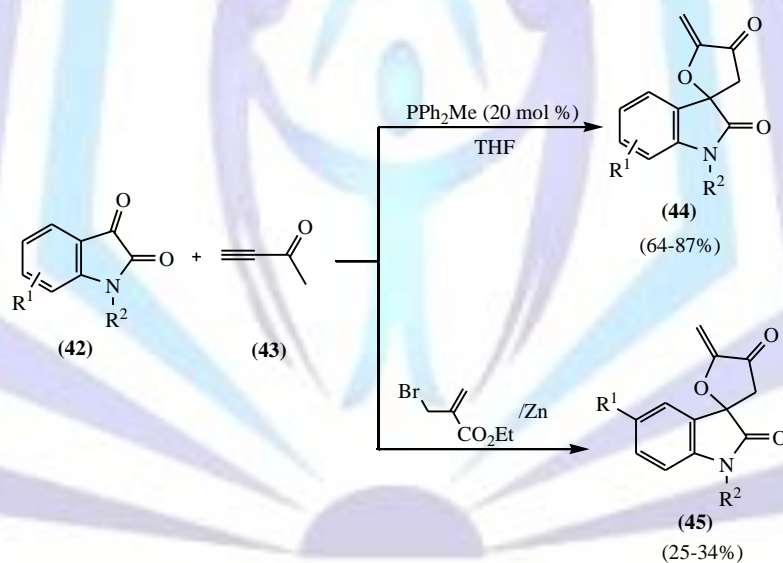
Oxindoles functionalised at C3 as spiro lactones, <sup>[113-116]</sup> spirocyclic ethers and spirocarbo- and heterocyclics are elegant targets in organic synthesis due to their significant biological activities <sup>[117-119]</sup>.

The reaction of Morita-Baylis-Hillman adduct of N-methylisatin **6** with excess of trimethyl orthoformate and montmorillonite K10 clay <sup>[120-123]</sup> catalyst at 110 °C for 0.5 h afforded a 1:3 mixture of *E*- and *Z*-isomer **40** and **41** with overall yield (75%) <sup>[124]</sup>. (**Scheme 11**)



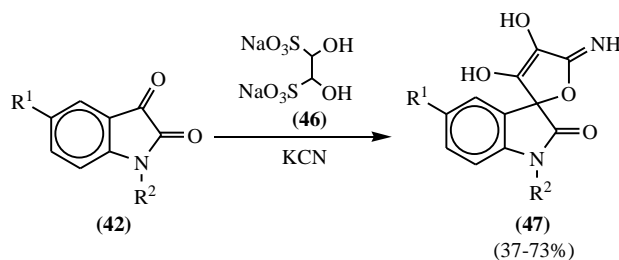
**Scheme 11.** Synthesis of 3-spiro- $\alpha$ -methylene- $\gamma$ -butyrolactone-*N*-methyl oxindoles **40** and **41**. a)  $\text{CH}(\text{OMe})_3/\text{Mont. K10}$ , neat,  $110^\circ\text{C}$ , 30 min; b) aq.  $\text{HCHO}$ , DABCO, r.t., acetone, 1.5 h; c) PTSA/benzene, 30 min.

Novel phosphorus-containing lewis bases catalyzed [3+2] annulation of isatin **42** with but-3-yn-2-one **43** giving the corresponding spiro[furan-2,3'-indoline]2',4-(5*H*)dione **44** in excellent yields under mild conditions<sup>[125]</sup>. Moreover, the reaction of **42** with ethyl-2-bromomethylacrylate with zinc under Reformatsky type reaction gave the spiro[furan-2,3'-indoline]2',5-(4*H*)dione **45**<sup>[126]</sup>. (**Scheme 12**)



**Scheme 12**

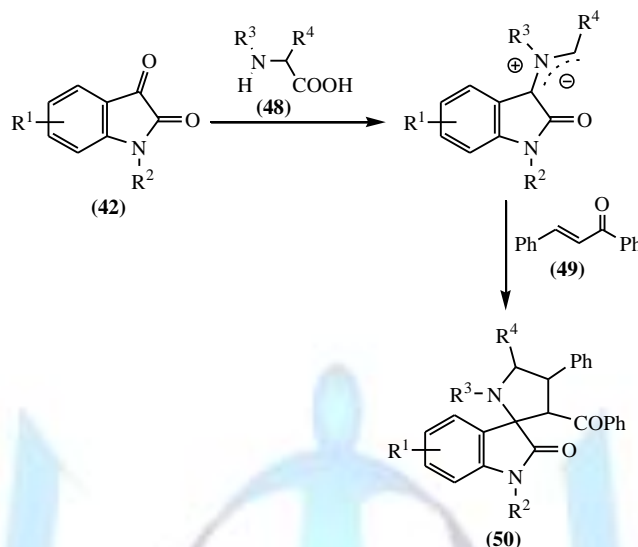
Sodium 1,2-dihydroxyethane-1,2-disulfonate **46** was reacted with *N*-alkyl isatin **42** in the presence of KCN and yielded 3,4-dihydroxy-5-imino spiro[furan-2,3'-indolin]-2'-one **47**<sup>[127]</sup>.



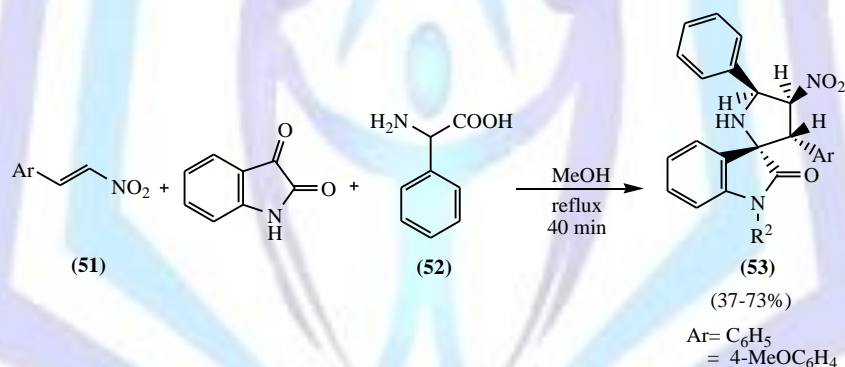


### iii. Spiropyrrolidine oxindoles

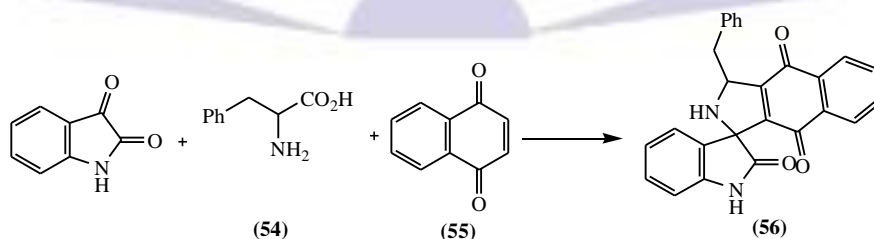
Spiro[pyrrolidine-2,3-oxindoles] **50** were synthesized from the reaction of isatin **42** with aminoacids **48** and chalcones **49**<sup>[128,129]</sup>. (**Scheme 13**)



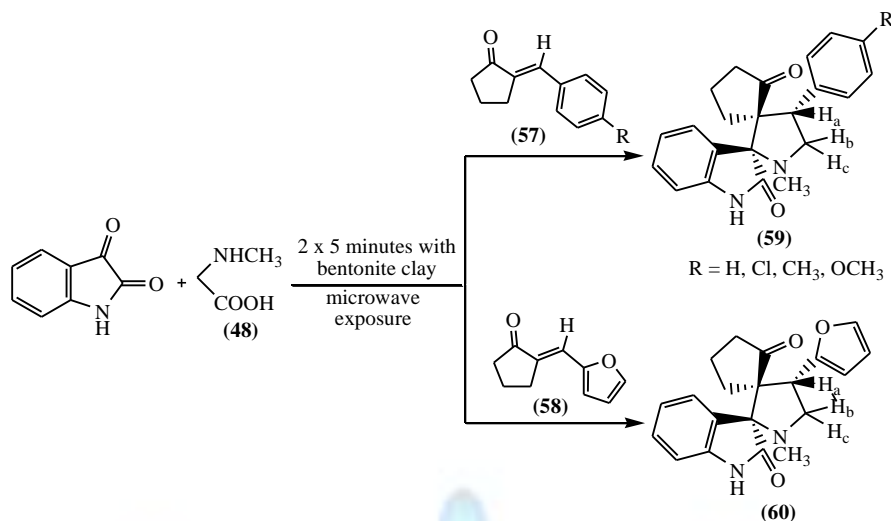
3-Aryl-4-nitro-5'-phenyl spiro[indoline-3,2'-pyrrolidin]-2-ones **53** were synthesized as pure region and stereoselective by heating a mixture of 2-nitrovinyl benzene or 1-methoxy-4-(2-nitrovinyl)benzene **51**, isatin and phenyl glycine **52**<sup>[130]</sup>. (**Scheme 14**)



Three components condensation of isatin, *L*-phenyl alanine **54** and 1,4-naphthoquinone **55** afforded 3'-benzyl-2,3'-dihydro-1H-spiro[indole-3,1'-naphtho[2,3-c]pyrrole]-2,4',9'-trione **56**<sup>[131]</sup>. (**Scheme 15**)

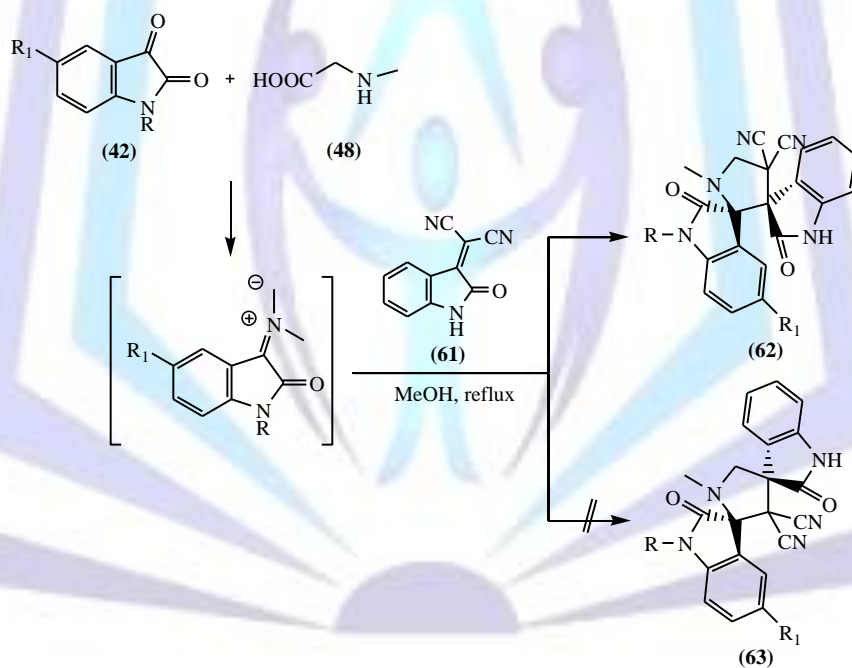


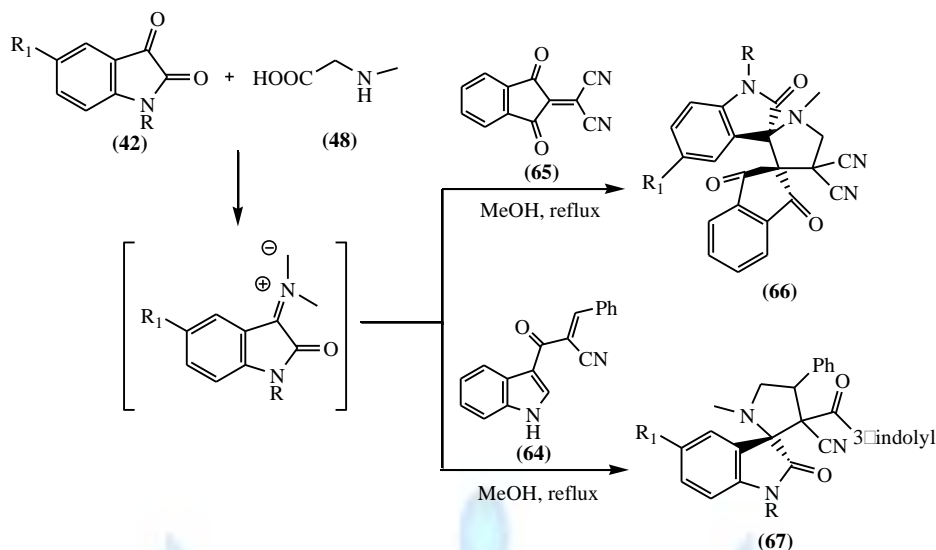
2-Arylidene-*l*-cyclopentanones **57** and **58** readily underwent 1,3-dipolar cycloaddition reactions with the non-stabilised ylide generated *in situ* by the decarboxylative condensation of isatin and sarcosine **48** to afford dispiropyrrolidinyloxindole derivatives **59** and **60** in a highly regioselective manner (**Scheme 16**). The reactions were carried out in a microwave oven for a period of 10 min under neat conditions. The results were compared with those obtained from the conventional method of refluxing with aqueous methanol<sup>[132]</sup>.



Scheme 16

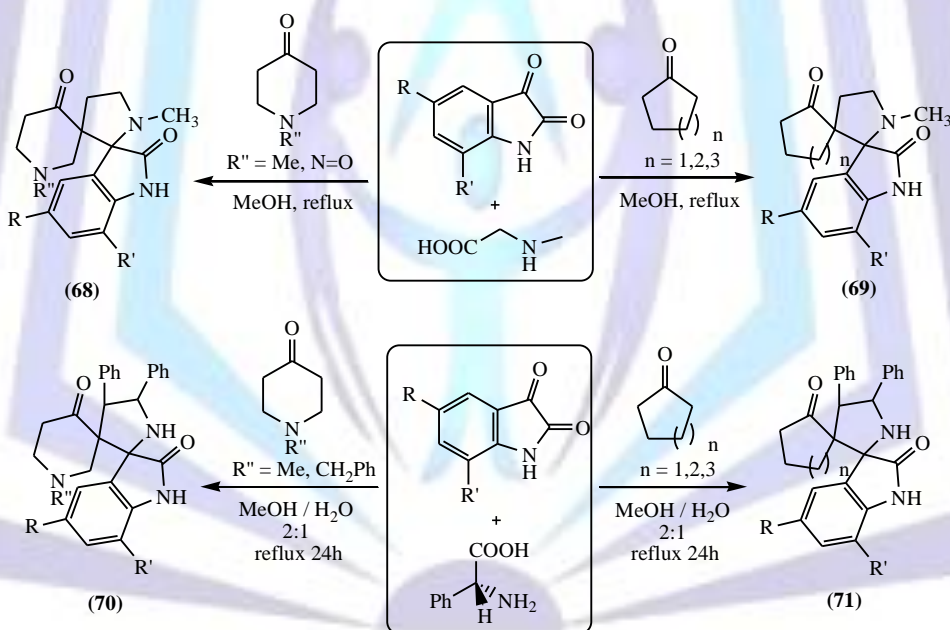
A series of dispiropyrrolidine bisoxindoles **62**, **63** were synthesized via a multicomponent 1,3-dipolar cycloaddition reaction<sup>[7,13,113,133-142]</sup> of isatin, sarcosine **48** and isatylidene malononitrile **61** in refluxing methanol (**Scheme 17**), also, a series of spiropyrrolidine oxindoles **66** and spiroindan-1,3-diones **67** were synthesized using 2-(1*H*-indole-3-carbonyl)-3-phenyl acrylonitrile **64** and 2-(1,3-dioxo-indan-2-ylidene)malononitrile **65** as dipolarophiles, respectively. (**Scheme 17,18**)


 Scheme 17. Synthesis of dispiropyrrolidine oxindoles **62**.



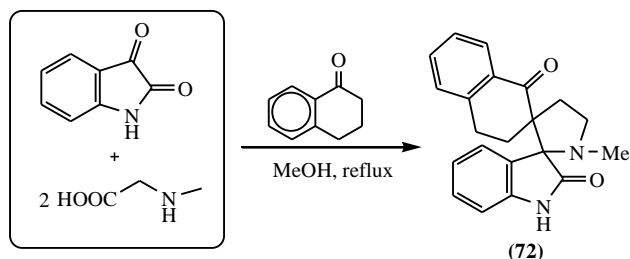
**Scheme 18. Synthesis of spiroindane-1,3-diones 66 and spiropyrrolidine oxindoles 67.**

One-pot three-component domino reactions of cyclic mono ketones, isatin and sarcosine/phenylglycine furnishing highly functionalised dispiropyrrrolidines **68-71** in moderate yields are described. The reaction when performed with cyclic amino acid, proline resulted in the dimerization of azomethine ylides. These compounds show high activity against mycobacterium tuberculosis<sup>[143]</sup>. (**Scheme 19**)



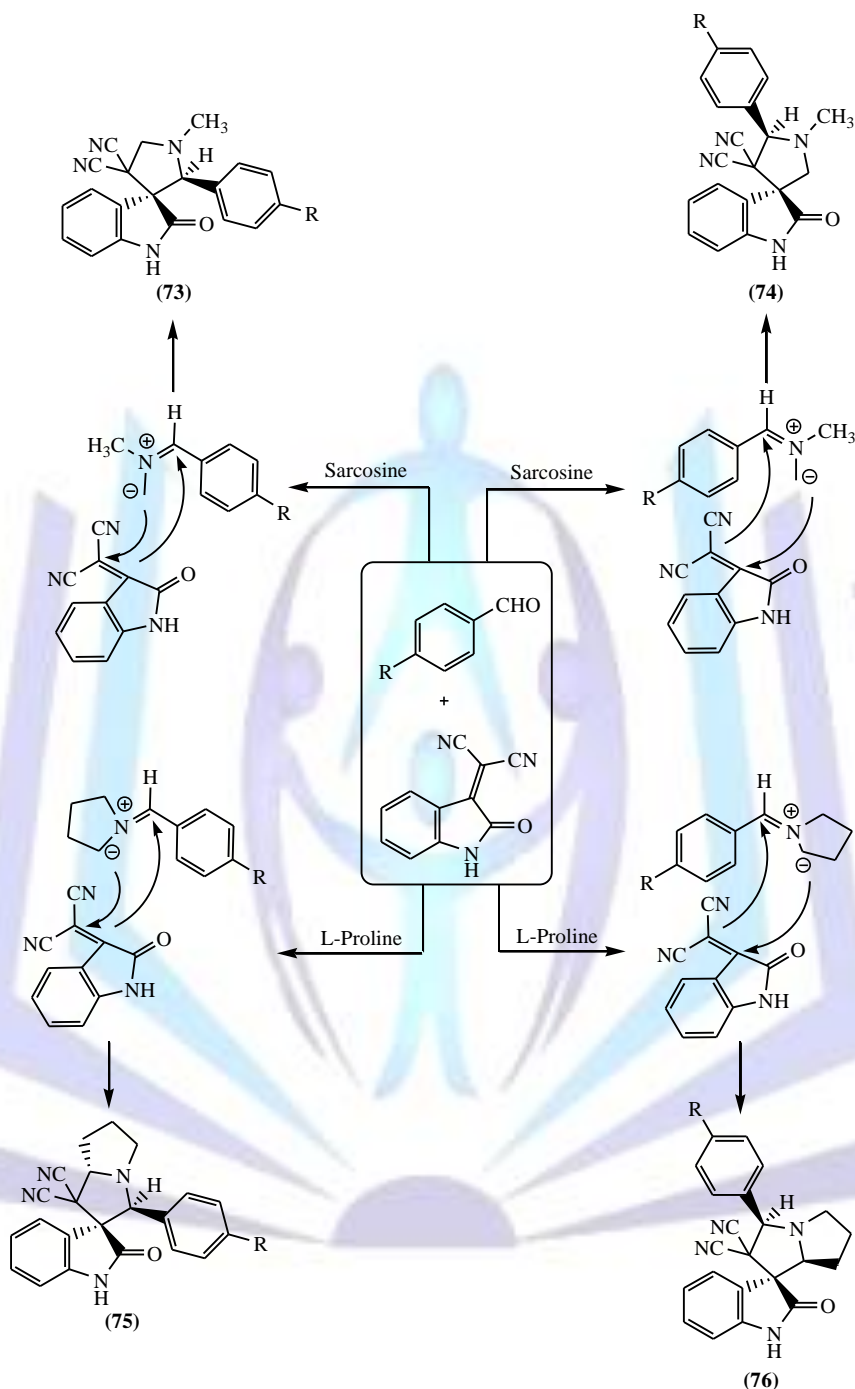
**Scheme 19**

Similarly, the reaction of isatin, sarcosine and tetralone afforded the desired dispiropyrrrolidine **72**<sup>[144]</sup>.



**Scheme 20**

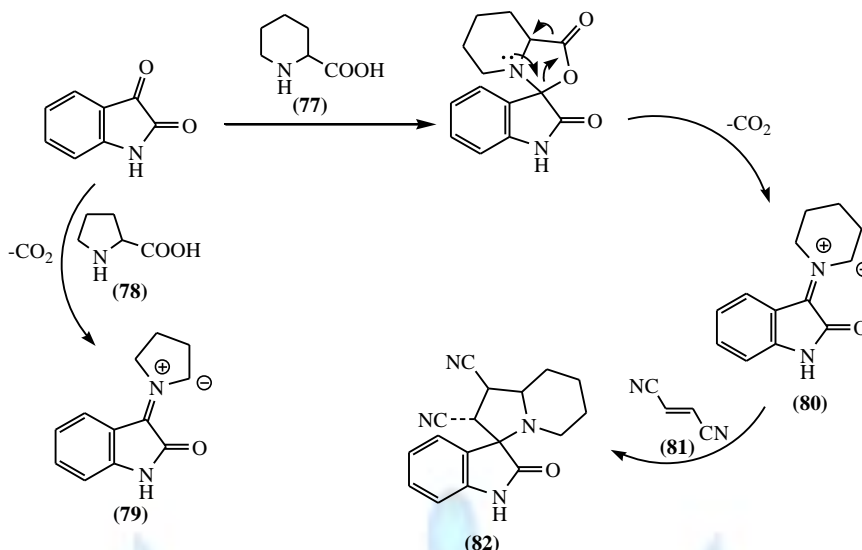
A facile synthesis of novel spiropyrrolidine, pyrrolizine oxindoles **73-76** via the one-pot three component condensation of azomethine ylides (generated *in situ* from sarcosine or proline and aromatic aldehyde) with the Knöevenagel adduct 2-oxo(3*H*)indole-3-ylidene malonitrile derived from the reaction of 2-oxo-(3*H*)indole with malononitrile [26,145]. (Scheme 21)



Scheme 21

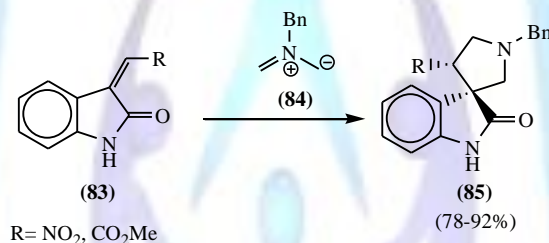
Secondary amines react with isatin to give 1:1 adduct as a result of nucleophilic attack of the amine at position C-3 [146].

Pipecolic acid **77** and proline **78** (a cyclic amino acid) when reacted with isatin suffers decarboxylation gave an azomethine ylid **79**, **80**, which reacts with dipolarophiles such as fumaronitrile **81** to yield spiro derivatives **82** [147,148]. (Scheme 22)



Scheme 22

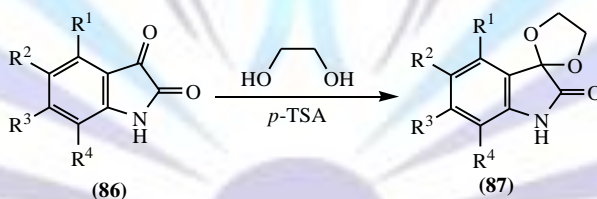
Ethyl-2-(2-oxoindolin-3-ylidene)acetate **83** with *N*-methyl-*N*-methylene (phenyl)methanaminium **84** undergo 1,3-dipolar cycloaddition and gave the spiropyrrolidine oxindole derivative **85** <sup>[149]</sup>. (Scheme 23)



Scheme 23

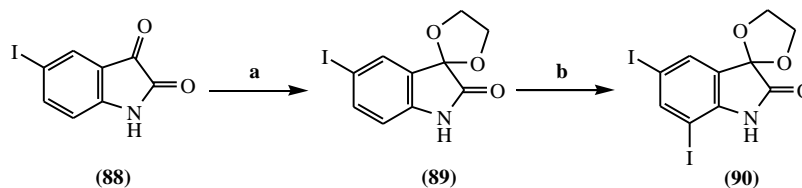
#### iv. Spiro 1,3-dioxolane and dithiolane oxindoles

Spiro[1,3-dioxolane-2,3'-indolin]-2'-ones **87** (cyclic ketals) were obtained using conventional procedures which consisted in the use of one diol (ethylene glycol for dioxolane group or 1,3-propanediol for dioxane group), isatin **86**, *p*-TSA as catalyst in toluene or benzene <sup>[150-153]</sup>. (Scheme 24)



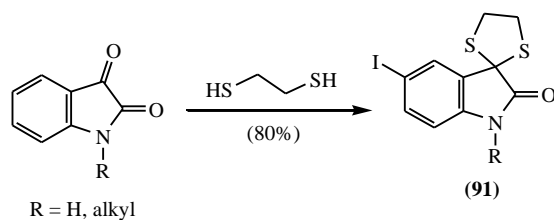
Scheme 24

The dioxolane ketals of isatin and 5-chloroisatin were prepared using an efficient and cleaner procedure than the usual synthetic routes. Keggin heteropolyacids, namely, heteropolyphosphotungstic acid (HPW), HPW/SiO<sub>2</sub> and Cs<sub>2.2</sub>HPW, have proven to be useful catalysts, allowing to the fast, selective and solvent-less preparation of ketals, with high yields and 100% selectivity <sup>[154]</sup>. (Scheme 25)



**Scheme 25. Synthesis of 90. Reagents and conditions:** a) ethylene glycol, *p*-TSA (cat.), toluene, reflux (Dean and Stark conditions) 24 h, 43%; b) ICl, MeOH, reflux, 5 h, 19%.

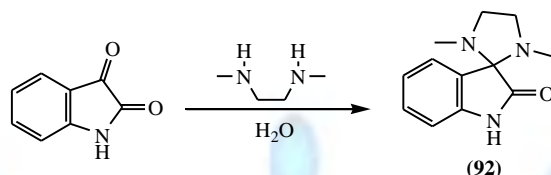
The reaction of isatins <sup>[155,156]</sup> and 1-alkyl isatins <sup>[157]</sup> with thiols yield isatin thioketals **91**. (Scheme 26)



Scheme 26

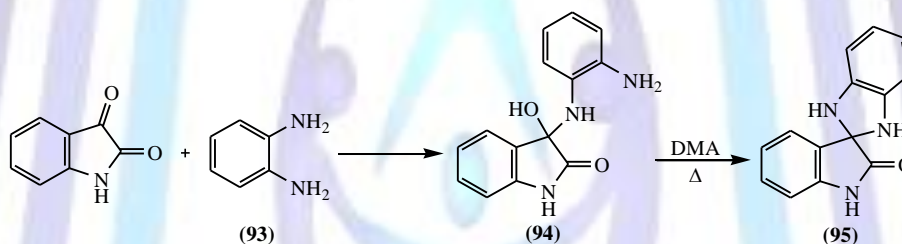
## v. Spirodiazolidene oxindole

The reaction of isatin with *N,N*-dimethylethylenediamine in water yields the spirodiazolaneoxindole **92** <sup>[146]</sup>. (Scheme 27)



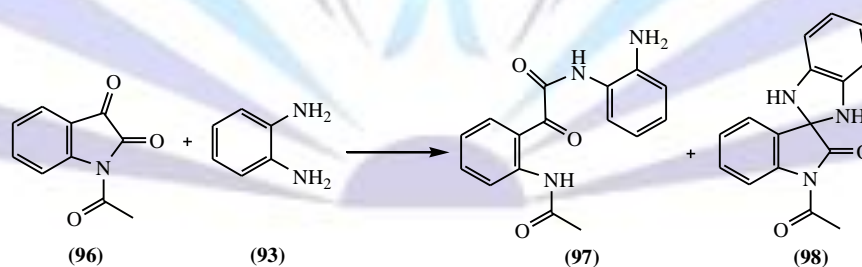
Scheme 27

Moreover, the reaction of isatins with *o*-phenylenediamines **93** was reported to give three products, the proportion between them being affected mostly by the solvent polarity, one of these product identified as spirobenzimidazoles oxindole derivative **95** <sup>[158]</sup>. (Scheme 28)



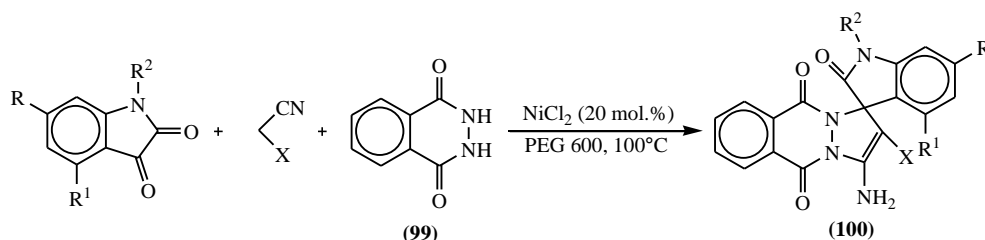
Scheme 28

When the reaction is carried out with 1-acylisatin **96**, ring opened product **97** was formed using benzene, acetic acid or ethanol as the solvent <sup>[159-162]</sup>. However, it has been reported that with the latter two solvents a spirobenzimidazole derivative **98** is also formed <sup>[163]</sup>. (Scheme 29)

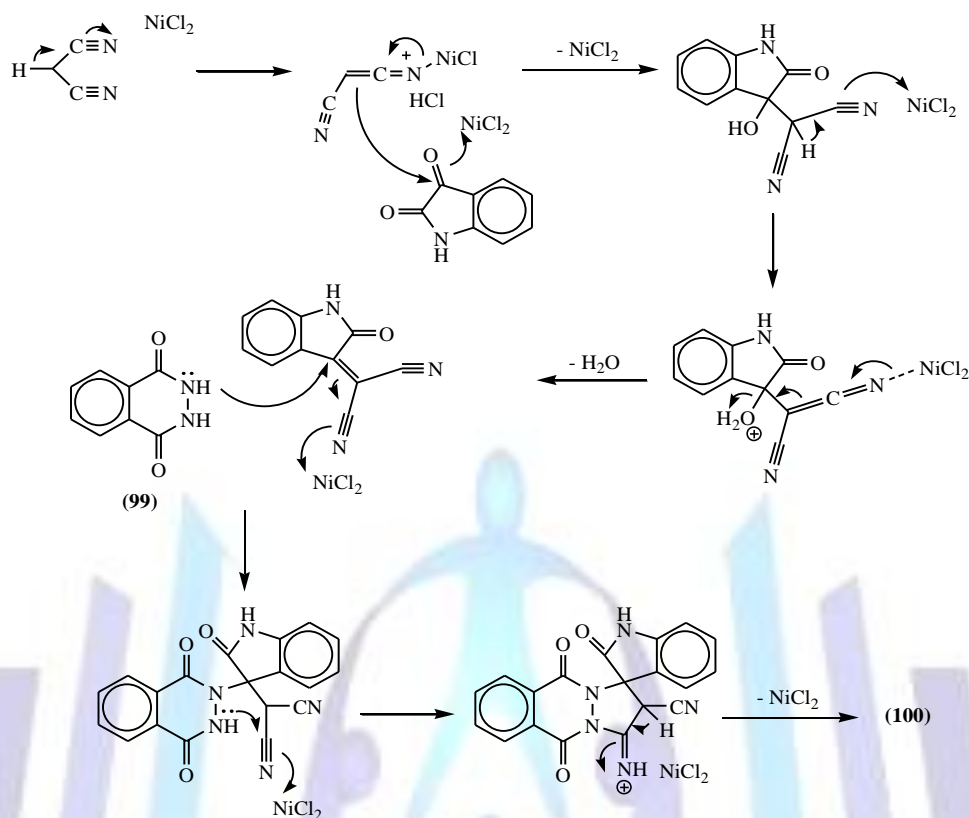


Scheme 29

A simple and facil procedure for the synthesis of pyrazolophthalazinyli spiro oxindoles through one-pot three component reaction of isatin, malonitrile or cyanoacetic ester and phthalhydrazide **99** catalyzed by NiCl<sub>2</sub> in polyethylene glycol (PEG 600) had been described <sup>[164]</sup>.

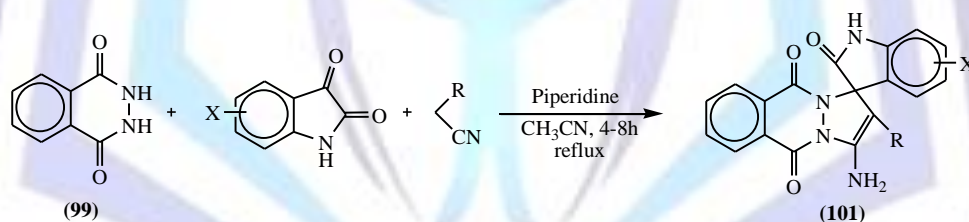


A possible mechanism for the one-pot reaction to give **100** was described. (Scheme 30)

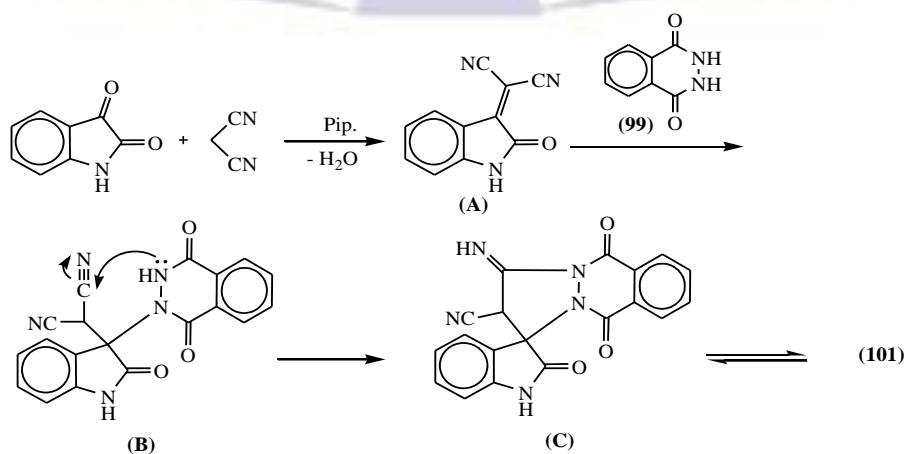


**Scheme 30**

A series of spiro[indoline-3,1'-pyrazolo[1,2-*b*]phthalazine] derivatives were synthesized via three-component reaction of phthalhydrazide, isatin and malononitrile (cyanoacetic ester) catalyzed by piperidine<sup>[165]</sup>.



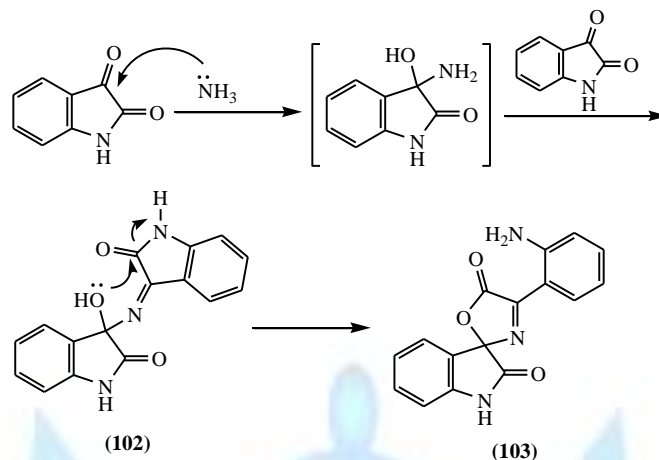
The proposed mechanism for the synthesis of spirooxindole derivatives **101** is described in Scheme 31. The process represents a typical cascade reaction in which the isatin first condenses with malononitrile to afford isatylidene malononitrile derivative A. Then, A is attacked via 1,4-conjugate addition of phthalhydrazide to give the intermediate B followed by cyclization affords the corresponding product **101**.



**Scheme 31**

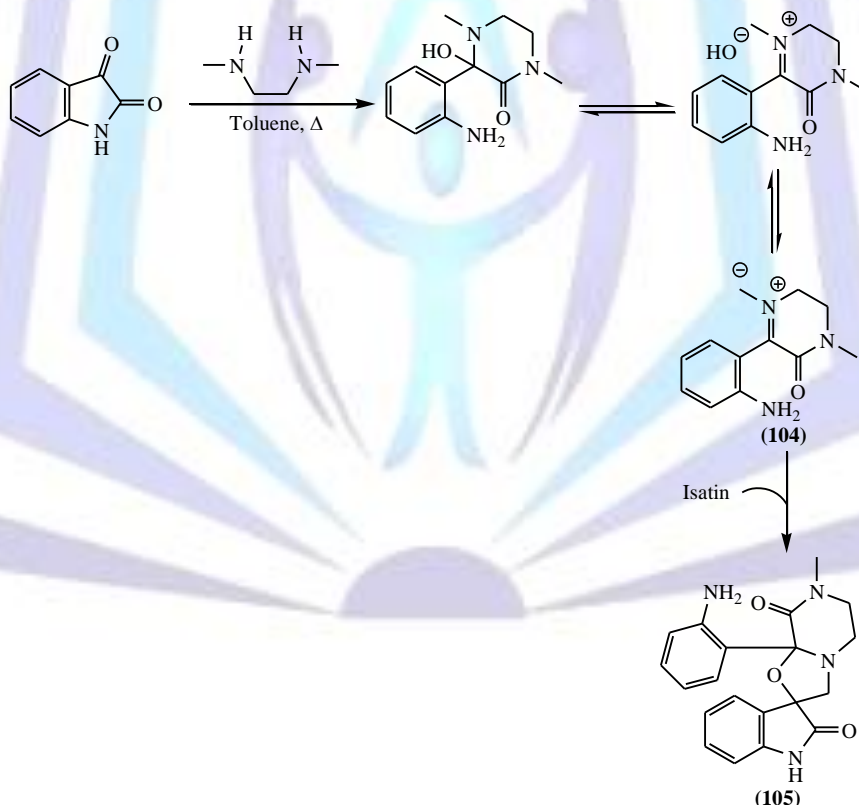
## vi. Spirooxazole oxindoles

Two equivalent of isatin reacted with one equivalent of ammonia to afford the intermediate **102** which suffers lactonization to give the spiro compounds **103** [166]. (Scheme 32)



Scheme 32

The reaction of isatin with *N,N*-dimethylethylenediamine when performed by azeotropic distillation in toluene yielded the unusual 2:1 adduct **105** as the result of the addition of an unstable azomethine ylide **104** to isatin [146]. (Scheme 33)

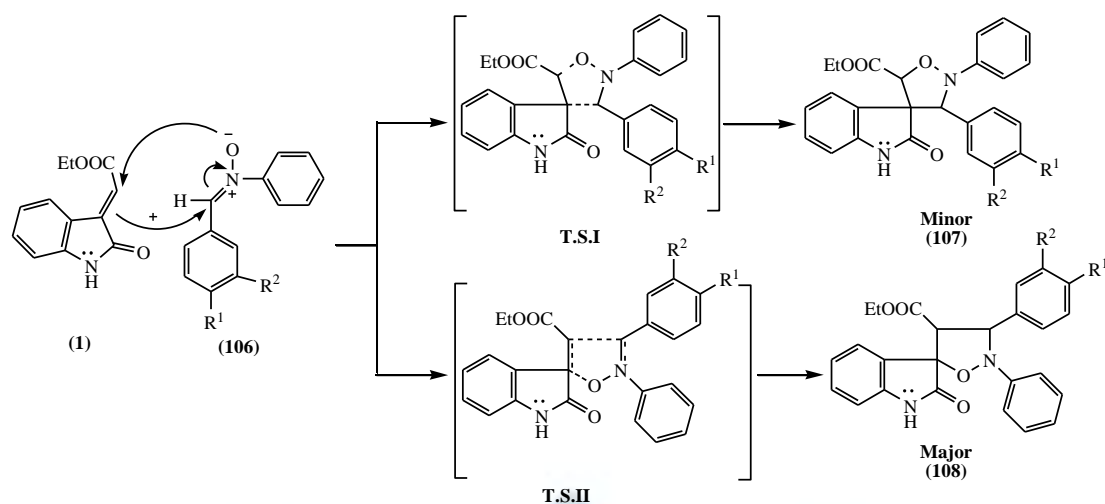


Scheme 33

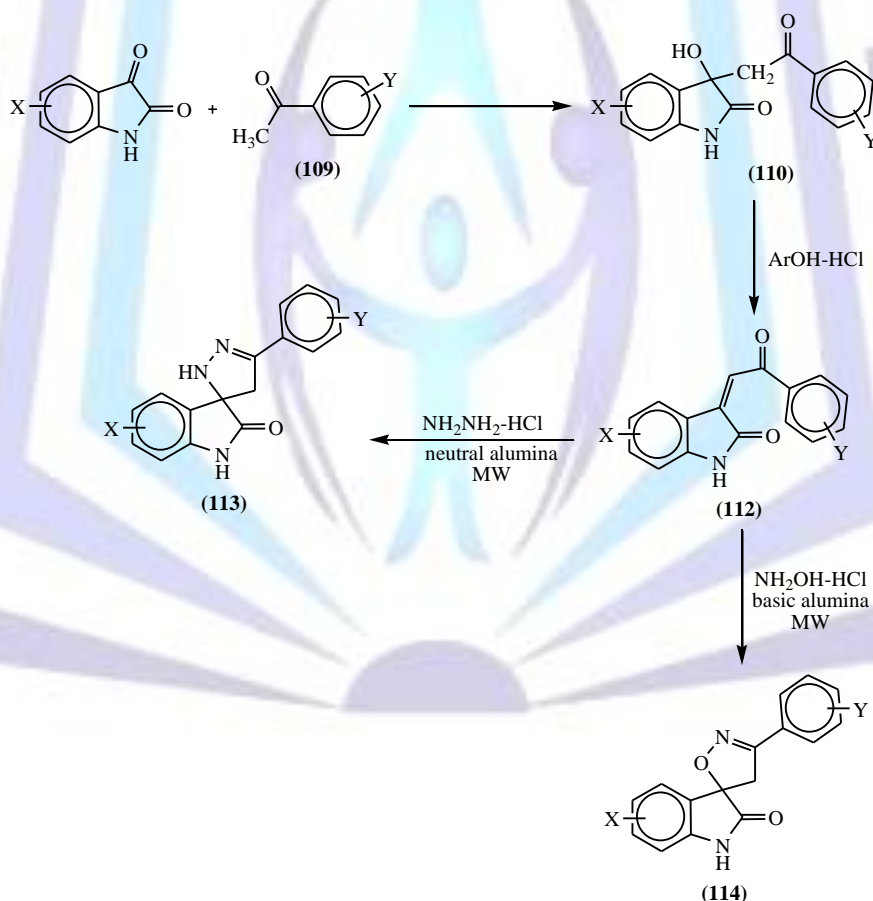
## vii. Spiroisoxazolidine oxindoles

Spiro-[indoline-isoxazolidines] were synthesized by the cycloaddition reaction between ethyl (3-indolydene)-acetate **1** [167] and various substituted  $\alpha,N$ -diphenylnitrones **106** (Scheme 34). The nitrones [168-171] were prepared by the condensation of appropriately substituted aromatic aldehydes with phenylhydroxylamine in ethanol at room temperature. Though, spiro compounds **107** and **108** have been prepared just by irradiating the mixture of ethyl(3-indolydene)acetate **1** and the  $\alpha,N$ -diphenylnitrones **106** in the absence of any solvent for 4-5 min [172].

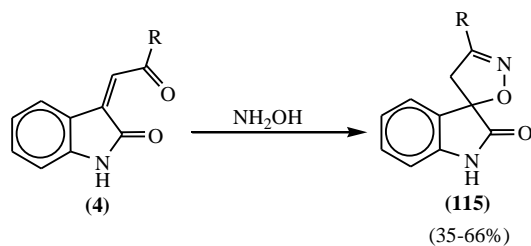




The spiro[indole-pyrazoles] **113**, spiro[indole-isoxazoles] **114** were synthesized through conventional, microwave solution phase and microwave solid phase reactions of 3-aryl methylene-indole-2-ones **112** with hydrazine hydrate and hydroxyl amine hydrochloride <sup>[173]</sup>. (**Scheme 35**)

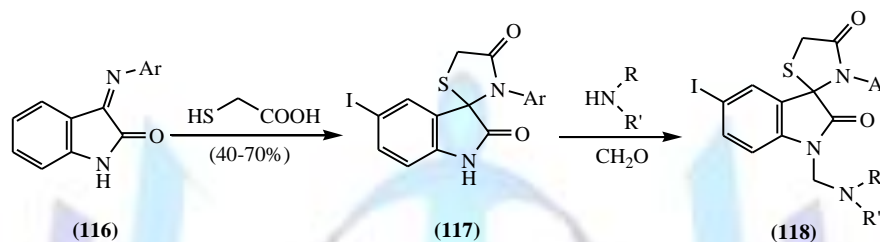


1-Alkyl (or Aryl)-3-(2-oxopropylidene)indolin-2-one **4** reacted with hydrazine hydrate, phenyl hydrazine, phenyl thiourea and/or hydroxyl amine hydrochloride gave spiro[pyrazole- and spiroisoxazole] oxindoles **115** <sup>[174-176]</sup>.



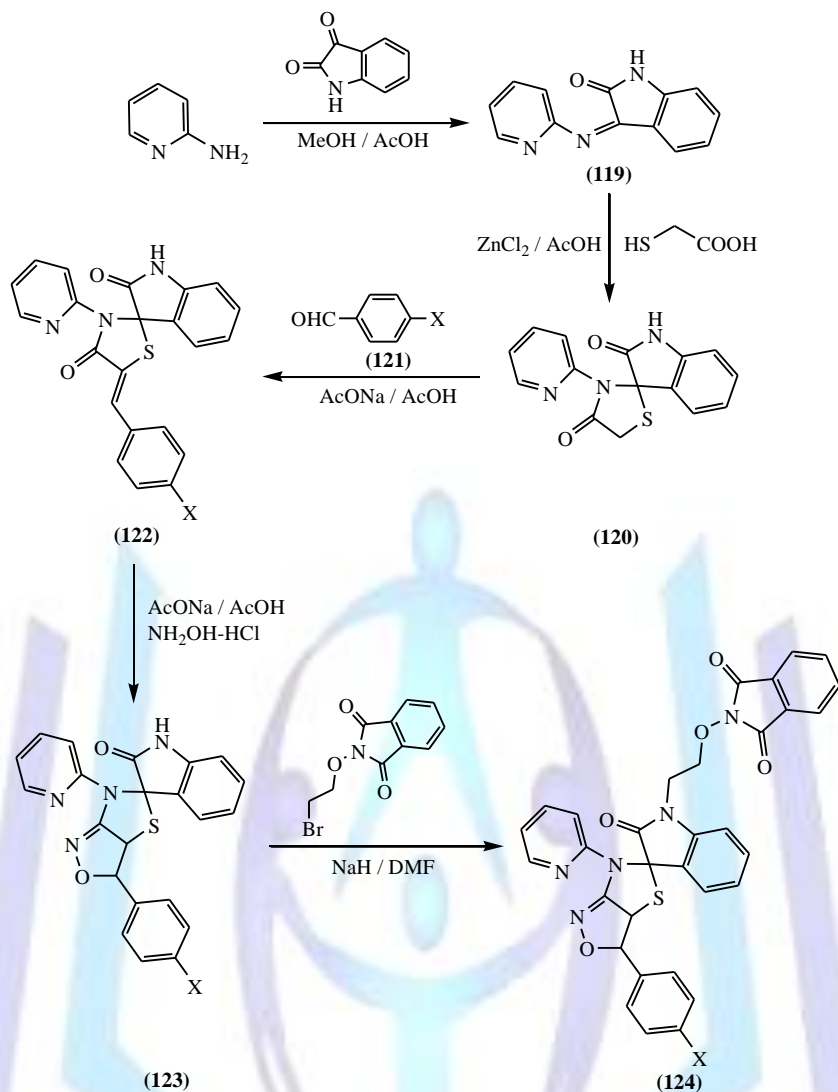
### viii. Spirothiazolidine oxoindoles

Isatin-3-*N*-arylamines **116** react with mercaptoacetic acid to yield spirothiazolidinones **117** <sup>[177]</sup> which can be further acylated or submitted to a Mannich reaction giving substitution product at the oxoindole nitrogen atom **118** <sup>[178]</sup>. (Scheme 36)

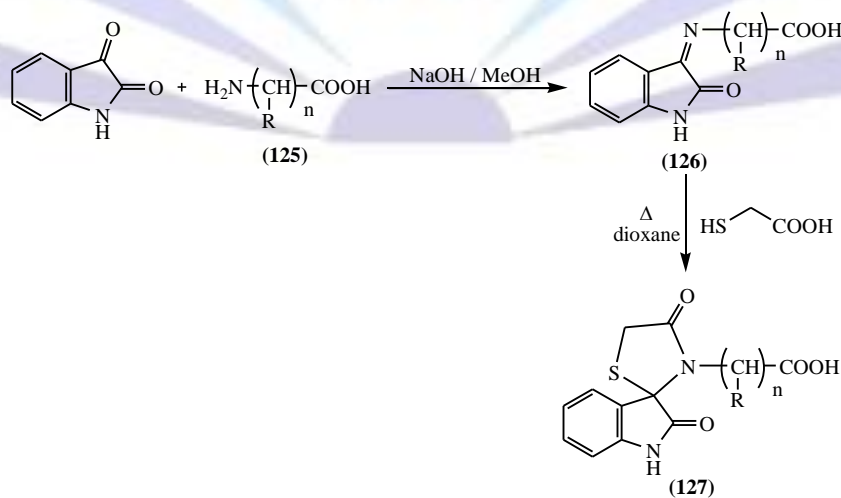


**Scheme 36**

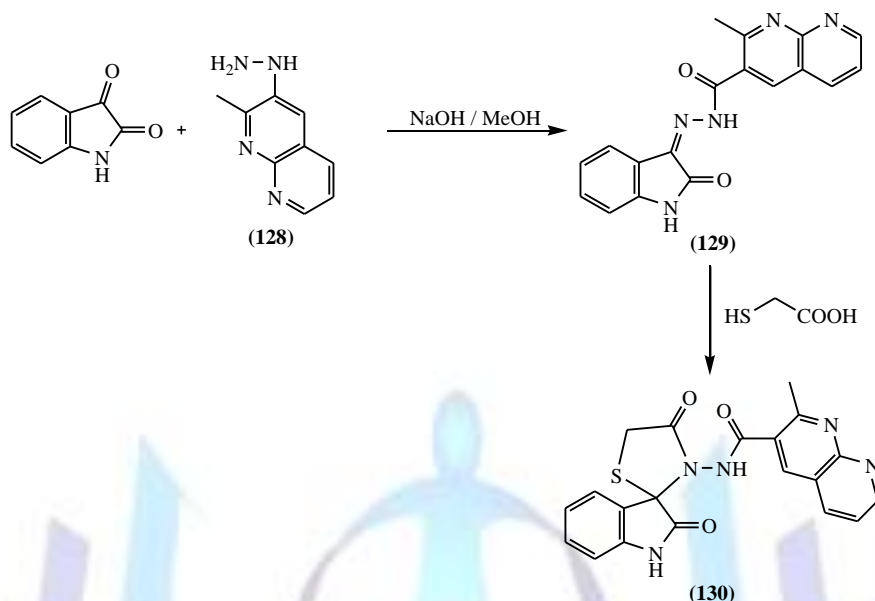
The synthesis of 3'-[(4-substituted phenyl-1-*N*-ethoxyphthalimido-6'-pyridin-2-yl]-3,3a'-dihydro-6'*H*-spiro[indole-3,5'-[1,3]-thiazolo[4,5-*c*]isoxazol]-2(1*H*)-ones **124** is carried out through a five step pathway starting from acid catalyzed condensation of 2-aminopyridine with isatin yielding 3-(pyridine-2-ylimino)-1,3-dihydro-2*H*-indol-2-one **119** which on reaction with thioacetic acid in the presence of anhydrous ZnCl<sub>2</sub> give 3'-pyridin-2-yl-4'*H*-spiro[indole-3,2'-[1,3]thiazolidine]-2,4'(1*H*)-dione **120**. Reaction of **120** with various araldehydes **121** affords the corresponding 5-[(4-[indole-3,2'-[1,3]thiazolidine]-2,4'(1*H*)-diones **122**. These chalcones are further cyclized with hydroxylamine hydrochloride to furnish 3'-(4-substituted phenyl)-6'-pyridin-2-yl-3,3a'-dihydro-6'*H*-spiro[indole-3,5'-[1,3]thiazolo [4,5-*c*]isoxazol]-2(1*H*)-ones **123** which are subsequently condensed with ω-bromoethoxyphthalimide to yield the targeted compounds **124** <sup>[179]</sup>. (Scheme 37)


**Scheme 37**

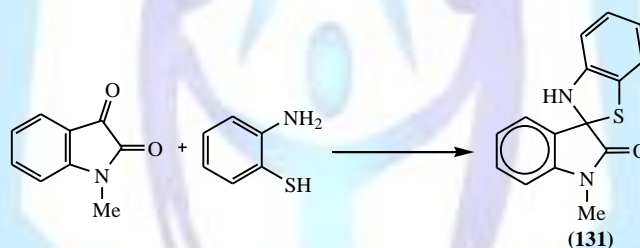
2-[2,4'-dioxospiroindole-3,2'-thiazolidin-3'-yl]alkanoic acids **127** have been prepared by reacting 2-indolone-3-yl imino alkanic acid **126** with mercapto acetic acid <sup>[180]</sup>. (**Scheme 38**)


**Scheme 38**

The hydrazide **128** condensed with isatin to give the desired condensation product **129** which when treated with thioglycolic acid afforded 2,4-(dioxospiro [indoline-3,2-thiazolidine]-3'-yl)-2-methyl-1,8-naphthylidine-3-carboxamide **130** <sup>[181]</sup>. (**Scheme 39**)

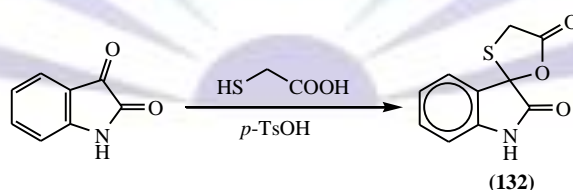


1-Methyl isatin reacts with 2-mercaptoaniline only at reflux furnishing solely the spiro[indole-3,2'-[1,3]benzothiazole-2(1*H*)]one **131** <sup>[182]</sup>. (**Scheme 40**)



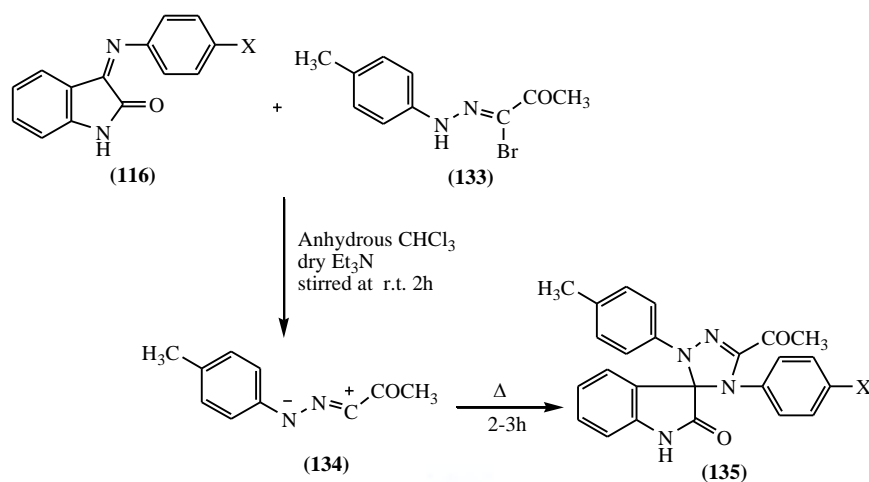
### ix. Spiro 1,3-oxathiolane oxoindoles

Spiro[indoline-3,2'-[1,3]-oxathiolane]2,5'-dione **132** was synthesized by the reaction of isatin with mercaptoacetic acid in the presence of *p*-toluene sulphonic acid <sup>[183]</sup>.

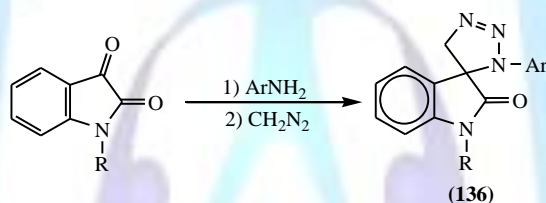


### x. Spirotriazole oxoindoles

The indole ring, linked to other heterocyclic system through the spiro carbon atom at C-3, are of interest. In addition, varied pharmacological properties are associated with 1,2,4-triazolines <sup>[184-189]</sup>. Spiro-[3*H*-indole-3,3'-[Δ<sup>2</sup>-1-2-4]-triazoline]-2-ones **135** were obtained by the reaction of isatin imines **116** <sup>[190]</sup> with C-acetyl nitrile imine **134**, generated *in situ* from the corresponding hydrazinoyl bromide **133**. (**Scheme 41**)

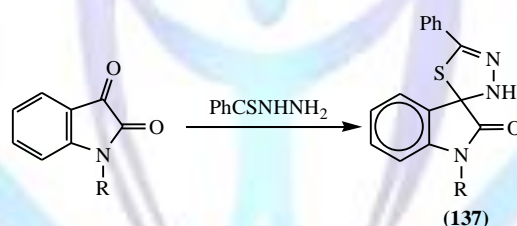


1-Alkyl-3'-aryl-3',5'-dihydrospiro[indoline-3,4'-[1,2,3]triazol]-2-one **136** was prepared via the condensation of *N*-alkyl isatin with aromatic amine followed by diazomethane <sup>[191,192]</sup>.

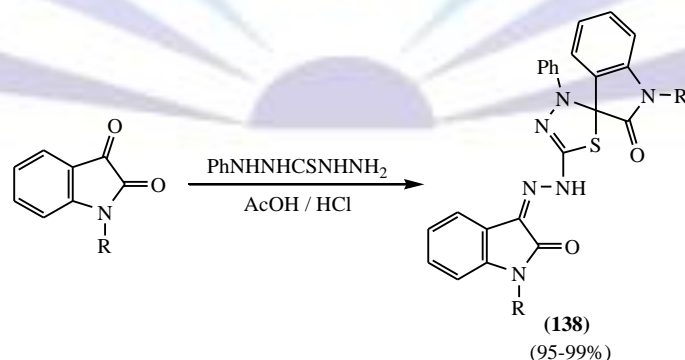


### xi. Spiro[1,3,4]thiadiazole oxindoles

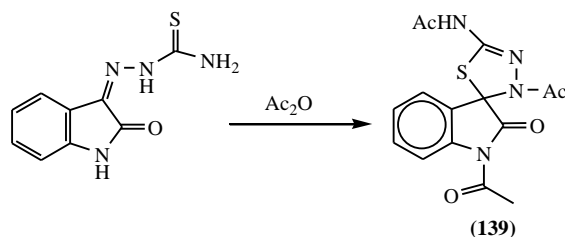
Spiro[indoline-3,2'-[1,3,4]thiadiazole **137** was obtained upon treatment of isatin with thiobenzoyl hydrazine <sup>[193,194]</sup>.



*N*-Substituted isatin when reacted with thioxodihydrazide in acetic acid with HCl afforded the spiro[1,3,4]thiadiazole oxindole derivative **138** <sup>[195]</sup>.

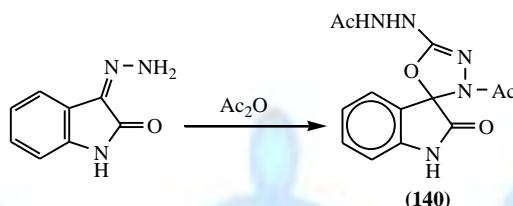


Isatin thiosemicarbazone was reacted with freshly distilled acetic anhydride yielded *N*-(1,3'-diacetyl-2-oxo-3'*H*-spiro[indoline-3,2'-[1,3,4]thiazole]-5'-yl)acetamide **139** <sup>[196]</sup>.



## xii. Spiro[1,3,4]oxadiazole oxindoles

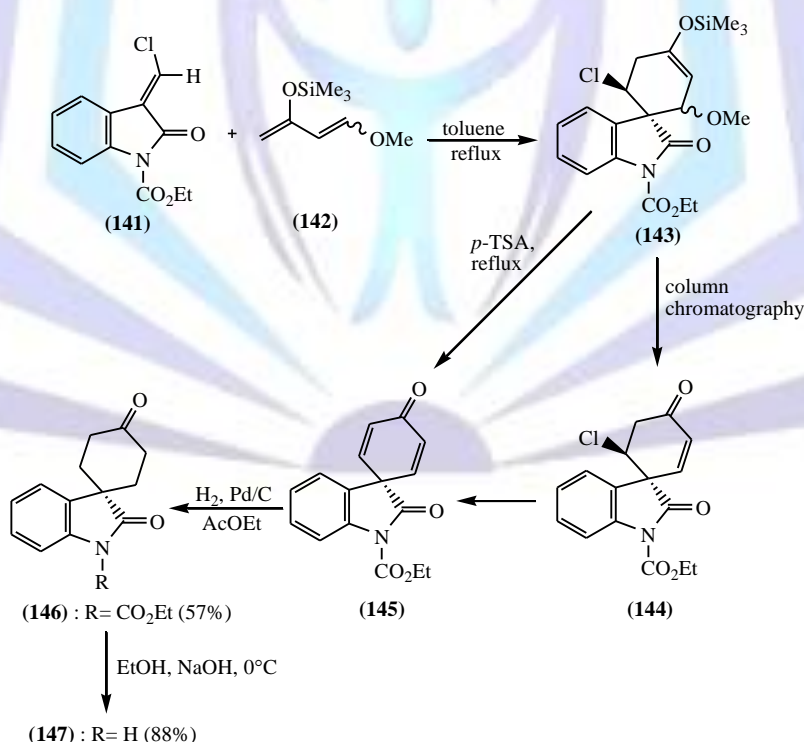
5-spiro(isatin)2(*N*-acetyl hydrazine)-4-(*N*-acetyl)- $\Delta^2$ -1,3,4-oxadiazoline **140** was formed by oxidative cyclization of isatin-3-carbohydrazone with freshly distilled acetic anhydride<sup>[197]</sup>.



## D) SPIRO[SIX-MEMBERED RING]OXOINDOLES

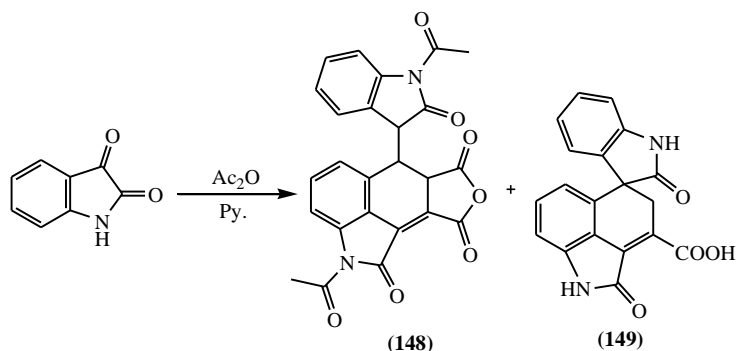
### i. Spiro cyclohexane-1,3'-indoline

A new synthetic pathway to spiro[cyclohexane-1,3'-indoline]-2',4-diones **146**, **147** was found starting from 3-chloromethylene-2-indolones **141** and Danishefsky's diene **142**. Their synthesis consist of several steps involving the formation of the cycloadducts, the 6-chloro-4-trimethylsilyloxy-2-methoxyspiro[cyclohex-3-en-1,3'-indolin]-2'-one **143** derivatives, transformed into spiro[cyclohexa-2,5-dien-1,3'-indoline]-2',4-diones **145** via 6-chloro-spiro[cyclohex-2-en-1,3'-indoline]-2',4-dione **144** intermediates. The reduction of spiro[cyclohexa-2,5-dien-1,3'-indoline]-2',4-diones **145** gave spiro[cyclohexane-1,3'-indoline]-2',4-diones **146,147**.<sup>[198]</sup> (Scheme 42)

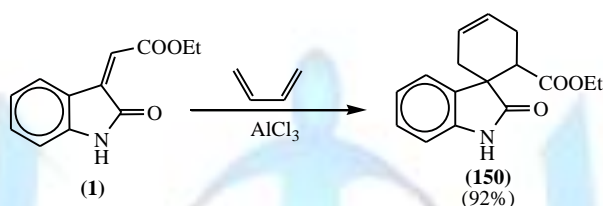


Scheme 42

The reaction of isatin and acetic anhydride in the presence of pyridine afforded the spiro cyclohexane oxindole **149** together with other polycyclic product **148**.<sup>[199,200]</sup>

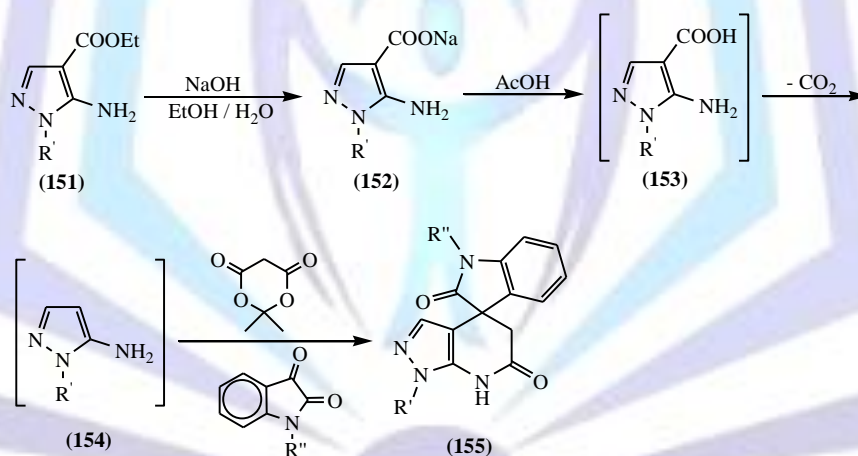


Ethyl 2-(2-oxoindolin-3-ylidene)acetate **1** was reacted with cisoid diene in anhydrous aluminium chloride to give the spiro cyclohexene oxindole derivative **150** <sup>[201]</sup>.



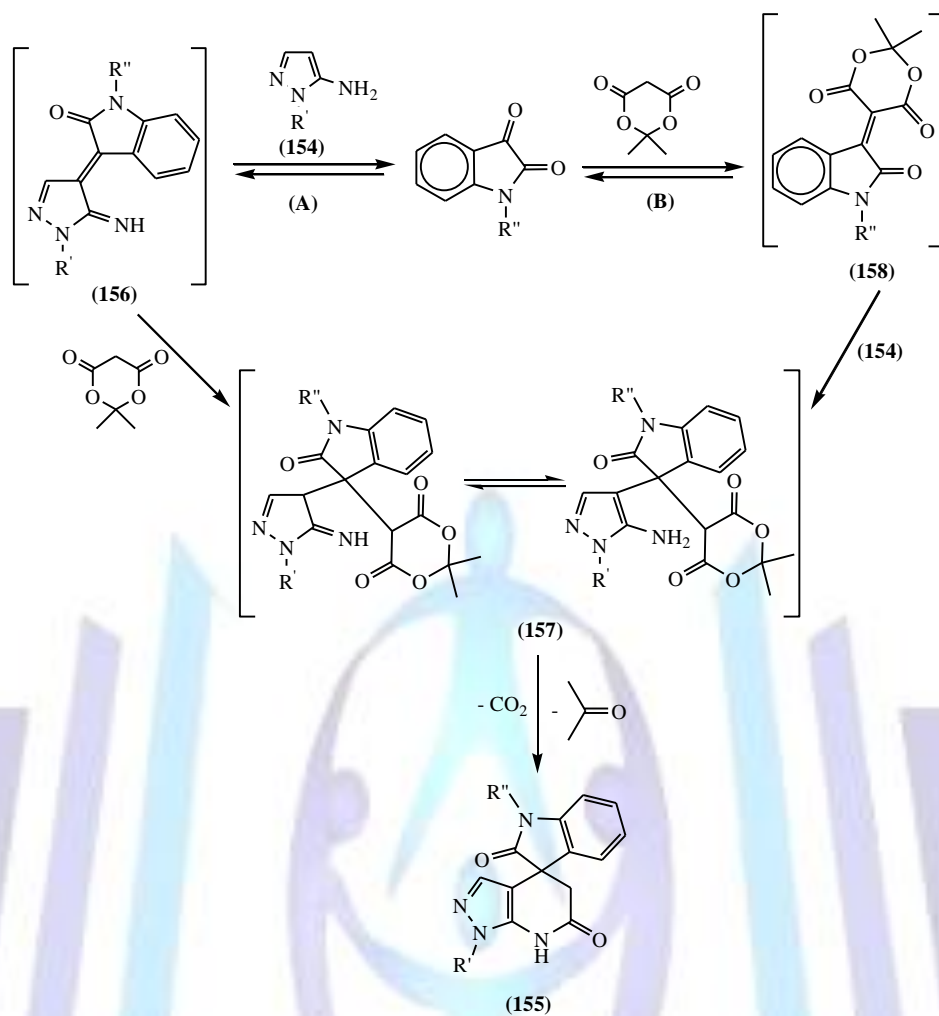
## ii. Spiro pyridine oxindole

The synthesis of spirooxy indole system based on the condensation of isatins with dimedone <sup>[202]</sup> and substituted 6-aminouracils <sup>[203]</sup> resulting in spiro[indoline-3,9'-xantene]trione and spiro[pyrimido[4,5-*b*]quinolone 5,5'-pyrrole[2,3-*d*]pyrimidine] pentone derivatives, respectively, have been described <sup>[202,203]</sup>. The synthesis of 1,7-dihydro spiro[pyrazolo[3,4-*b*]pyridine-4,3'-indole]-2',6(1'*H*,5'*H*)diones based on a three-component condensation of 5-aminopyrazole derivatives **154**, isatin and Meldrum's acid <sup>[204]</sup>. (**Scheme 43**)

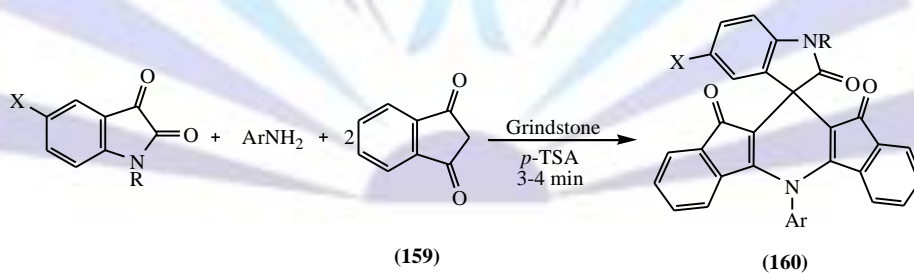


**Scheme 43**

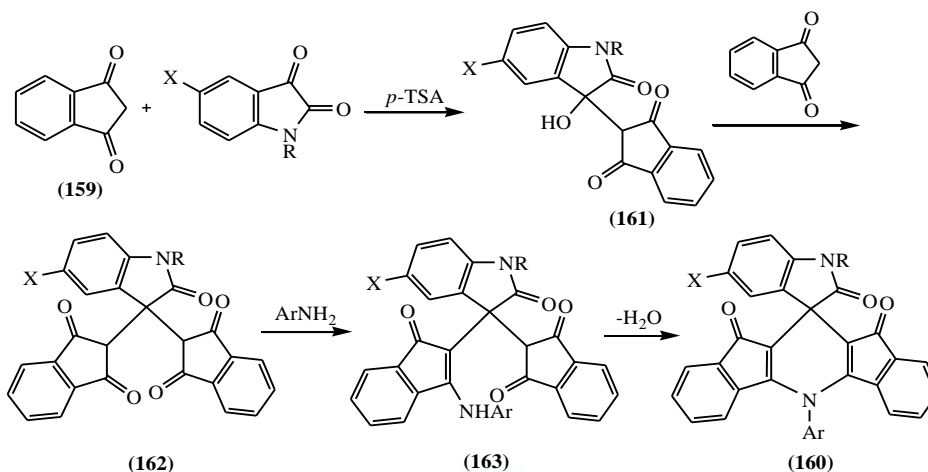
It was assumed that the reaction occurs according to one of two most probable paths (**Scheme 44**). Thus, isatin can first add to 5-aminopyrazole **154** giving the adduct **156**, which further reacts with Meldrum's acid to form unstable intermediate **157**, which eliminates CO<sub>2</sub> and acetone (**path A**) affording the final product **155**. An alternative scheme of the process includes the Michael addition of 5-aminopyrazole **154** to oxindolylidene derivative of Meldrum's acid **158** followed by the intermolecular cyclization (**path B**).



A one-pot, pseudo four-component, and simple synthesis of spiro[diindenopyridine-indoline]triones **160** via the reaction of 1,3-indandione **159**, aromatic amines and isatins using a 'Grindstone Chemistry' method is reported <sup>[75]</sup>. (Scheme 45,46)

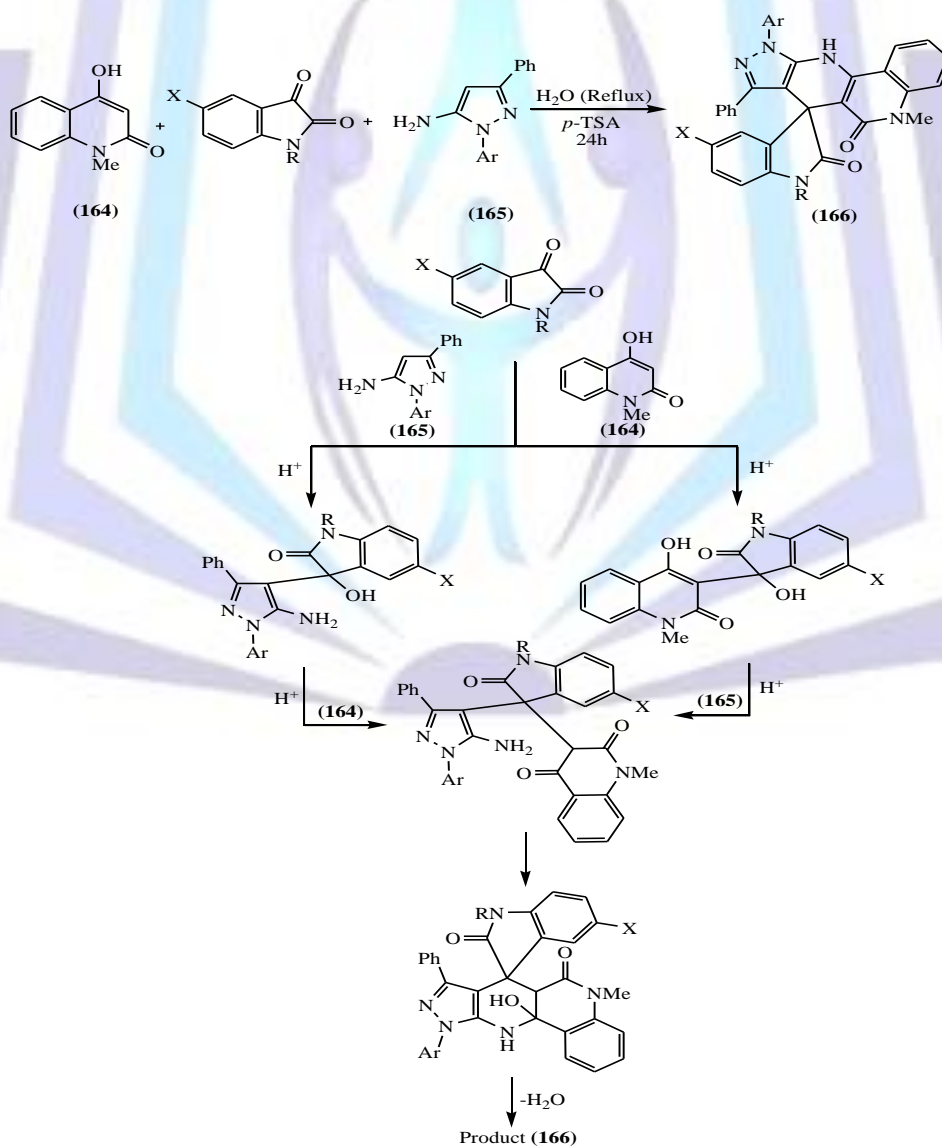




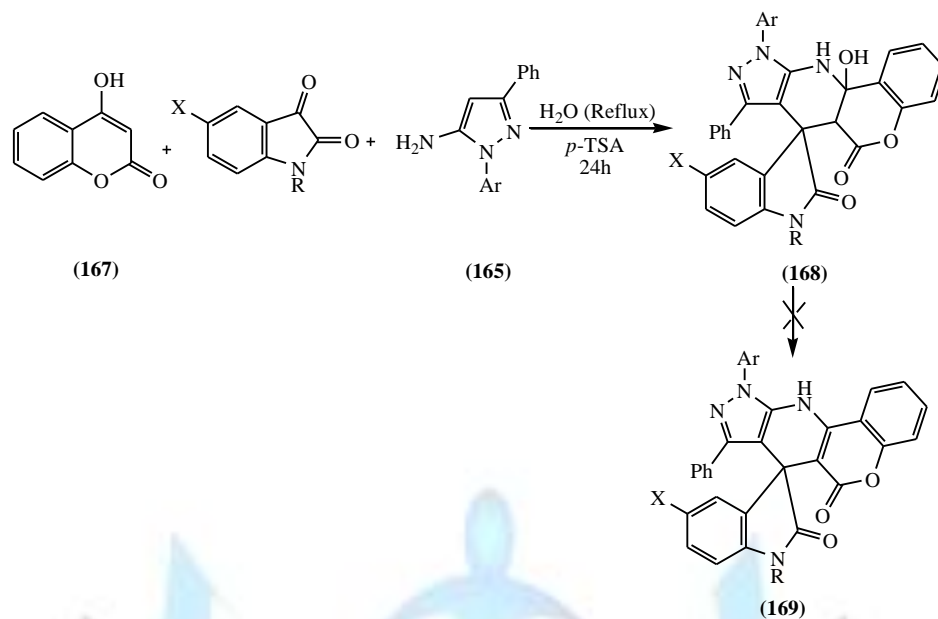


**Scheme 46. Proposed mechanism for the synthesis of spirodiindenopyridine-indoles 160.**

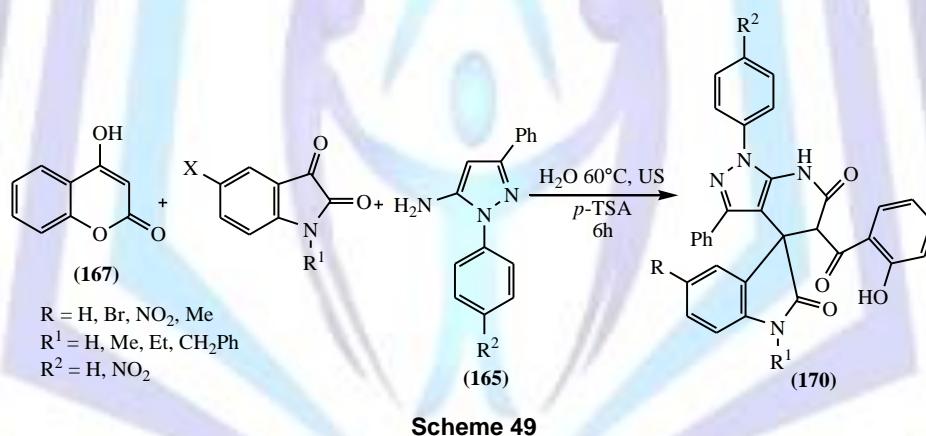
The synthesis of spiro[benzo[*h*]pyrazolo[3,4-*b*][1,6] naphthyridine-7,3'-indoline]-2',6(5*H*)diones **166** and spiro[chromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridine-7,3'-indoline]-2',6(6*aH*,10*H*)diones **168** via a one-pot, three-component reaction of 4-hydroxy-1-methyl quinolin-2(1*H*)-one **164**, or 4-hydroxy coumarin **167**, isatin and 1*H*-pyrazol-5-amines in water was reported<sup>[205]</sup>. (**Scheme 47,48**)



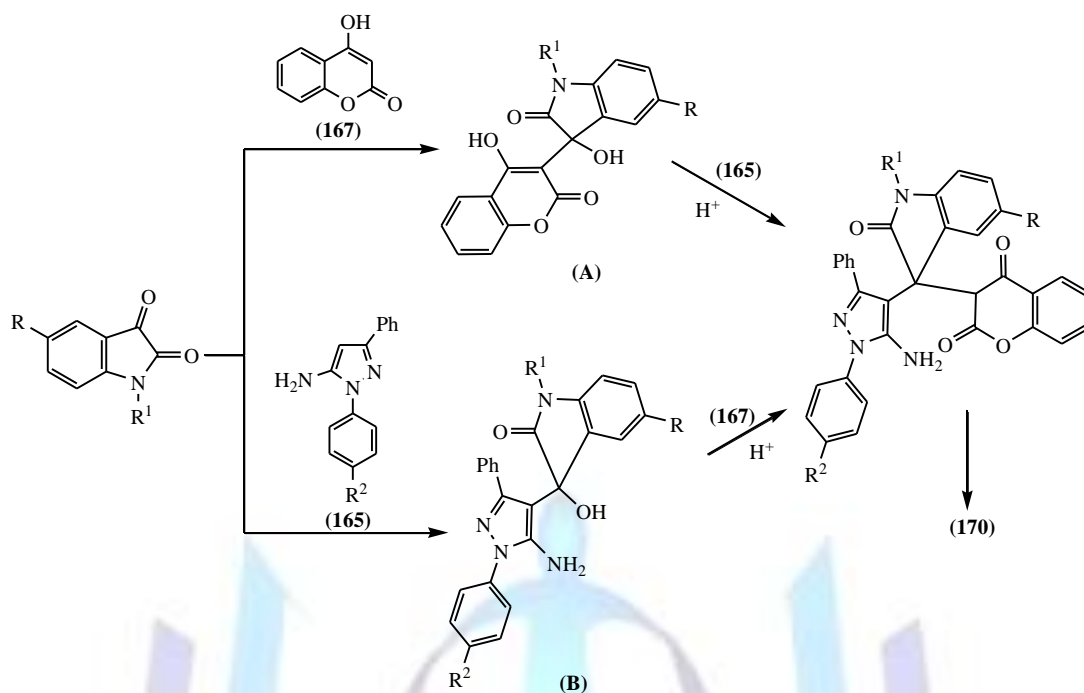
**Scheme 47**



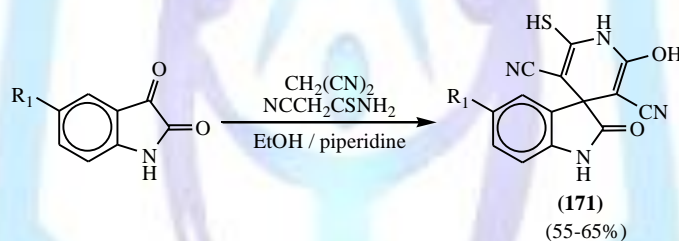
The synthesis of spiro[indoline-3,4'-pyrazolo[3,4-*b*]pyridine]-2,6'(1'*H*)-diones **170** by the reaction of 4-hydroxycoumarin, isatins and 1*H*-pyrazol-5-amines in water under ultrasonic irradiation is reported. The advantages of this method are the use of an inexpensive and readily available catalyst, easy work-up, good yields, and the use of water as a solvent that is considered to be relatively environmentally benign<sup>[206]</sup>. (**Scheme 49**)



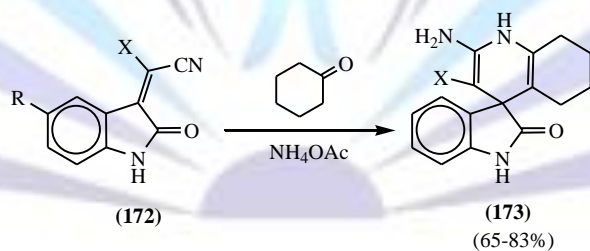
Exact mechanism for the formation of spiro[indoline-3,4'-pyrazolo[3,4-*b*]pyridine]-2,6'(1'*H*)-diones **170**, however, two reasonable possibilities are indicated in (**Scheme 50**). Addition of 4-hydroxycoumarin to isatin leads to highly reactive intermediate **A** via standard nucleophilic addition. Interception of **A** by 1*H*-pyrazol-5-amines **165** and followed by cyclization produces the corresponding spirooxindole **170** (**Pathway A**). Isatin and 1*H*-pyrazol-5-amines **165** would react to produce highly reactive intermediate **B**, followed by a nucleophilic addition with 4-hydroxycoumarin and cyclization to afford spirooxindole **170** (**Pathway B**). (**Scheme 50**)



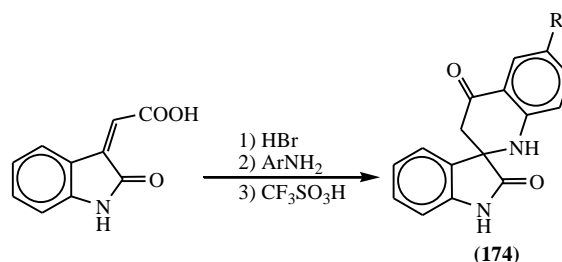
2'-Hydroxy-6'-mercapto-2-oxo-1*H*-spiro[indolin-3,4'-pyridine]3,5-dicarbonitrile **171** was prepared from the reaction of isatin with malononitrile followed by cyanothioacetamide in presence of piperidine in refluxing ethanol <sup>[207]</sup>.



2-Oxoindol-3-ylidene malononitrile **172** (X= CN, CO<sub>2</sub>Et) when react with cyclohexanone in anhydrous ammonium acetate afforded the spiroindole oxindole derivative **173** <sup>[208]</sup>.

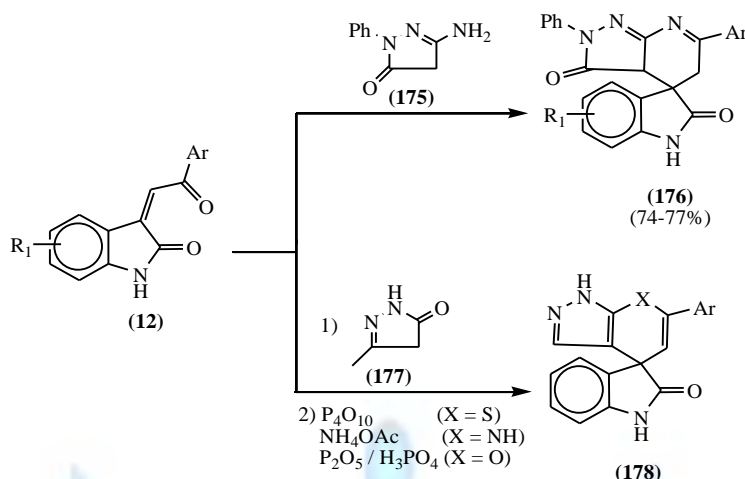


2-(2-oxoindolin-3-ylidene)acrylic acid was converted to spiroindole oxindole derivative **174** via the reaction with HBr, aromatic amine and trifluoromethyl sulphonic acid <sup>[209]</sup>.



3-(2-oxopropylidene)indolin-2-one **12** reacted with 3-amino-1-phenyl pyrazolo-5-one **175** to give the spiro[indolin-3,4'-pyrazolo[3,4-*b*]pyridine]2,3' (2'*H*)dione **176** whereas, the reaction of **12** with pyrazolone **177** in P<sub>4</sub>S<sub>10</sub>, ammonium

acetate and/or  $P_2O_5/H_3PO_4$  yielded spirothiine-, spiropyridine-, and spiropyrane oxindoles derivative **178** respectively [210,211]. (Scheme 51)



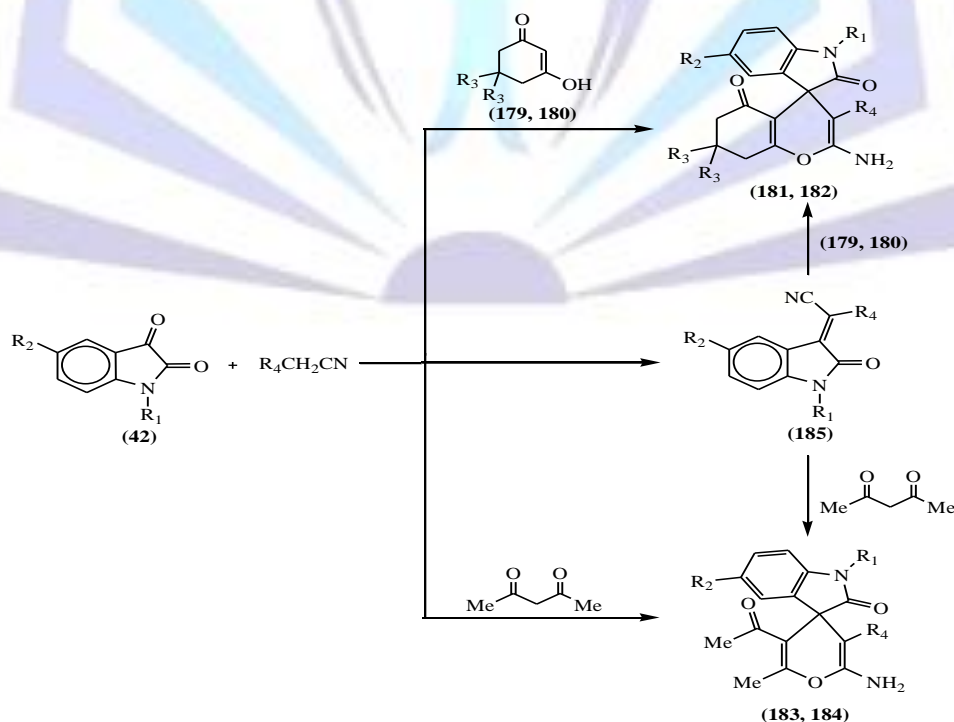
Scheme 51

### iii. Spiropyrane oxindoles

Three-component condensation of isatins with malononitrile or ethyl cyanoacetate and cyclic 1,3-diketone, cyclohexane-1,3-dione **179** or dimedone **180**, on heating for a short time in ethanol in the presence of an equimolar amount of tris(2-hydroxyethyl)amine gave the corresponding 2-amino-3-R-5,6,7,8-tetrahydrospiro[chromene-4,3'-indole]-2',5(1'*H*,4*H*)-diones **181** or 2-amino-3-R-7,7-dimethyl-5,6,7,8-tetrahydrospiro[chromene-4,3'-indole]-2',5(1'*H*,4*H*)-diones **182**. (Scheme 52)

Replacement of cyclic 1,3-diketones by acetylacetone in the condensation with isatin and malononitrile or ethyl cyanoacetate in the presence of tris(2-hydroxyethyl)amine in ethanol (short heating or reflux for 2 h) also resulted in 2'-amino-2-oxo-3'-R-1,2-dihydrospiro[indole-3,4'-pyran] derivatives **183** and **184**. (Scheme 52)

When 2-(2-oxoindol-3-ylidene)malononitriles or ethyl 2-(2-oxoindol-3-ylidene)cyanoacetate derivatives **185** were used as  $\alpha$ -cyanoethylene component in the Michael reactions with 1,3-dicarbonyl compounds in the presence of a catalytic amount of tris(2-hydroxyethyl)amine, yielded the same fused 4*H*-pyran derivatives **181-184**. Obviously, compounds are key intermediates in the three-component condensation of isatins with CH-active nitriles and 1,3-diketones, which is consistent with the generally accepted mechanism of such reactions [212].

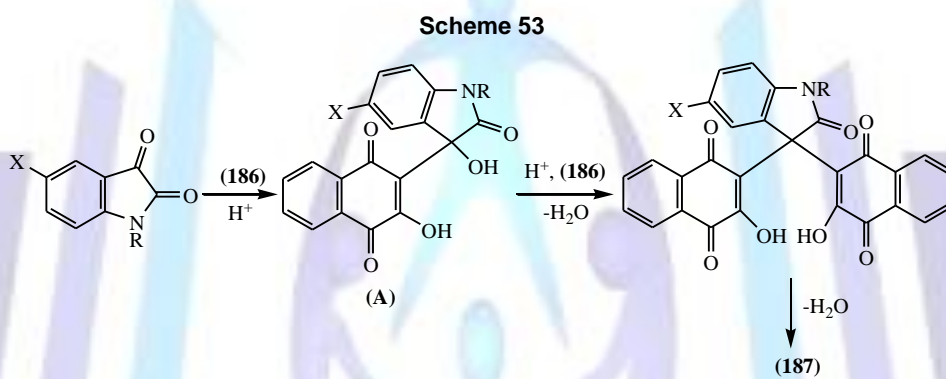
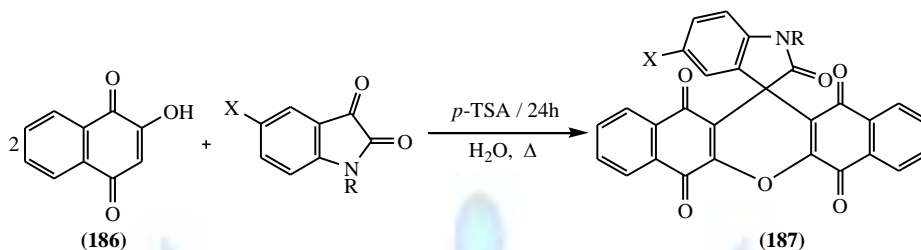


Scheme 52

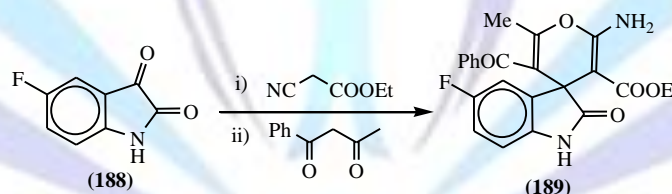
It has been reported that sharing of the indole-3-carbon atom during the formation of spiroindoline derivatives enhances the biological activity highly [6,26,27,35,213,214].

Reaction of 2-hydroxynaphthalene-1,4-dione **186** and isatins in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive and readily available catalyst proceeded smoothly in water at reflux for 24 h to produce spiro[dibenzo[*b*,*l*]-xanthene-13,3'-indoline]-2',5,7,12,14-pentaones **187** in 75-82% yields (**Scheme 53**). Without *p*-TSA, for long periods of time (60 h), the yields of products were low (<30%).

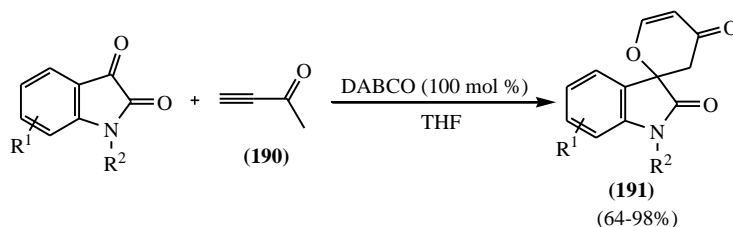
It is thought that compounds **187** result from initial addition of 2-hydroxynaphthalene-1,4-dione **186** to the isatin to yield intermediates **A**, which react further with another molecule of **186**. Finally, cyclization afforded the corresponding products **187**. (**Scheme 54**)



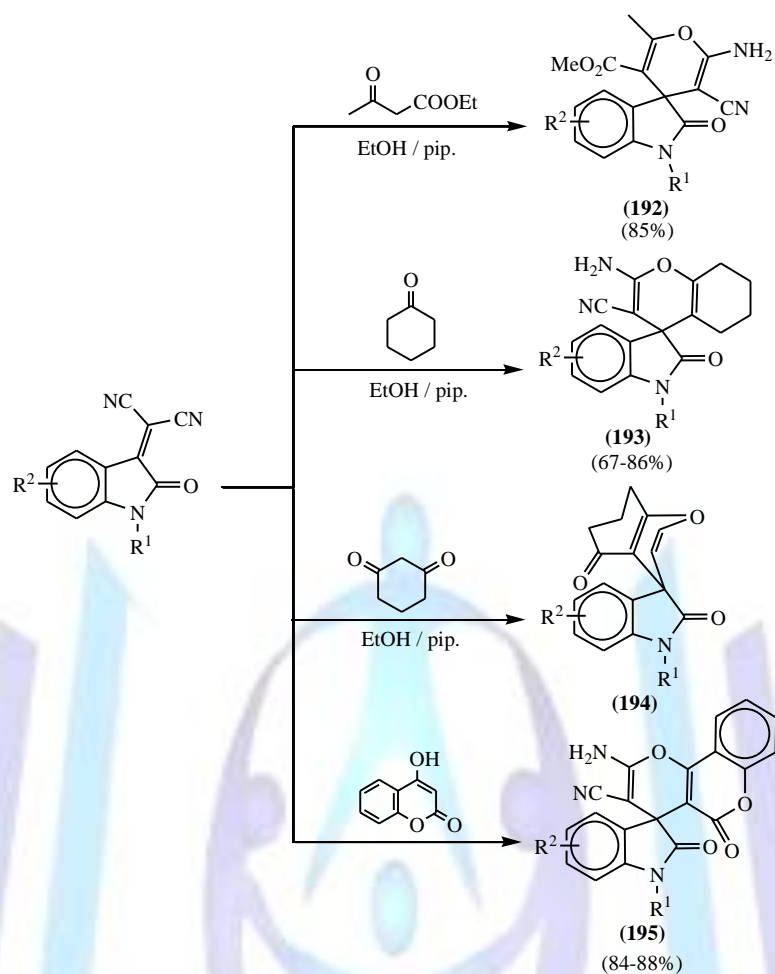
5-Fluoroisatin **188** reacted with ethyl cyanoacetate and substituted ketones affording the spiropyrane oxindole derivative **189** which shows anticonvulsant activity [215].



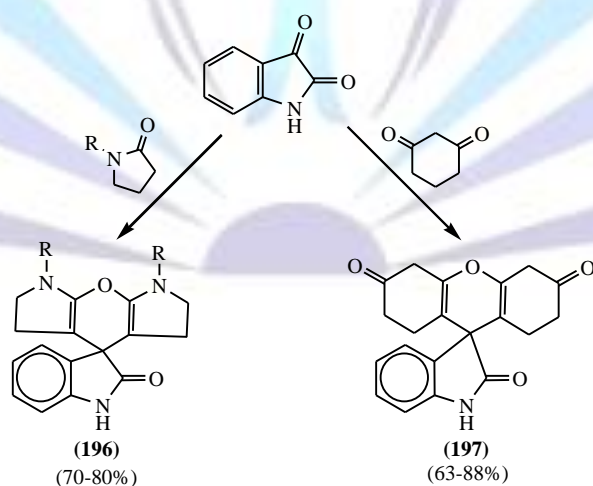
Novel nitrogen and phosphorus-containing lewis bases catalyzed [4+2]annulation of isatin with but-3-yn-2-one giving the corresponding spiro[indoline-3',2'-pyran]-2,4'-(3'*H*)dione **219** [125]. (**Scheme 56**)



The reaction of 2-oxindol-3-ylidene malononitrile with ethyl acetoacetate [216], cyclohexanone, cyclohexan-1,3-dione [217] and/or 4-hydroxycoumarin [218] in the refluxing ethanol in the presence of piperidine afforded the corresponding spiropyrane oxindole derivatives **192-195**, respectively. (**Scheme 57**)

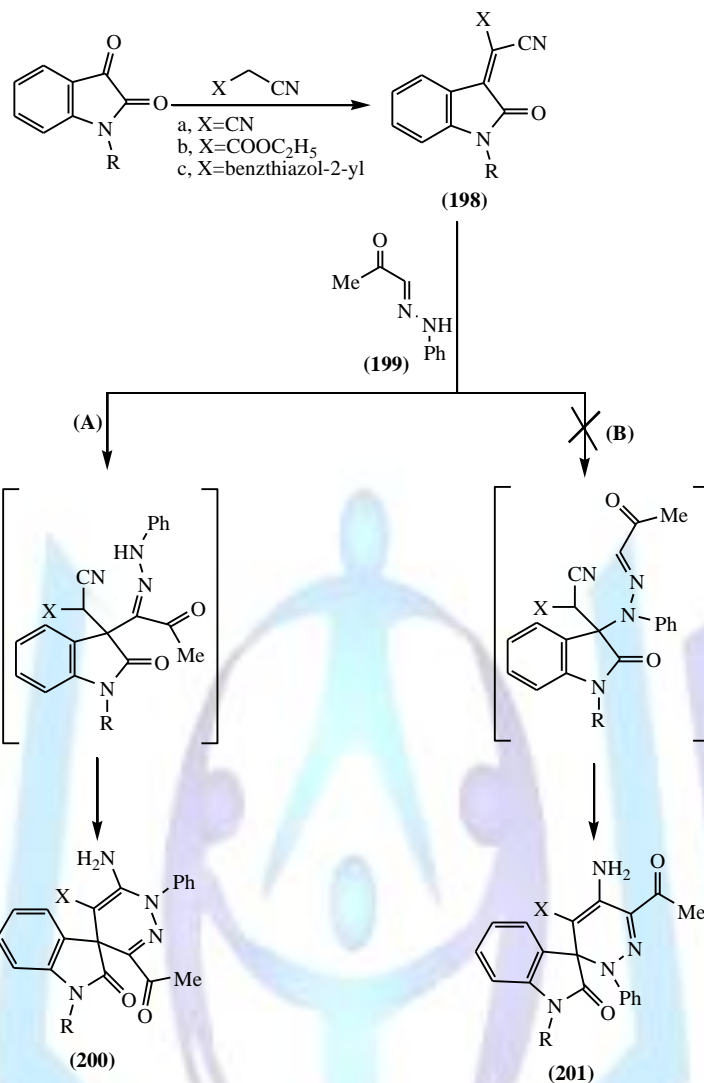

**Scheme 57**

Isatin reacted with *N*-substituted pyrrolidin-2-one <sup>[219]</sup> **190** and/or with cyclohexan-1,3-dione <sup>[220]</sup> and yielded the spiro pyrane oxindole derivatives **196** and **197**, respectively. (**Scheme 58**)


**Scheme 58**

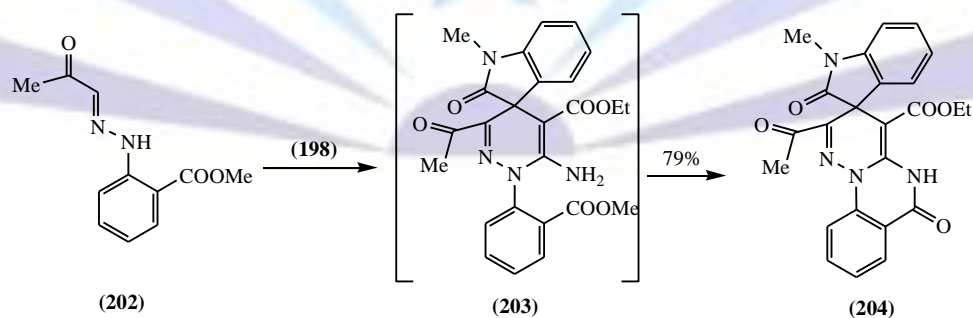
#### iv. Spiropyridazine oxindole

3-Cyanomethylidene oxindole **198** derivatives were prepared in excellent yields utilizing DBU-promoted Knoevenagel condensation of isatin derivatives with active methylene reagents. The isolated products were then reacted with azaenamines **199** via a DBU-promoted Michael addition to yield spirocyclic 2-oxindole derivatives **200,201** incorporated with 6-amino-4*H*-pyridazines <sup>[221]</sup>. (**Scheme 59**)



Scheme 59

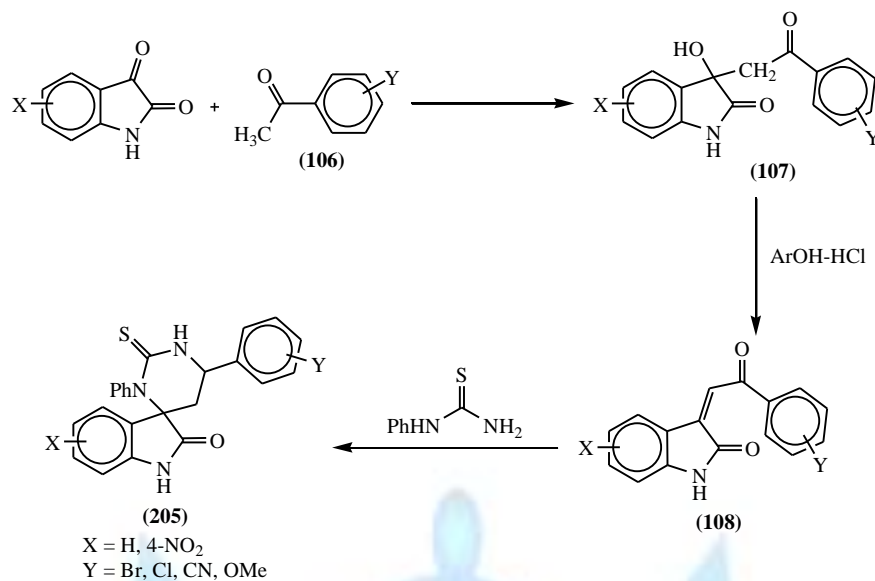
Similarly azaenamine **202** reacted with 3-cyano methylidene-2-oxindole **198** to yield the spiro compound **204** through the intermediate <sup>[205]</sup> **203**. (Scheme 60)



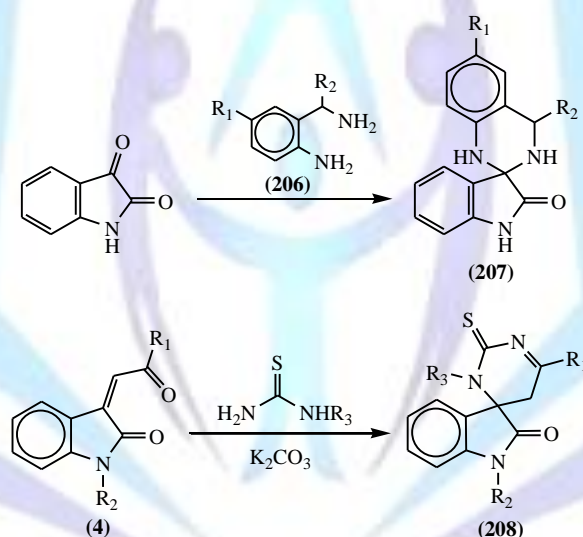
Scheme 60. Synthesis of compound 204.

## v. Spiropyrimidine oxindoles

3-Aroyl methylene-indole-2-ones **108** was synthesized and reacted with phenyl thiourea via conventional, microwave solution phase and microwave solid phase reactions to give the spiro pyrimidine oxindoles <sup>[173]</sup> **205**. (Scheme 61)

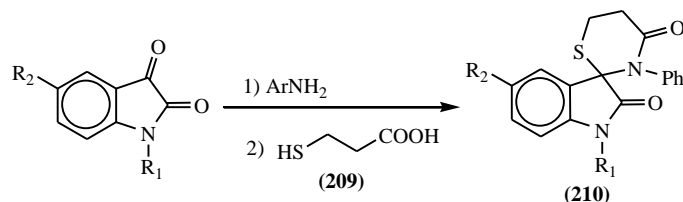

**Scheme 61**

Isatin when reacted with diamine **206** afforded spiro benzopyrimidine oxindole derivative <sup>[222,223]</sup> **207**. Moreover, 2-oxopropylidene indolin-2-one **4** reacted with *N*-substituted thiourea gave the spiro pyrimidine oxindoles derivatives **208** <sup>[224-226]</sup>.



## vi. Spiro 1,3-thiazine oxindole

The reaction of isatin with aromatic amine followed by 3-mercaptopropionic acid **209** afforded spiro 1,3-thiazine oxindole derivative **210** <sup>[227-229]</sup>. (**Scheme 62**)


**Scheme 62**

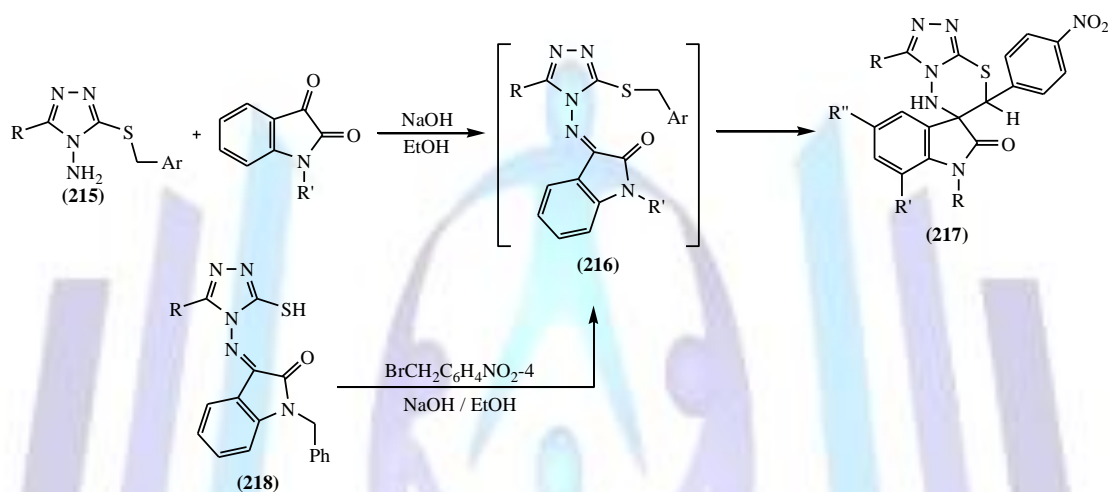
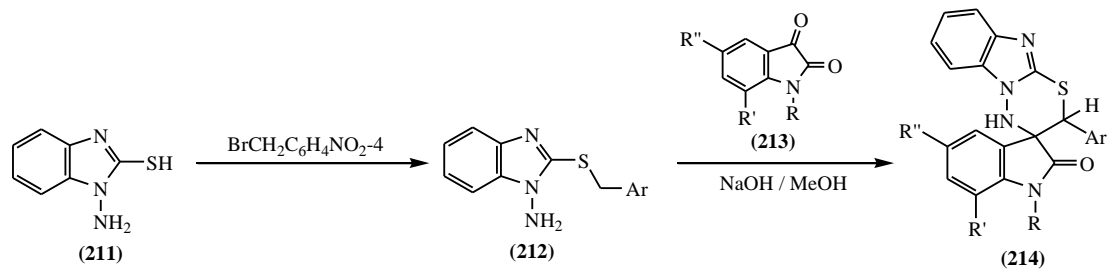
A reaction of 1-amino-1*H*-benzimidazole-2-thiol **211** with 4-nitrobenzyl bromide yielded 1-amino-2-[(4-nitrobenzyl)thio]-1*H*-benzimidazole **212**, which underwent base-catalyzed cyclization with isatins **213** to give the corresponding spirocyclic [1,3,4]thiadiazino[3,2-*a*]benzimidazoles **214**. (**Scheme 63**)

A similar transformation in the base-catalyzed condensation of 4-amino-3-[(4-nitrobenzyl)thio]-4*H*-1,2,4-triazoles **215** with alkylisatins afforded spirocyclic triazolo [3,4-*b*] [1,3,4]thiadiazines **217** (**Scheme 64**).

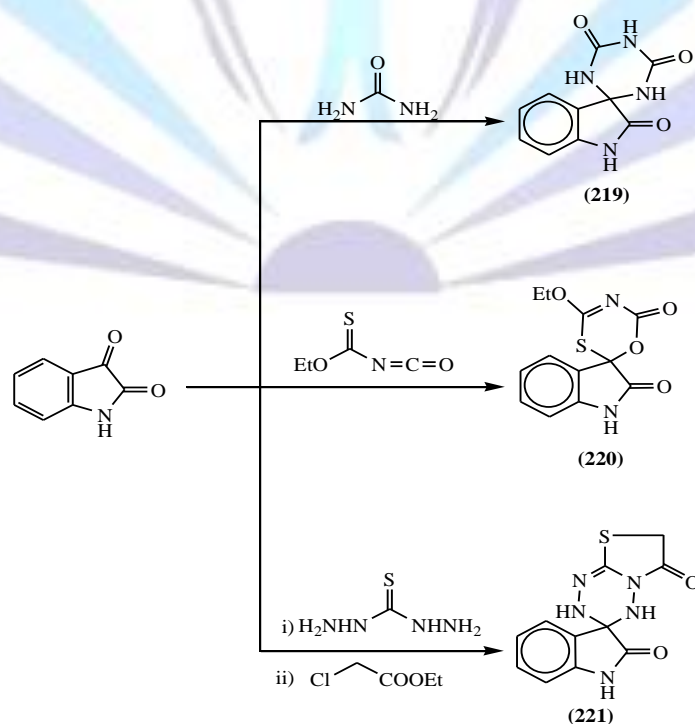




Triazolothiadiazine **217** was also obtained by an independent synthesis from *N*-triazolyl imine **218** and 4-nitrobenzyl bromide in the presence of NaOH (2 equiv.). In both cases, the reaction obviously proceeds through the formation of the corresponding acyclic *N*-benzylthiotriazolyl imine **216**<sup>[230]</sup>.



Spiro 1,3,5-triazine oxindole **219**, spiro 1,3,5-oxathiazine oxindole **220** and spiro 1,2,3,4-tetrazine **221** were synthesized by treating isatin with urea, ethoxy thiocarbonyl cyanate and/or thioxodihydrazide followed by chloroacetic acid, respectively<sup>[231-233]</sup>. (**Scheme 65**)



**References:**

1. Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007.
2. James, D. M.; Kunze, H. B.; Faulkner, D. J. *J. Nat. Prod.* **1991**, *54*, 1137.
3. Kobayashi, J.; Tsuda, M.; Agemi, K.; Shigemiri, H.; Ishibashi, M.; Sasaki, T.; Mikami, Y. *Tetrahedron* **1991**, *47*, 6617.
4. Srivastav, N.; Mittal, A.; Kumar, A. *J. Chem. Soc., Chem. Commun.* **1992**, 493.
5. Williams, R. M.; Cox, R. *J. Acc. Chem. Res.* **2003**, *36*, 127.
6. Da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, *12*, 273.
7. Basavaiah, D.; Reddy, K. R. *Org. Lett.* **2007**, *9*, 57.
8. Miyamoto, H.; Okawa, Y.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2274.
9. Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507.
10. Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wring, S. *J. Med. Chem.* **2006**, *49*, 3432.
11. Teng; Zhang, H.; Mendonca, A. *Molecules* **2006**, *11*, 700.
12. Lo, M. M.-C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Screiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077.
13. Hilton, S. T.; Ho, T. C. T.; Pljevaljcic, G.; Jones, K. *Org. Lett.* **2000**, *2(17)*, 2639.
14. Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 4083.
15. Nakagawa, M.; Taniguchi, M.; Sodeoka, M.; Ito, M.; Yamaguchi, K.; Hino, T. *J. Am. Chem. Soc.* **1983**, *105*, 3709.
16. Chang, K.-T.; Shechter, H. *J. Am. Chem. Soc.* **1979**, *101*, 5084.
17. Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043.
18. Bagul, T. D.; Lakshmaiah, G.; Kawabata, T.; Fuji, K. *Org. Lett.* **2002**, *4*, 249.
19. Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.
20. Trost, B. M.; Frederiksen, M. U. *Angew. Chem.* **2005**, *117*, 312; *Angew. Chem., Int. Ed.* **2005**, *44*, 308.
21. Yong, S. R.; Willams, M. C.; Pyne, S. G.; Ung, A. T.; Skelton, B. W.; White, A. H.; Turner, P. *Tetrahedron* **2005**, *61*, 8120.
22. Beccalli, E. M.; Cleriici, F.; Gelmi, M. L. *Tetrahedron* **2003**, *59*, 4615.
23. Kawasaki, T.; Ogawa, A.; Terashima, R.; Saheki, T.; Ban, N.; Sekiguchi, H.; Sakaguchi, K.; Sakamoto, M. *J. Org. Chem.* **2005**, *70*, 2957.
24. Mao, Z.; Baldwin, S. W. *Org. Lett.* **2004**, *6*, 2425.
25. Somei, M.; Yamada, F.; Izumi, T.; Nakajou, M. *Heterocycles* **1997**, *45*, 2327.
26. Abdel-Rahman, A. H.; Keshk, E. M.; Hanna, M. A.; El-Bady, Sh. M. *Bioorg. Med. Chem.* **2004**, *12*, 2483.
27. Kang, T.-H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. *Eur. J. Pharmacol.* **2002**, *444*, 39.
28. Ma, J.; Hecht, S. M. *Chem. Commun.* **2004**, 1190.
29. Zhu, S.-L.; Jia, S.-J.; Zhang, Y. *Tetrahedron* **2007**, *63*, 9365.
30. Kumar, R. S.; Perumal, S. *Tetrahedron Lett.* **2007**, *48*, 7164.
31. Redkin, R. Gr.; Shemchuk, L. A.; Chernykh, V. P.; Shishkin, O. V.; Shishkina, S. V. *Tetrahedron* **2007**, *63*, 11444.
32. Shanthi, G.; Subbulakshmi, G.; Perumal, P. T. *Tetrahedron* **2007**, *63*, 2057.
33. Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, **1996**.
34. Joshi, K. C.; Chand, P. *Pharmazie* **1982**, *37*.
35. Khafagy, M. M.; El-Wahas, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. *Farmaco* **2002**, *57*, 715.
36. Mohammadi, A. A.; Dabiri, M.; Qaraat, H. *Tetrahedron* **2009**, *65*, 3804.



37. Bose, A. K.; Pednekar, S.; Ganguly, S. N.; Chakraborty, G.; Manhas, M. S. *Tetrahedron Lett.* **2004**, *45*, 8351.
38. Varughese, D. J.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **2006**, *47*, 6795.
39. Toda, F.; Tanaka, K.; Sekikawa, A. *J. Chem. Soc., Chem. Commun.* **1987**, 279.
40. Bazgir, A.; Mohammadi Khanaposhtani, M.; Abolhasani Soorki, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5800.
41. Bazgir, A.; Seyyedhamzeh, M.; Yasaei, Z.; Mirzaei, P. *Tetrahedron Lett.* **2007**, *48*, 8790.
42. Sayyafi, M.; Seyyedhamzeh, M.; Khavasi, H. R.; Bazgir, A. *Tetrahedron* **2008**, *64*, 2375.
43. Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H. R.; Bazgir, A. *J. Heterocycl. Chem.* **2007**, *44*, 1009.
44. Dabiri, M.; Azimi, S. C.; Arvin-Nezhad, H.; Bazgir, A. *Heterocycles* **2008**, *75*, 87.
45. Dabiri, M.; Delbari, A. S.; Bazgir, A. *Synlett* **2007**, 821.
46. Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H. R.; Bazgir, A. *Tetrahedron* **2007**, *63*, 1770.
47. Dabiri, M.; Delbari, A. S.; Bazgir, A. *Heterocycles* **2007**, *71*, 543.
48. Ghahremanzadeh, R.; Imani Shakibaei, G.; Bazgir, A. *Synlett* **2008**, 1129.
49. Bazgir, A.; Noroozi Tisseh, Z.; Mirzaei, P. *Tetrahedron Lett.* **2008**, *49*, 5165.
50. Jadidi, K.; Ghahremanzadeh, R.; Bazgir, A. *Tetrahedron* **2009**, *65*, 2005.
51. Dabiri, M.; Azimi, S. C.; Khavasi, H. R.; Bazgir, A. *Tetrahedron* **2008**, *64*, 7307.
52. Jadidi, K.; Ghahremanzadeh, R.; Bazgir, A. *J. Comb. Chem.* **2009**, *11*, 341.
53. Ghahremanzadeh, R.; Sayyafi, M.; Ahadi, S.; Bazgir, A. *J. Comb. Chem.* **2009**, *11*, 393.
54. Hailer, N.; Holzer, W. *Sci. Synthesis* **2004**, *16*, 125.
55. Woo, G. H. C.; Snyder, J. K.; Wan, Z.-K. *Prog. Heterocycl. Chem.* **2002**, *14*, 279.
56. Cignarella, G.; Barlocco, D. *J. Heterocycl. Chem.* **2002**, *39*, 545.
57. Ghozlan, S. A. S.; Mohamed, M. H.; Abdelmoniem, A. M.; Abdelhamid, I. A. *ARKIVOC* **2009**, x, 302.
58. Abdelhamid, I. A.; Ghozlan, S. A. S.; Kolshorn, H.; Meier, H.; Elnagdi, M. H. *Heterocycles* **2007**, *71*, 2627.
59. Al-Awadi, N. A.; Ibrahim, M. I.; Abdelhamid, I. A.; Elnagdi, M. H. *Tetrahedron* **2008**, *64*, 8202.
60. Ghozlan, S. A. S.; Abdelhamid, I. A.; Gaber, H.; Elnagdi, M. H. *J. Chem. Res.* **2004**, *12*, 789.
61. Ghozlan, S. A. S.; Abdelhamid, I. A.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2005**, *42*, 1185.
62. Ghozlan, S. A. S.; Abdelhamid, I. A.; Al-Dib, H. I.; Elnagdi, M. H. *ARKIVOC* **2006**, xv, 53.
63. Yong, S. R.; Ung, A. T.; Pyne, S. G.; Skelton, B. W.; White, A. H. *Tetrahedron* **2007**, *63*, 1191.
64. Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505.
65. Robertson, D. W.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Kauffman, R. F.; Hayes, J. S. *J. Med. Chem.* **1987**, *30*, 824.
66. Feldman, K. S.; Vidulova, D. B.; Karatjas, A. G. *J. Org. Chem.* **2005**, *70*, 6429.
67. Feldman, K. S.; Karatjas, A. G. *Org. Lett.* **2006**, *8*, 4137.
68. Ghozlan, S. A. S.; Abdelhamid, I. A.; Hassaneen, H. M.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2007**, *44*, 105.
69. Abdelhamid, I. A. *Synlett* **2009**, 625.
70. Ghozlan, S. A. S.; Abdelhamid, I. A.; Elnagdi, M. H. *ARKIVOC* **2006**, xiii, 147.
71. Al-Awadi, N.; Abdelhamid, I. A.; Al-Etaibi, A.; Elnagdi, M. H. *Synlett* **2007**, 2205.
72. Al-Awadi, N. A.; Abdelkhalik, M. M.; Abdelhamid, I. A.; Elnagdi, M. H. *Synlett* **2007**, 2979.
73. Warea, M.; Madjeb, B.; Pokalwara, R.; Kakadea, G.; Shingarea, M. *Bull. Cat. Soc. Ind.* **2007**, *6*, 104.
74. Yeom, C.-E.; Kim, M. J.; Kim, B. M. *Tetrahedron* **2007**, *63*, 904.
75. Ramin, G.; Somayeh, A.; Ghazaleh, I. S.; Ayoob, B. *Tetrahedron Lett.* **2010**, *51*, 499.
76. Franke, A. *Justus Liebigs Ann. Chem.* **1978**, *5*, 717.
77. Bennet, G. B.; Mason, R. B.; Shapiro, M. J. *J. Org. Chem.* **1978**, *43*, 4383.
78. Joshi, K. C.; Jain, R.; Arora, S. *Heterocycles* **1987**, *26*, 1853.



79. Martin, M.; Nadler, G.; Zimmermann, R. *Eur. Pat. Appl. Ep.* **1989**, 303, 418, 59.
80. Ponnusamy, S.; Vadivel, V.; Baby, V. *Tetrahedron* **2006**, 62, 4342.
81. Kandapalam, A. P. L.; Asit, B. M.; Ponnusamy, S. *Tetrahedron Lett.* **2011**, 52, 3610.
82. Mesropyan, E. G.; Ambartsumyan, G. B.; Avetisyan, A. A.; Sarkisyan, M. G.; Galstyan, A. S. *Zh. Org. Khim.* **2005**, 41(1), 150.
83. Kennewell, P. D.; Miller, D. J.; Scrowston, R. N.; Westwood, R. *J. Chem. Res. (S)* **1995**, 396.
84. Jain, R. S. *Ind. J. Heterocycl. Chem.* **1992**, 2, 59.
85. Coda, A. C.; Desimoni, G.; Riguetti, P. P.; Tacconi, G.; Dradi, E. *Gazz. Chim. Ital.* **1983**, 113, 191.
86. Koch, T. H.; Olesen, J.; Foy, J. *J. Org. Chem.* **1975**, 40, 117.
87. Dipak, P.; Sunil, G. *Tetrahedron* **2004**, 60, 4909.
88. Graf, R. *Liebig's Ann. Chem.* **1963**, 661, 111.
89. Moriconi, E. J.; Kelley, J. F. *J. Am. Chem. Soc.* **1966**, 88, 3657.
90. Bose, A. K.; Garratt, G.; Pelosi, J. J. *J. Org. Chem.* **1963**, 28, 730.
91. Singh, S. B.; Mehrotra, K. N. *Can. J. Chem.* **1982**, 60, 1901.
92. Singh, G. S.; Mehrotra, K. N. *Indian J. Chem.* **1985**, 24B, 129.
93. Singh, G. S.; Singh, T.; Lakhan, R. *Indian J. Chem.* **1997**, 36B, 951-954.
94. Singh, G. S.; *Heterocycl. Chem.* **2000**, 37, 1355.
95. Alonso, E.; Del Pozo, C.; Gonzalez, J.; *J. Chem. Soc. Perkin Trans.* **2002**, 1, 571.
96. Azizian, J.; Sarrafi, M.; Mehrdad, K. *Indian J. Chem.* **2000**, 39B, 304.
97. Arjona, O.; Csaky, A. G.; Murcia, M. C.; Plumet, J. *Tetrahedron Lett.* **2002**, 43, 6405.
98. Nishikawa, T.; Kajii, S.; Isobe, M. *Chem. Lett.* **2004**, 33, 440.
99. Zanobini, A.; Gensini, M.; Magull, J.; Vidovic, D.; Kozhushkov, S. I.; Brandi, A.; De Meijere, A. *Eur. J. Org. Chem.* **2004**, 4158.
100. Nishikawa, T.; Kajii, S.; Isobe, M. *Synlett* **2004**, (11), 2025.
101. Khasanov, A. B.; Ramirez-Weinhouse, M. M.; Webb, T. R.; Thiruvazhi, M. *J. Org. Chem.* **2004**, 69, 5766.
102. Singh, G. S.; Mmolotsi, B. J.; *J. Heterocycl. Chem.* **2006**, 43, 1665.
103. Singh, G.S. *Tetrahedron* **2003**, 59, 7631.
104. Singh, G. S.; D'hooghe, M.; De Kimpe, N. in: Katritzky, A. R.; Ramsden, C.; Scriven, E. F. V.; Taylor (Eds.), R. *Comprehensive Heterocyclic Chemistry III, Elsevier, New York*, **2008**, 2, 1.
105. Staudinger, H. *Liebig's Ann.* **1907**, 356, 51.
106. Girija, S. S.; Patrick, L. *Eur. J. Med. Chem.* **2009**, 44, 2265.
107. Skiles, J. W.; McNeil, D. *Tetrahedron Lett.* **1990**, 31, 7277
108. Manju, P.; Neeraj, K. S.; Priyanka, K. K. J. *J. Adv. Sci. Res.* **2011**, 2(2), 35.
109. Pai, N. R.; Suryanvansi, J. P. *Ind. J. Chem.* **2006**, 25B, 1226.
110. Zhang, X.-C.; Cao, S.-H.; Wei, Y.; Shi, M. *Chem. Commun.* **2011**, 1548.
111. Zhang, X.-C.; Cao, S.-H.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, 13, 1142.
112. Al-Thebeiti, M. S.; El-Zohry, M. F. *Heterocycles* **1995**, 41, 2475.
113. Wang, L.; Zhang, Y.; Hu, H. -Y.; Fun, H. K.; Xu, J.-H. *J. Org. Chem.* **2005**, 70, 3850.
114. Booker-Milburn, K. I.; Fedoulo, M.; Paknoham, S. J.; Strachan, J. B.; Melville, J. L.; Voyleb, M. *Tetrahedron Lett.* **2000**, 41, 4657.
115. Xue, J.; Zhang, Y.; Wang, X.; Fun, H. K.; Xu, J.-H. *Org. Lett.* **2000**, 2, 2583.
116. Tratat, C.; Giorgi-Renault, S.; Husson, H.-P. *J. Org. Chem.* **2000**, 65, 6773.
117. Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 12, 2209.
118. Toyota, M.; Ihara, M. *Nat. Prod. Rep.* **1998**, 15, 327.



119. Dounary, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261.
120. Balogh, M.; Laszlo, P. *Organic Chemistry Using Clays; Springer: New York, NY*, **1993**, 29, 184.
121. Corma, A. *Chem. Rev.* **1995**, *95*, 559.
122. Chakrabarty, M.; Sarkar, S. *Tetrahedron Lett.* **2003**, *44*, 8131.
123. Dintzner, M. R.; Morse, K. M.; McClelland, K. K.; Coligado, D. M. *Tetrahedron Lett.* **2004**, *45*, 78.
124. Ponnusamy, S.; Vadivel, V. *Tetrahedron* **2008**, *64*, 3322.
125. Lian, Z.; Shi, M. *Eur. J. Org. Chem.* **2012**, *3*, 581.
126. Heindel, N. D.; Minatell, J. A. *J. Pharm. Sci.* **1981**, *70*, 84.
127. Soliman, F. S. G.; Salama, H. M. *pharmazie* **1983**, *38*, 585.
128. Fokas, D.; Ryan, W. J.; Casebier, D. S.; Coffen, D. L. *Tetrahedron Lett.* **1998**, *39*, 2235.
129. Fokas, D.; Coffen, D. L.; Ryan, W. J. WO; 9912904 **1999** [C. A.: 130,237550v].
130. Jeyaperumal, K. S.; Stephen, M. R.; Jeyaraman, S.; Subbu, P.; Subramanian, N. *Chem. Central J.* **2011**, *5*, 45.
131. Garima, S. S.; Vasanth, K.; Habibah, A. W.; Mohd, M. R.; Hoong-Kun, F. *Acta. Cryst.* **2012**, *E68*, 2769.
132. Gowri, S.; Gunasundari, T.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 319.
133. Casaschi, A.; Desimoni, G.; Faita, G.; Invernizzi, A. G.; Grunanger, P. *Heterocycles* **1994**, *37*, 1673.
134. Neelakandan, V. L.; Prakasam, T.; Paramasivan, T. P. *Tetrahedron Lett.* **2010**, *51*, 1064.
135. Kumar, R. R.; Perumal, S.; Senthikumar, P.; Yogeewari, P.; Sriram, D. *Eur. J. Med. Chem.* **2009**, *44*, 3821.
136. Shanmugam, P.; Viswambharan, B.; Madhavan, S. *Org. Lett.* **2007**, *9*, 4095.
137. Shanmugam, P.; Viswambharan, B.; Selvakumar, K.; Madhavan, S. *Tetrahedron Lett.* **2008**, *49*, 2611.
138. Murugan, R.; Anbazhagan, S.; Narayanan, S. S. *Eur. J. Med. Chem.* **2009**, *44*, 3272.
139. Babu, A. R. S.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 6809.
140. Bovio, B.; Locchi, S. *J. Chem. Crystallogr.* **2002**, *32*, 69.
141. Rehn, S.; Bergman, J.; Stensland, B. *Eur. J. Org. Chem.* **2004**, *2*, 413.
142. Babu, A. R. S.; Raghunathan, R. *Tetrahedron* **2007**, *63*, 8010.
143. Raju, S. K.; Stephen, M. R.; Subbu, P.; Debjani, B.; Perumal, Y.; Dharmarajan, S. *Eur. J. Med. Chem.* **2010**, *45*, 411.
144. Raju, S. K.; Subbu, P. *Tetrahedron Lett.* **2007**, *48*, 7164.
145. Mehdi, G.; Ahmed, Y.; Seyed, J. T. R.; Abuzar, T. *Tetrahedron Lett.* **2009**, *50*, 4724.
146. Bergman, J.; Stalhandske, C.; Vallberg, H. *Acta. Chem. Scand.* **1997**, *51*, 753.
147. Grigg, R.; Aly, M. F.; Sridharan, V.; Thianpatanagul, S. *J. Chem. Soc. Chem. Commun* **1984**, *3*, 182.
148. Coulter, T.; Grigg, R.; Malone, J. F.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 5417.
149. Nyergers, M.; Gajdics, L.; Szöllösy, A.; Töke, L. *Synlett.* **1999**, 111.
150. Agarwal, S.; Pande, A.; Saxena, V. K.; Chowdhury, S. R. *Indian Drugs* **1985**, *22*, 633.
151. Gisele, Z. S.; Luana, B. P.; Daniele, G.; Thaian, E. F. M.; Nubia, M. R.; Angelo, C. P.; Margarete, M. T.; Roberto, T. S. *Pharmacology Biochemistry and Behavior* **2007**, *86*, 678.
152. Kara, L. V.; Julie, M. L.; Marie, R.; Stephen, G. P.; John, B. B. *Bioorg. Med. Chem.* **2007**, *15*, 931.
153. Botov, V. V.; Nambelbal, A.; Drogovoz, S. M.; Vereitinova, V. P. *Khim. Farm. Zh.* **1986**, *20*, 1463 [C. A.: 106,196188s].
154. Edeliza, L. D. S.; Walter, A. G.; Nubia, M. R.; Heloysa, M. C. A. *Journal of Molecular catalysis A: Chemicals* **2008**, *295*, 18.
155. Sakai, S.; Aimi, N.; Kubo, A.; Kitagawa, M.; Hanasawa, M.; Katano, K.; Yamaguchi, K.; Haginiwa, J. *Chem. Pharm. Bull.* **1975**, *23*, 2805.
156. Rucker, J. W.; Freeman, H. S.; Hsu, M. N. *Text. Chem. Color* **1992**, *24*, 66.



157. Kaupp, G.; Matties, D. *Chem. Ber.* **1987**, *120*, 1897.
158. Niume, K.; Toda, F.; Uno, K.; Hasegawa, M.; Iwakura, Y. *J. Polymer Sci. Polymer Chem. Ed.* **1983**, *21*, 615.
159. Ivaschchenko, A. V.; Agafonova, I. F. *Khim. Gaterotsikl Soedin* **1981**, 249 [C. A.: 1981, 95,7219y].
160. Ivaschchenko, A. V.; Drushlyak, A.-G.; Titov, V. V. *Khim. Gaterotsikl Soedin* **1984**, *5*, 667 [C. A.: 1984, 101,110872x].
161. Drushlyak, A.-G.; Ivaschchenko, A. V.; Titov, V. V. *Khim. Gaterotsikl Soedin* **1984**, 1399 [C. A.: 1985, 102,113423h].
162. Sarkin, G. Y.; Al-Badri, H. T. *J. Heterocycl. Chem.* **1980**, *17*, 813.
163. Joshi, K. C.; Chand, P.; Dandia, A. *Indian J. Chem.* **1984**, *23B*, 743.
164. Xiao-Nan, Z.; Yong-Xiao, L.; Zhan-Hui, Z. *Tetrahedron* **2011**, *67*, 7426.
165. Hui, C.; Da-Qing, S. *J. Heterocyclic Chem.* **2013**, *50*, 56.
166. Cornforth, J. W. *J. Chem. Soc. Perkin Trans 1* **1976**, 2004.
167. Bradman, H. A. *J. Heterocycl. Chem.* **1973**, *10*, 383.
168. Kamlet, M. J.; Kaplan, L. A. *J. Org. Chem.* **1957**, *22*, 576.
169. Mukherjee, S.; Raunak; Dhawan, A.; Poonam; Prasad, A. K.; Olsen, C. E.; Cholli, A. L.; Errington, W.; Raj, H. G.; Watterson, A. C.; Parmar, V. S. *Indian J. Chem.* **2004**, *43B*, 2670.
170. Venkatachalapathy, C.; Thirumalaikumar, M.; Muthusubramanian, S.; Pitchumani, K.; Sivasubramanian, S. *Synth. Commun.* **1997**, *27*, 4041.
171. Ciesielski, W.; Kundzin, Z. H.; Tasz, M.; Drabowicz, J. *Can. J. Chem.* **1990**, *68*, 679. [C. A.: 1990, 113, 108479].
172. Raunak; Vineet, K.; Shubhasish, M.; Poonam; Ashok, K. P.; Carl, E. O.; Susan, J. C. S.; Sunil, K. S. Arthur, C. W.; William, E.; Virinder, S. P. *Tetrahedron* **2005**, *61*, 5687.
173. Mishra, A. D. *J. Nepal. Chem. Soc.* **2009**, *24*, 49.
174. Joshi, K. C.; Jain, R.; Sharma, K. *J. Indian chem. Soc.* **1988**, *65*, 640.
175. Joshi, K. C.; Jain, R.; Garg, S.; Arora, S. *J. Indian chem. Soc.* **1989**, *66*, 176.
176. Joshi, K. C.; Dandia, A.; Bhagat, S. *Indian J. Chem.* **1992**, *31B*, 98.
177. Otomasu, H.; Ohmiya, S. *Japan Kokai* **1975**, *75*, 137, 976 [C. A.: 1975, 85,21357s].
178. Joshi, K. C.; Pardasani, R. T.; Dandia, A.; Bhagat, S. *Heterocycles* **1981**, *16*, 1555.
179. Bhawana, T.; Devendra, S.; Gangotri, P.; Talesara, G. L. *Ind. J. Chem.* **2010**, *49B*, 368.
180. Alauddin, S.; Hayat, F. *Indian. J. Sci. Res.* **2012**, *3(1)*, 191.
181. Rani, H. S.; Mogilaiah, K.; Rao, I. S.; Sreenivasulu, B. *Indian, J. Chem.* **1995**, *34B*, 1035.
182. Mostafa, M. H. K.; Foziah, A. A. *J. Soudi. Chem. Soc.* **2010**, *14*, 33.
183. Althebeiti, M. S.; El-Zohry, M. F. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1994**, *88*, 251.
184. Wagner, H. U.S. *Patent* 4 405 780, **1983**; [C. A.: 1983, 100, 6550].
185. Omodei-Sale, A.; Consonni, P.; Lerneer, U. S. *Patent*, 4 075 341, **1978**; [C. A.: 1978, 89, 24316w].
186. Maclauchlin, C.; Hall, I. H.; Izydore, R. A. *Arch. Pharm.* **1999**, *332*, 225.
187. Clitherow, J. W.; Bradshaw, J.; Price, B. J.; Martin-Schmith, M.; Mackinnon, J. W. M.; Judd, D. B.; Hayes, R.; Carey, L. (Glaxo Group Ltd.) *Eur. Patent* 16565, **1980**; [C. A.: 1980, 94, 192345b].
188. Hall, I. H.; Wong, O. T.; Simlot, R.; Miller, M. C.; Izydore, R. A. *Anticancer Res.* **1992**, *12*, 1355.
189. Ito, Y.; Nie, Y.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1979**, 2521.
190. Kajopadhye, M.; Popp, F. D. *J. Heterocycl. Chem.* **1985**, *22*, 93.
191. Yousef, M. S. K. *J. Chem. Tech. Biotechnol.* **1981**, *31*, 363.
192. Yousef, M. S. K. *Rev. Roum. Chim.* **1981**, *26*, 471.
193. Tomchin, A. B. *Zh. Org. Khim.* **1981**, *17*, 1561.
194. Tomchin, A. B. *Zh. Org. Khim.* **1981**, *17*, 589.



195. Tomchin, A. B.; Dmitrukha, V. S. *Zh. Org. Khim.* **1975**, *11*, 184.
196. Somogyi, L. *Liebigs Ann. Chem.* **1993**, 931.
197. Islam, M. R.; Mohsin, M. *Bangladesh J. Pharmacol.* **2007**, *2*, 7.
198. Egle, M. B.; Francesca, C.; Maria, L.G. *Tetrahedron* **2003**, *59*, 4615.
199. Pandeya, S. N.; Mishra, B.; Singh, P. N.; Rupainwar, D. C. *Pharmacol. Res.* **1998**, *37*, 17.
200. Kondo, Y.; Mitadera, Y.; Nozoe, S. *Yakugaku Zasshi* **1985**, *105*, 724 [C. A.: 1985, 105,133701n].
201. Wenkert, E.; Liu, S. *Synthesis* **1992**, 323.
202. Ahadi, S.; Khavasi, H. R.; Bazgir, A. *Chem. Pharm. Bull.* **2008**, *56*, 1328.
203. Ghahremanzadeh, R.; Azimi, S. A.; Gholami, N.; Bazgir, A. *Chem. Pharm. Bull.* **2008**, *56*, 1617.
204. Lichitsky, B. V.; Komogortsev, A. N.; Dudinov, A. A.; Krayushkin, M. M. *Russ. Chem. Bull. Internation Eddition* **2009**, *58*, 7, 1504.
205. Somayeh, A.; Ramin, G.; Peiman, M.; Ayoob, B. *Tetrahedron* **2009**, *65*, 9316.
206. Ayoob, B.; Somayeh, A.; Ramin, G.; Hamid, R. K.; Peiman, M. *Ultrasonics Sono. Chem.* **2010**, *17*, 447.
207. Abdel-Latif, F. F. *Phosph. Sulfur Silicon* **1990**, *53*, 145.
208. Abdel-Latif, F. F.; Shaker, R. M. *Bull. Soc. Chim. Fr.* **1991**, *127*, 87.
209. Al-Thebeiti, M. S. *Heterocycles* **1998**, *48*, 145.
210. Joshi, K. C.; Dandia, A.; Khanna, S. *Indian J. Chem.* **1990**, *29B*, 1125.
211. Al-Thebeiti, M. S.; El-Zohry, M. F. *Heteroatom Chem.* **1995**, *6*, 567.
212. Shemchuk, L. A.; Chernykh, V. P.; Redkin, R. G.; *Russ. J. Org. Chem.* **2008**, *44(12)*, 1789.
213. Ayoob, B.; Zeinab, N. T.; Peiman, M. *Tetrahedron Lett.* **2008**, *49*, 5165.
214. Dandia, A.; Sing, R.; Khaturia, S.; Merienne, C.; Morgant, G.; Loupy, A. *Bioorg. Med, Chem.* **2006**, *14*, 2409.
215. Jain, R. *Pharmazie* **1995**, *50*, 224.
216. El-Ahl, A. A.; Afeefy, H.; Metwally, M. A. *J. Chem. Res.* **1994**, 14.
217. Joshi, K. C.; Jain, R.; Nishith, S. *J. Indian. Chem. Soc.* **1990**, *67*, 490.
218. Joshi, K. C.; Dandia, A.; Beweja, S.; Joshi, A. *J. Het. Chem.* **1989**, *26*, 1097.
219. Dandia, A.; Sehgel, V.; Singh, P.; *Chem. Pharm. Bull.* **1994**, *42*, 1909.
220. Joshi, K. C.; Jain, R.; Arora, S. *J. Fluorin Chem.* **1988**, *42*, 149.
221. Ismail, A. A.; Mona, H. M.; Amr, M. A.; Said, A. S. G. *Tetrahedron* **2009**, *65*, 10069.
222. Kempter, G.; Ehrlichmann, W.; Plesse, M.; Lehm, H. U. *J. Prakt. Chem.* **1982**, *324*, 832.
223. Kempter, G.; Lehm, H. U.; Plesse, M.; Ehrlichmann, W.; Jumar, A.; Kuehne, S. *Ger (East) DD 04 12 Oct 1983*, 203, 8.
224. Joshi, K. C.; Jain, R.; Sharma, K. *Heterocycles* **1990**, *31*, 473.
225. Joshi, K. C.; Dandia, A.; Sanan, S. *J. Fluorine Chem.* **1989**, *44*, 59.
226. Joshi, K. C.; Jain, R.; Arora, S. *Ind. J. Chem.* **1990**, *29B*, 369.
227. Joshi, K. C.; Dandia, A.; Ahmed, N. *Heterocycles* **1986**, *24*, 2479.
228. Popp, F. D.; Rajopadhye, M.; Brown, D. S.; Waddington, D.; Uff, B. C. *J. Heterocycl. Chem.* **1987**, *24*, 261.
229. Rajopadhye, M.; Popp, F. D. *J. Heterocycl. Chem.* **1985**, *22*, 93.
230. Gaponenko, N. I.; Kolodina, A. A.; Lesin, A. V.; Kurbatov, S. V.; Starikova, Z. A.; Nelyubina, Yu. V. *Russ. Chem. Bull. Int. Edi.* **2010**, *59*, 4, 838.
231. Tomchin, A. B.; Marysheva, V. V. *Zh. Org. Khim.* **1989**, *25*, 2248.
232. Schulze, A.; Goerdeler, *J. Chem. Ber.* **1982**, *115*, 3063.
233. Sharma, R.; Dahiya, R.; Pujari, H. K. *Indian J. Chem.* **1991**, *30B*, 508.