

The thesis entitled “**Synthesis of Structurally Diversified Spirooxindole and 3-Alkylidene Oxindole Heterocycles via Aryne and Alkyne Insertion; Total Synthesis of Spindomycin-B**” has been divided into four chapters. **Chapter-I** deals with the introduction to spirooxindoles, 3-alkylidene oxindoles and arynes. **Chapter-II** deals with the synthesis of indanone fused and cyclopentannulated spirooxindoles. **Chapter-III** deals with the synthesis of 3-spirocyclohexanyl-2-oxindoles and total synthesis of spindomycin-B. **Chapter-IV** deals with the synthesis of 3-alkylidene oxindole heterocycles.

**Chapter-I: Introduction to spirooxindoles, 3-alkylidene oxindoles and arynes.**

**Spirooxindoles:**

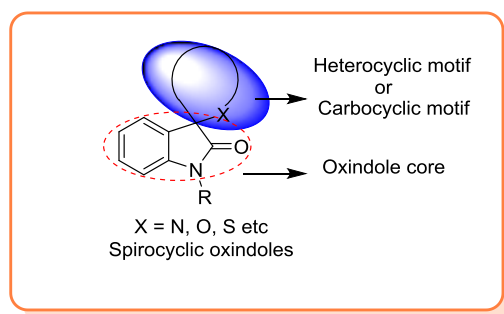


Figure 1: Spirooxindole motif

Spirocyclic compounds have been prevalent in organic synthesis due to their unique three dimensional structures, as well as their broad range of biological activity profiles. In particular, during the past decade spirooxindoles have emerged as attractive synthetic targets because of their occurrence in numerous natural products and biologically active molecules. The key structural features of these spirooxindoles are characterized by the presence of wide-ranging spiro rings fused at the C3 position of the oxindole core, in particular with diverse heterocyclic and carbocyclic motifs. Few representative examples of numerous natural products (e.g., **1–5**, Figure 2) and pharmacologically relevant drugs (e.g., **6–10**, Figure 2) representing structural diversity shown here. Spirooxindoles seems to be promising candidates for drug discovery, since they incorporate both oxindole and heterocyclic moieties simultaneously. A number of spirooxindoles have shown different degrees of anticancer activities mainly based on the spiro rings fused at the C3 position of oxindole scaffold and substituents on the oxindole nucleus. Among these, many

natural spirooxindoles like spirotryprostatins **A (1)** and **B (2)** also shown excellent anticancer activities. More importantly, some synthetic spirooxindoles such as MI-888 (**6**) and NITD 609 (**7**, Fig. 2) have been in preclinical research for the treatment of human cancers and malaria respectively.

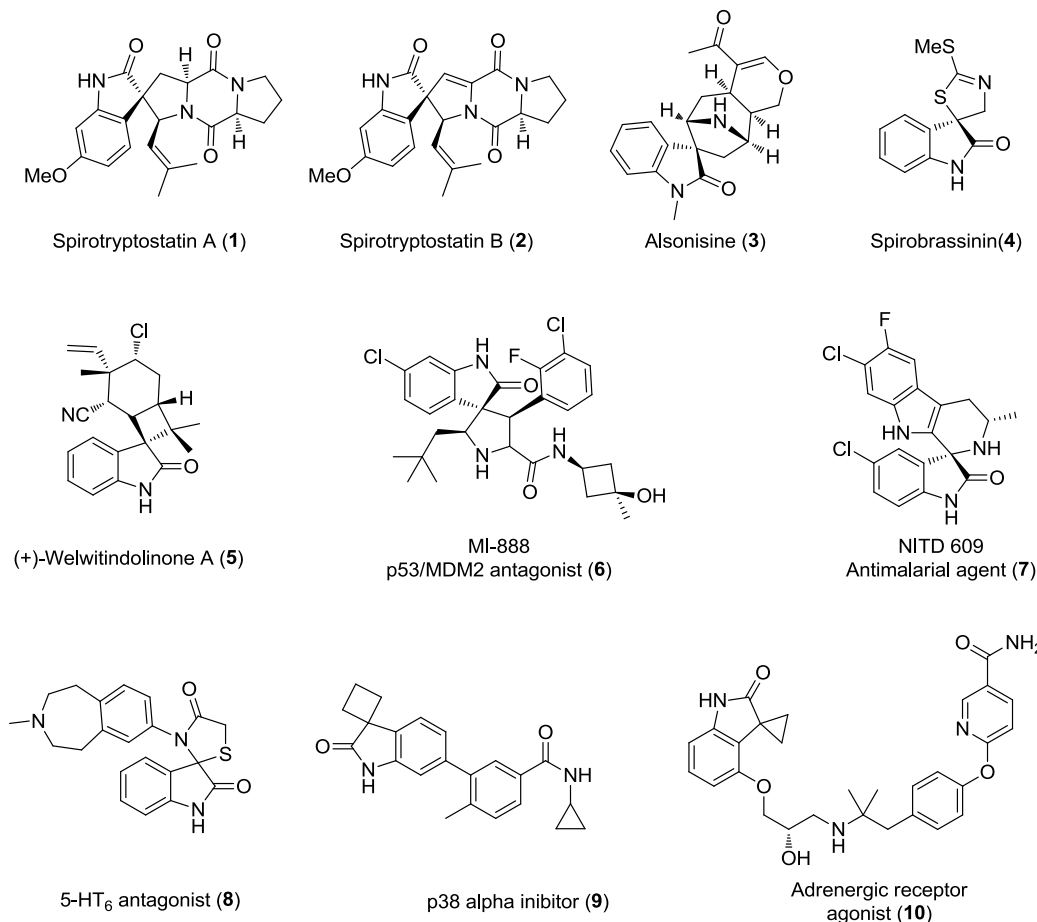


Figure 2: Natural and Synthetic lead compounds with spirooxindole scaffold

### 3-Alkylidene oxindoles:

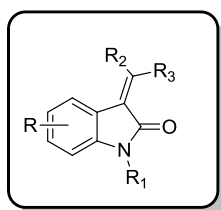


Figure 3: 3-Alkylidene oxindole core

3-Alkylidene oxindoles represent a privileged scaffold in medicinal chemistry, as they are ubiquitous in wide range of pharmaceutical agents and biologically active molecules. In addition to their therapeutic value, they are also useful intermediates in total synthesis, frequently exploited in cycloaddition reactions to gain access to

spirocyclic oxindole natural products. Many of which exhibit potent biological activities, such as anticancer, antibacterial, antifungal, antiviral and antiangiogenic properties. For instance, sunitinib (SU11248, **11**) is a orally active receptor tyrosine kinase (RTK) inhibitor marketed by Pfizer as Sutent<sup>®</sup> and was approved by the FDA in 2006 for the treatment of advanced renal cell carcinoma and gastrointestinal stromal tumours.

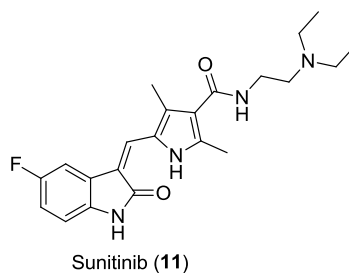


Figure 4: Synthetic drug(Sutent<sup>®</sup>) with 3-alkylidene oxindole moiety

Despite the large number of 3-alkylidene oxindoles isolated from natural sources display significant biological activities (Figure 5, **12–16**), the synthetically developed 3-alkylidene oxindoles have also been found to display significant biological activities and many are drug candidates in the market (Figure 5, **17–20**).

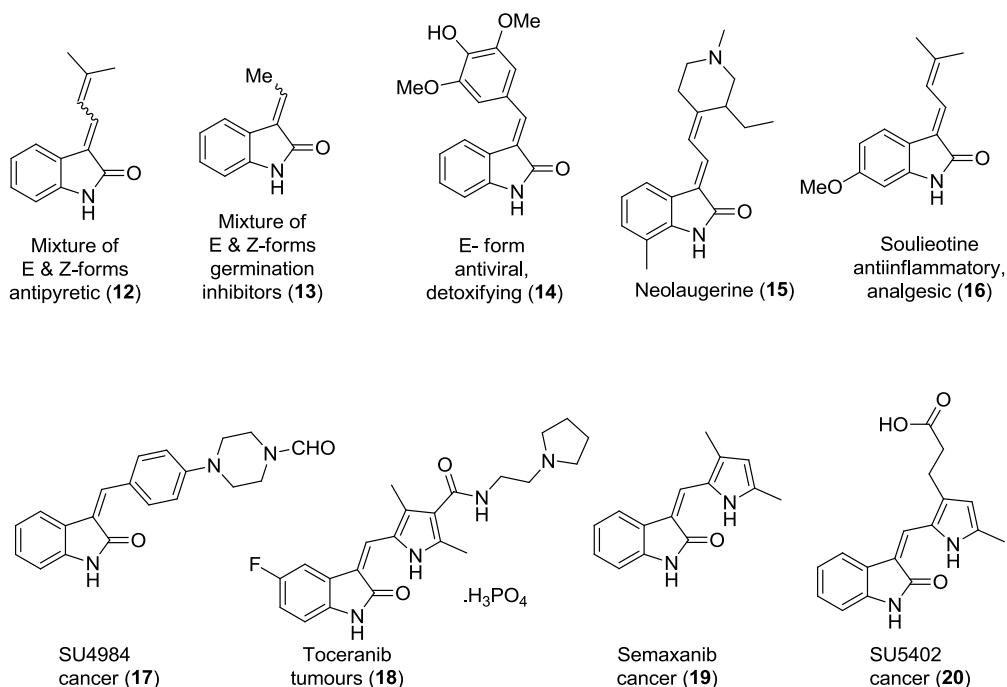


Figure 5: Natural and synthetic compounds with 3-alkylidene oxindole core

**Arynes:**

In the preceding decade, aryne chemistry has re-emerged as a powerful synthetic tool for synthesizing biologically active complex natural products and diverse chemical entities. Benzyne or 1,2-dehydrobenzene is an extremely reactive species due to the nature of its strained triple bond formed by the overlap of two  $sp^2$  orbitals orthogonal to the aromatic  $\pi$ -system (see Figure 6). The weakness of the bond due to poor orbital overlap produces a highly unstable, electrophilic intermediate which has to be generated *in situ*. This intermediate cannot be isolated under most reaction conditions; thus, it must be trapped *in situ*.

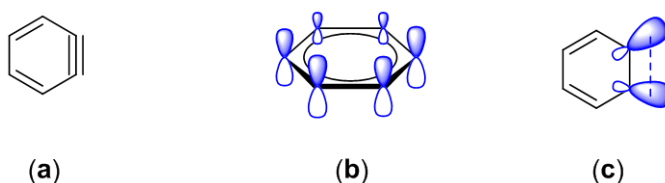
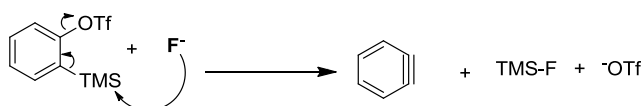


Figure 6: (a) *Ortho*-Benzyne; (b) Overlap of p-orbitals to form aromatic  $\pi$ -system; (c) Overlap of  $sp^2$  orbitals to form strained p-bond

Generally, arynes are quite electrophilic. Thus, a broad range of nucleophiles are capable of reacting with an aryne, and this reactivity has been exploited to a great extent in organic synthesis.

**Kobayashi method for generation of benzyne:**

In 1983, Kobayashi first introduced a new mild method for generating benzyne by the fluoride-induced 1,2-elimination of *o*-(trimethylsilyl)aryl triflates (scheme 1). Synthetic chemists have been attracted to Kobayashi's method for its convenience, efficiency, tolerance of functional groups, and mild reaction conditions. Thus, aryne chemistry has quickly emerged as an important synthetic tool in the field of synthetic organic chemistry.



Scheme 1: Kobayashi method for generation of aryne

**Aryne Reactions:**

The synthetic applications of arynes are remarkably diverse and a large number of aryne reactions found in the literature can be classified into several main categories

shown in (Figure 7). Mainly aryne reactions are categorised into arylation, insertion, annulation and transition- metal catalyzed and multicomponent reactions.

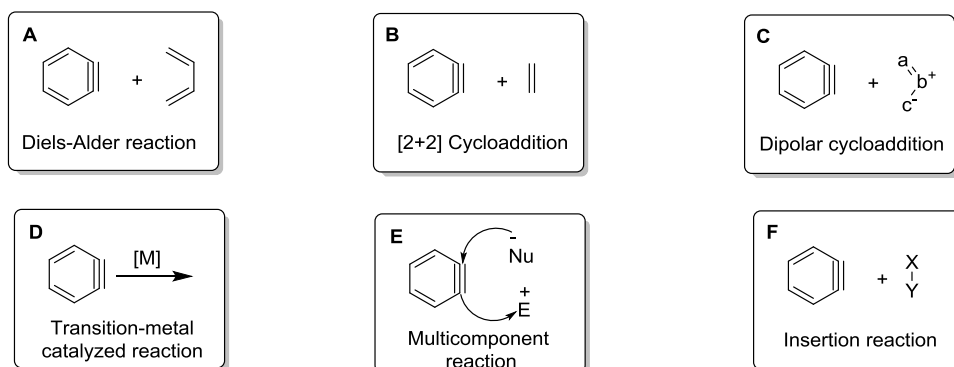


Figure-7: Representative reactions of benzyne

## Chapter-II: Synthesis of indanone fused and cyclopentannulated spirooxindoles:

In this chapter, we reported a transition-metal free, one-pot access to 3,3-five membered fused carbocyclic spirooxindoles through the incorporation of arynes and activated alkynes (as alkynones) into 3-carboethoxy methyl oxindoles to furnish diverse range of spirooxindoles.

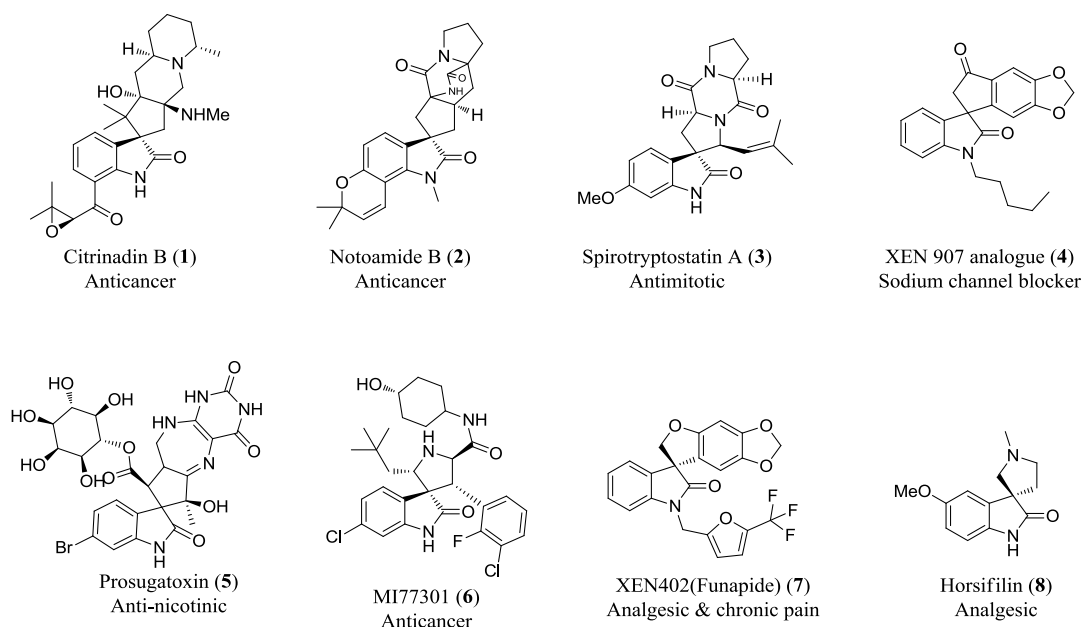


Figure-1: Natural and Synthetic spirooxindoles containing five membered spiro-fusion

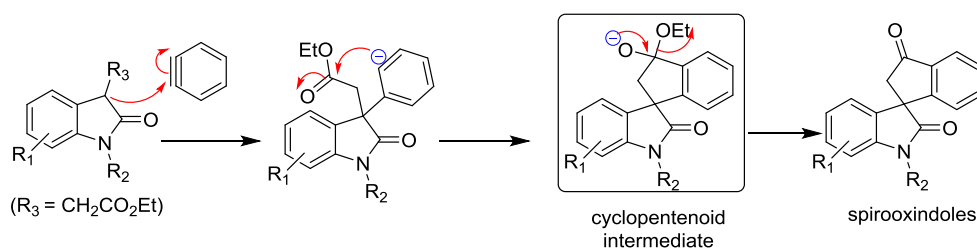
3,3'-five membered (carbocyclic or heterocyclic) ring fused spirooxindole motifs are found in numerous natural products and pharmaceutically lead compounds. These spirooxindoles exhibits wide spectrum of biological activities like anticancer, antiviral, antifungal, and antimigraine activities. Representative natural products citrinadin B **1** (anticancer), notoamide B **2** (anticancer), spirotryptostatin A **3** (antimitotic), prosugatoxin **4** (anti-nicotinic), Horsifiline **8** (analgesic) and pharmaceutically lead compounds XEN 907 **5** (sodium channel blocker), MI77301 **6** (anticancer), XEN402 **7** (analgesic & chronic pain) are showed in (Figure 1, **1-8**). Owing to the importance of 5-membered spirocyclic oxindoles, for the first time we have developed an efficient method for the synthesis of pharmaceutically relevant indanone fused and cyclopentannulated spirooxindoles in high yields by reacting various 3-carboethoxy methyl oxindoles with arynes and ynenones.

Towards this initially we have studied the reaction of variously substituted 3-carboethoxy methyl oxindoles with arynes in the presence of CsF as base in THF at 100 °C to deliver the anticipated indanone fused spirooxindoles in decent yields (Table 1).

**Table 1:** Synthesis of various substituted indanone fused spirooxindoles.

Entry	3-carboethoxy oxindole	aryne precursor	spirooxindole	time(h)	%yield <sup>a</sup>
a	 R1 = H, R2 = Me		 R1 = H, R2 = Me	24	61
b	R1 = 5-Cl, R2 = Me		R1 = 5-Cl, R2 = Me	24	68
c	R1 = 5-Br, R2 = Me		R1 = 5-Br, R2 = Me	24	59
d	R1 = 5-F, R2 = Me		R1 = 5-F, R2 = Me	24	66
e	R1 = 5-OMe, R2 = Me		R1 = 5-OMe, R2 = Me	24	62
f	R1 = 5-Me, R2 = Me		R1 = 5-Me, R2 = Me	24	65
g	R1 = 5-OCF <sub>3</sub> , R2 = Me		R1 = 5-OCF <sub>3</sub> , R2 = Me	24	60
h	R1 = H, R2 = Ph		R1 = H, R2 = Ph	24	71
i		 II		24	67
j				24	69
k				24	63
l				24	56
<sup>a</sup> Isolated yields. All products gave satisfactory <sup>1</sup> H & <sup>13</sup> C, IR and HRMS spectral data.					

It was predicted that the reaction occurs through the cyclopentenoid intermediate to deliver the spirooxindoles.

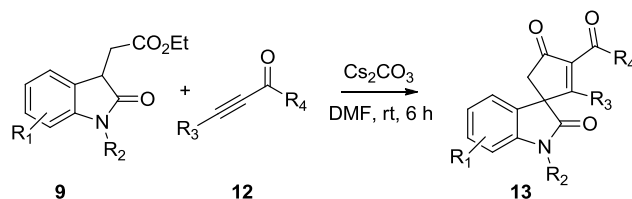


Scheme 1: Plausible mechanism for the formation of indanone fused spirooxindoles

### Synthesis of cyclopentannulated spirooxindoles:

After the successful demonstration of arynes with 3-carboethoxy methyl oxindoles, we have also studied the reaction of alkynes (as alkynones) with 3-carboethoxy methyl oxindoles to extend the scope and potentiality of the reaction. In this study, we have obtained cyclopentannulated spirooxindoles in good yields by reacting 3-carboethoxy methyl oxindoles with alkynes in the presence of  $\text{Cs}_2\text{CO}_3$  as a base in DMF at room temperature as shown in (Table 2).

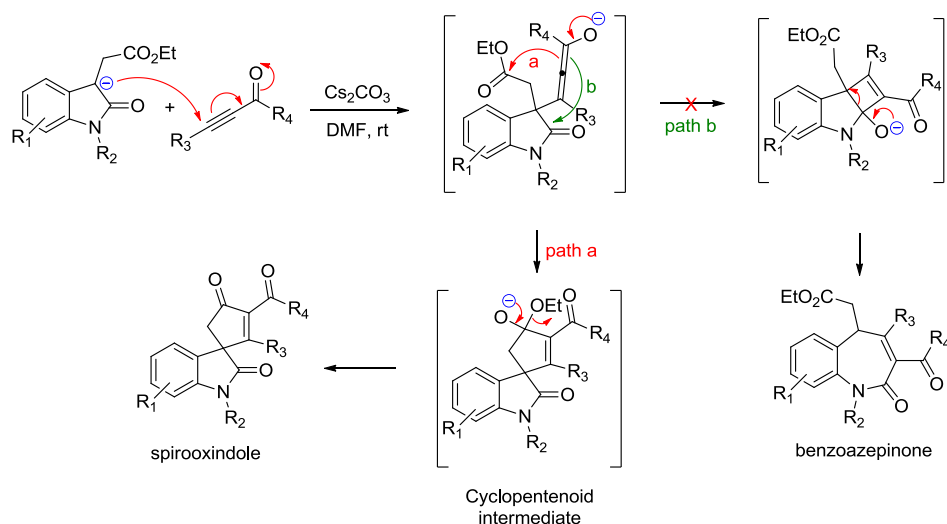


**Table 2:** Synthesis of various substituted cyclopentannulated spirooxindoles

Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	time(h)	Yield <sup>a</sup>
a	H	Me	Ph	Ph	6	89
b	H	Me	Ph	2-BrPh	6	85
c	H	Me	Ph	furan-3-yl	6	81
d	H	Me	Ph	thiophen-2-yl	6	82
e	H	Me	Ph	pyridin-3-yl	6	81
f	H	Me	Ph	3,5-dimethoxyphenyl	6	79
g	H	Me	Ph	3,4,5-trimethoxyphenyl	6	83
h	5-F	Me	Ph	Ph	6	85
i	5-OCF <sub>3</sub>	Me	Ph	Ph	6	81
j	5-Cl	Me	Ph	furan-3-yl	6	88
k	5-OMe	Me	Ph	thiophen-2-yl	6	86
l	5,7-diMe	Me	Ph	3,5-dimethoxyphenyl	6	82
m	5,7-diMe	Me	Ph	3,4,5-trimethoxyphenyl	6	79
n	5,7-diMe	Me	Ph	furan-3-yl	6	83
o	5,7-diMe	Me	Ph	thiophen-2-yl	6	85
p	5-Me	Me	4-MeOPh	Ph	6	77
q	5,7-diMe	Me	4-MeOPh	Ph	6	76
r	H	Me	Heptyl	2-BrPh	6	66

<sup>a</sup>isolated yields. All products gave satisfactory <sup>1</sup>H & <sup>13</sup>C, IR and HRMS spectral data.

The possible mechanism for the formation of the cyclopentannulated spirooxindoles is depicted in Scheme 2.



Scheme-2: Plausible reaction mechanism for the formation of spirooxindoles

In conclusion, we have developed a new efficient method for the synthesis of indanone fused and cyclopentannulated spirooxindoles via aryne and alkyne incorporation, in one-pot, transition-metal free operation and successfully synthesized various substituted indanone fused cyclopentannulated spirooxindoles in good yields. Synthesized compounds were characterized by  $^1\text{H}$  &  $^{13}\text{C}$ , IR, HRMS spectral studies, and also confirmed by analyzing one of scaffold with single crystal X-Ray analysis. Utilising this method we synthesized 31 new spirooxindole molecules and submitted these scaffolds for national mol bank for screening their biological properties.

### Chapter-III: Synthesis of 3-spirocyclohexanyl-2-oxindoles and total synthesis of spindomycin B:

In this chapter a novel and one-pot approach for accessing 6-membered spirooxindoles and the synthesis of spindomycin B is discussed.

Spirooxindoles those embodying a 3,3'-fused six-membered rings are often found in many bioactive natural products and are considered as privileged scaffolds in medicinal chemistry. The spirooxindole motif is essential for the biological activity of the molecule, and therefore play an important role in the synthesis of new pharmaceutical products. Representative natural products include spindomycin A **1** and B **2** (tyrosine kinase inhibitor), gelsemine **3**, gelseverine **4** (antidepressant),

maremycin F **5** and synthetic compounds satavaptan **6** (hyponatremia), **7** (MDM2-p53 inhibitor) and NITD609 **8**, a potent antimalarial lead in nanomolar scale which kills the blood strain of *Plasmodium falciparum* (Figure 1, **1-8**). The synthesis of spirooxindoles has been an active research field because of their numerous applications. There is continuing interest in the development of improved methods for the synthesis of spirooxindoles. Owing to their importance as one of the most represented building block in natural bioactive products. The continuous development of different routes to spirooxindoles has been a growing field in medicinal chemistry.

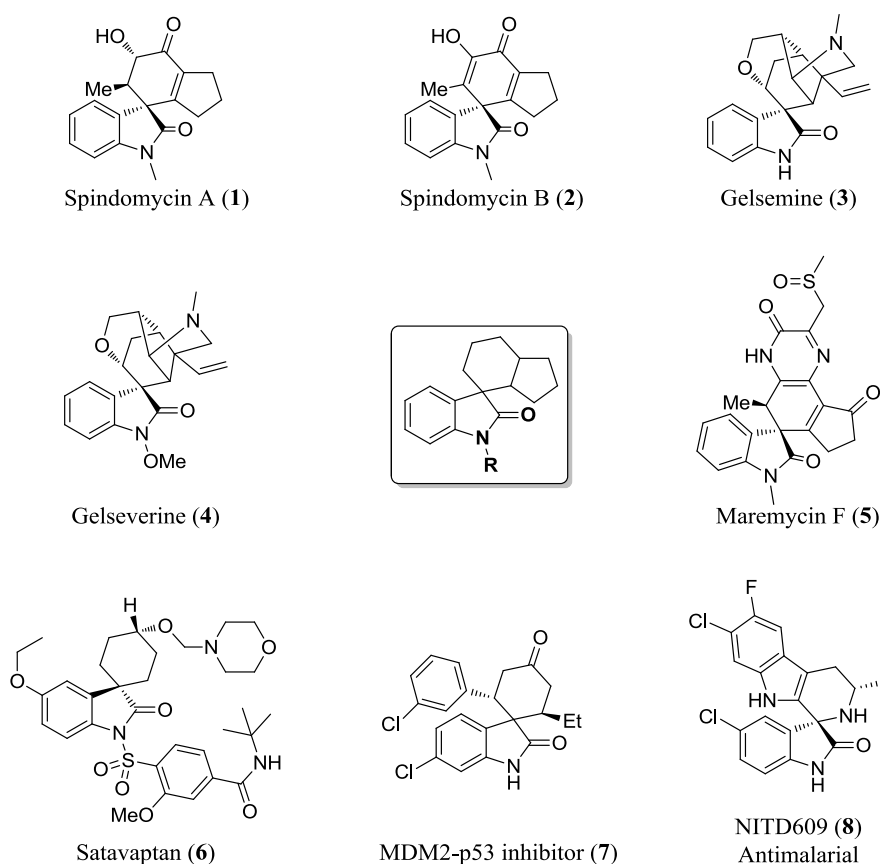
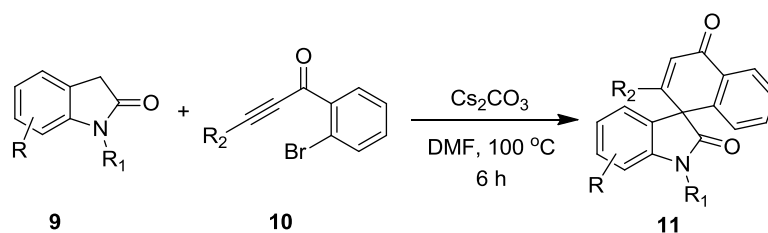


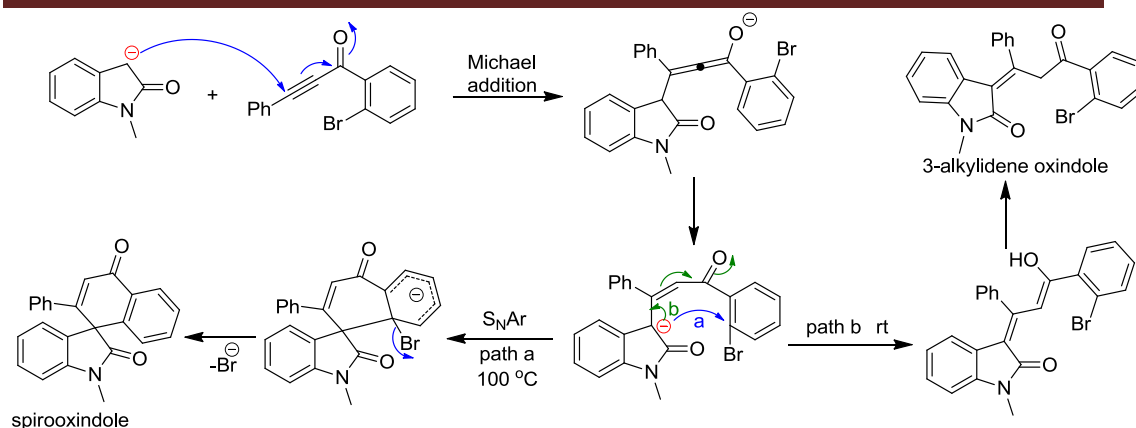
Figure-1: 3,3'-Fused six-membered spirooxindoles

Our own interest in 3-spirocyclohexanyl-2-oxindoles, has led to the development of an efficient domino protocol (Michael addition followed by  $S_NAr$ ) for the synthesis of pharmaceutically relevant 3-spirocyclohexanyl fused spirooxindoles in high yields. Accordingly, various substituted oxindoles were treated with several ortho bromo ynenones at 100 °C using  $Cs_2CO_3$  as the base, to give the corresponding products. Shown in (Table 1).

**Table 1:** Reaction of various substituted oxindoles with *o*-bromoaryl ynones

entry	R	R <sub>1</sub>	R <sub>2</sub>	time(h)	yield <sup>a</sup>
a	R = H	R <sub>1</sub> = Me	R <sub>2</sub> = Ph	6	63
b	R = 5-Br	R <sub>1</sub> = Me	R <sub>2</sub> = Ph	6	60
c	R = 5-I	R <sub>1</sub> = Me	R <sub>2</sub> = Ph	6	59
d	R = Me	R <sub>1</sub> = Me	R <sub>2</sub> = Ph	6	62
e	R = OMe	R <sub>1</sub> = Me	R <sub>2</sub> = Ph	6	64
f	R = H	R <sub>1</sub> = Ph	R <sub>2</sub> = Ph	6	75
g	R = H	R <sub>1</sub> = Bn	R <sub>2</sub> = Ph	6	72
h	R = 5-Cl	R <sub>1</sub> = Bn	R <sub>2</sub> = Ph	6	74
i	R = H	R <sub>1</sub> = Me	R <sub>2</sub> = 4-ethyl Ph	6	59
j	R = H	R <sub>1</sub> = Ph	R <sub>2</sub> = 4-ethyl Ph	6	69
k	R = H	R <sub>1</sub> = Me	R <sub>2</sub> = 4- OMe Ph	6	57
l	R = H	R <sub>1</sub> = Ph	R <sub>2</sub> = 4- OMe Ph	6	71
m	R = H	R <sub>1</sub> = Me	R <sub>2</sub> = 3,4,5- Trimethoxy Ph	6	53
n	R = H	R <sub>1</sub> = Ph	R <sub>2</sub> = 3,4,5- Trimethoxy Ph	6	65
o	R = H	R <sub>1</sub> = Ph	R <sub>2</sub> = 6-methoxynaphthyl	6	60

<sup>a</sup>Isolated yields. All products have been characterized by <sup>1</sup>H & <sup>13</sup>C, IR, and HRMS spectral data



Scheme -1: Plausible reaction mechanism for the spirooxindole formation

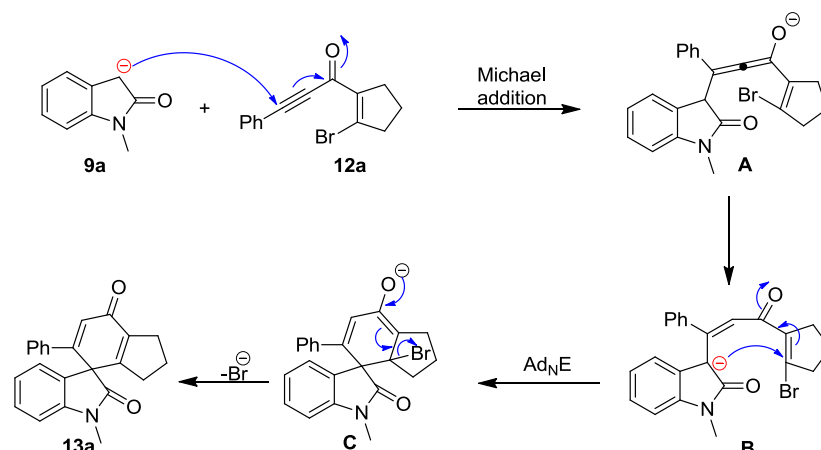
After successful spiroannulation of oxindoles with *o*-bromoaryl ynones *via* Michael followed by  $S_NAr$  reaction, we have also implemented similar protocol on  $\beta$ -bromoalkenyl ynones to explore the scope of our domino reaction.

Accordingly, various substituted oxindoles were engaged with readily obtainable diverse cyclic  $\beta$ -bromoalkenyl ynones under our optimized conditions ( $CS_2CO_3$ , DMF, 100 °C) to afford the corresponding tetracyclic spiroannulated compounds, in good yields, as shown Table 2.

**Table 2:** Reaction of various substituted oxindoles with  $\beta$ -bromoalkenyl ynones

Entry	Oxindoles	$\beta$ -bromoalkenyl ynones	product	time(h)	yield <sup>a</sup>
a				6	75
b				6	84
c				6	81
d				6	73
e				6	77
f				6	68
g				6	79

<sup>a</sup>isolated yields. All products have been characterized by <sup>1</sup>H & <sup>13</sup>C, IR and HRMS spectral data



Scheme 2: Plausible mechanism Tandem Michael addition followed by addition-elimination ( $\text{Ad}_{\text{N}}\text{E}$ ) reactions ( $\text{A} \rightarrow \text{B} \rightarrow \text{C} \rightarrow \mathbf{13a}$ ).

#### Total synthesis of alkaloid spindomycin B:

To further evaluate the scope and efficiency of our one-pot  $\beta$ -bromoalkenyl ynone mediated oxindole spiroannulation methodology, we extended it to  $\beta$ -bromoalkenyl enones as partners for oxindole and synthesized recently isolated natural product spindomycin B.

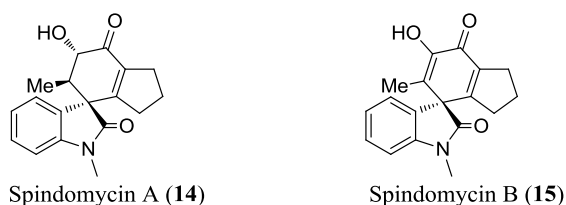
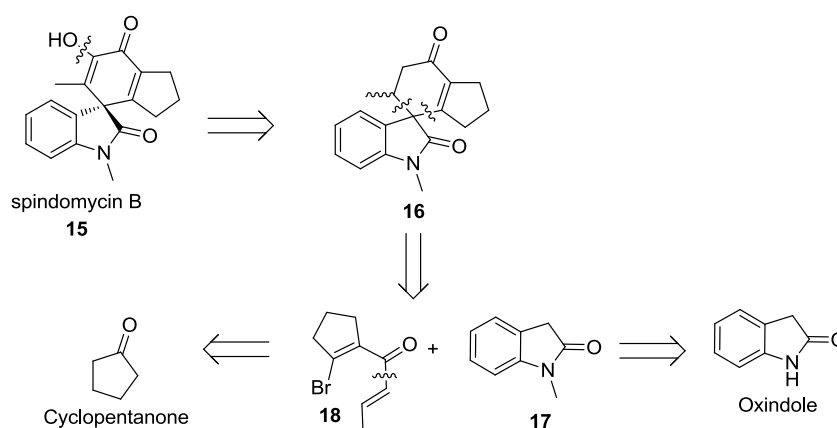


Figure 3

These tetracyclic alkaloids were isolated from rhizosphere strain *Streptomyces* sp. xzqh-9 in 2014 by X. Deng et. al., and their structures and absolute configuration have been determined through 2D NMR and electronic circular dichroism (ECD). Among the two sibling alkaloids spindomycin B displayed weak ( $30\mu\text{M}$ ) inhibitory activity against tyrosine kinase Bcr-Abl implicated in chronic myeloid leukemia (CML).

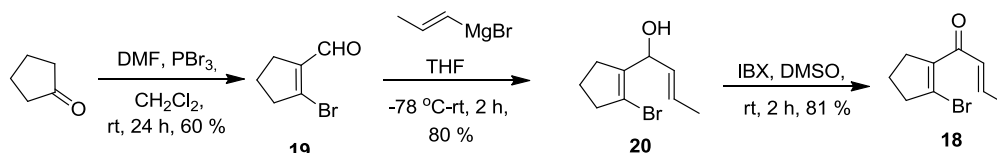
### Retrosynthetic analysis of spindomycin B:

While looking at the molecule in retrosynthetic perspective, it can be cleaved at enolic hydroxy to get compound **16**, which can be synthesized using Rubottom oxidation followed by DMP oxidation. Compound **16** in turn is disconnected at benzylic linkage to give two fragments **17** and **18**. Both the fragments **17** and **18** can be coupled using our domino process (Michael addition followed by Ad<sub>N</sub>E). The fragment **18** can be accessed from commercially available cyclopentanone, whereas the fragment **17** can be prepared from known protocol starting from commercially available oxindole (Scheme 7).



Scheme-3: Retrosynthetic analysis for spindomycin B

### Synthesis of fragment 18:



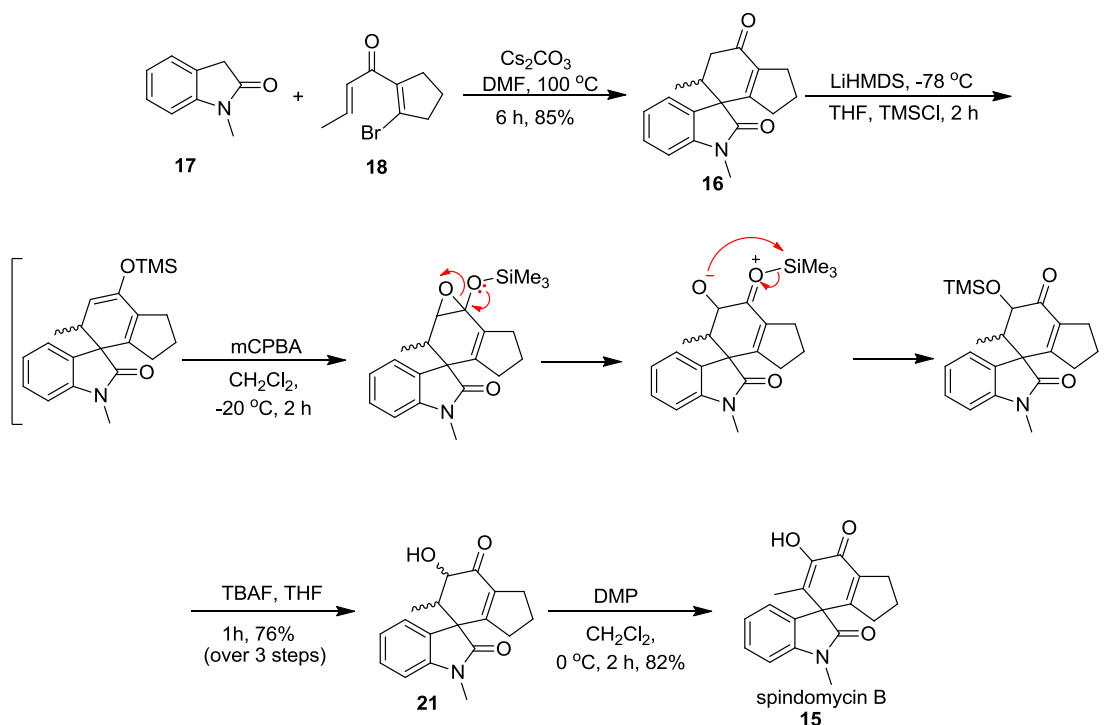
Scheme-4: Synthesis of fragment 20

We began our synthesis for fragment **18** from the commercially available cyclopentanone, which was converted to its corresponding 2-bromocyclopent-1-enecarbaldehyde using known Vilsmeier–Haack reaction protocol to afford compound **19** in 60% yield. The compound **19** was treated with propenylmagnesiumbromide in THF (2.0 M in THF) at -78 °C to obtain vinylic alcohol **20** in 80% yield. The compound **20** was converted to the corresponding keto using IBX in DMSO at room temperature to give compound **18** in 81% yield (Scheme 4).



Coupling of **17** and **18**:

The reaction between *N*-methyl oxindole **17** and cross conjugated  $\beta$ -bromocyclopentenyl enone **18** probed under optimized conditions ( $\text{Cs}_2\text{CO}_3$ , DMF,  $100^\circ\text{C}$ ) to afford the expected spiroannulated tetracyclic oxindole **16** as a mixture of inseparable diastereomers and was as such elaborated to diastereomeric  $\alpha$ -hydroxyketones **21** following Rubottom oxidation protocol. Thus, **16** with LiHMDS and TMSCl afforded silyl-enol ether, which upon further epoxidation with *m*CPBA and TBAF exposure led to  $\alpha$ -hydroxyketone **21** as a mixture of diastereomers. DMP (Dess-Martin periodinane) oxidation of **21** and concomitant enolization afforded spindomycin B (**15**) in 53% overall yield. The spectral data of the synthetic spindomycin B was found to be identical with that reported natural product. We also determined the structure by investigating its single crystal X-ray analysis Scheme 5.



Scheme-5: Synthesis of spindomycin B

In conclusion, we have developed a one-pot, metal free spiroannulation strategy to conveniently access 3-spirocyclohexanyl-2-oxindole motif from oxindoles and  $\beta$ -bromoaryl ynones and further extended this domino protocol to  $\beta$ -bromoalkenyl ynones and  $\beta$ -bromoalkenyl enones. As an application of this new method, the first total synthesis of tetracyclic alkaloid spindomycin B has been accomplished.

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**Chapter-IV : Synthesis of 3-alkylidene oxindole heterocycles:**

In this chapter we reported a simple and an efficient method for the synthesis of 3-alkylidene oxindoles *via* a base promoted Michael addition followed by double bond migration reaction, endowed with an interesting 3-alkylidene oxindole moiety suitable for further elaboration (indole, quinoline, pyridine and pyran derivatives) .

3-alkylidene oxindoles are found in various biologically active natural products, pharmaceutical lead compounds and important synthetic intermediates in accessing the complex natural products. This class of compounds always a valuable targets for both synthetic and medicinal chemists. Characteristic examples of natural and synthetic 3-alkylidene oxindoles **1-8** are shown in Figure 1. Representative synthetic drug candidates that structurally features 3-alkylidene oxindole is nintedanib **5** (idiopathic pulmonary fibrosis (IPF), non-small-cell lung cancer) approved by the FDA in 2014. Sunitinib **6** (renal cell carcinoma and gastrointestinal and stromal tumours) approved by FDA in 2006. Natural product soulieotine **4** (inflammatory analgesic), that fall into the class of 3-alkylidene oxindoles. 3-alkylidene oxindoles are benzofused  $\gamma$ -lactam holding exocyclic olefins known for their vinylogous reactivity, and crucial for the spirocyclization reactions.

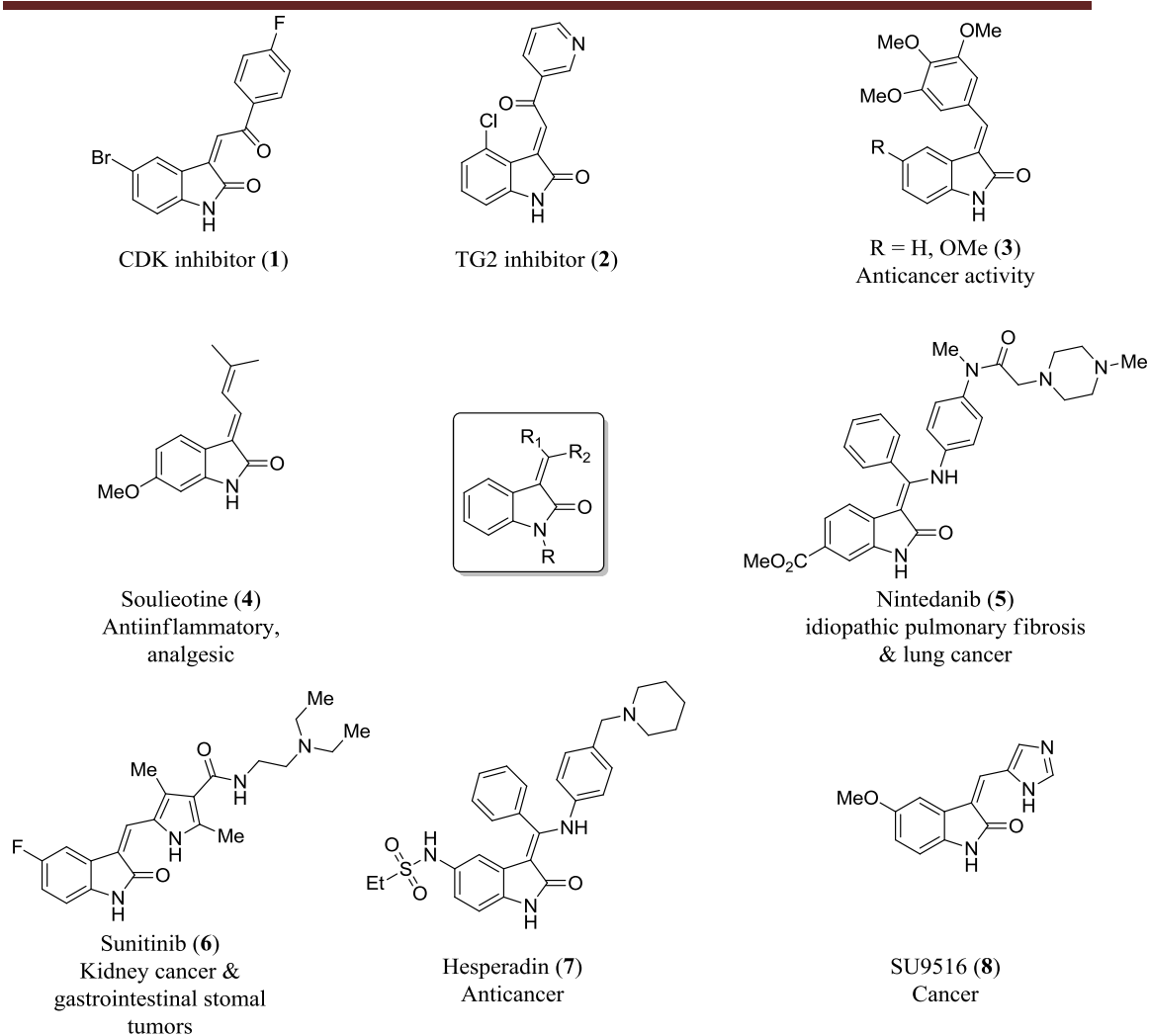
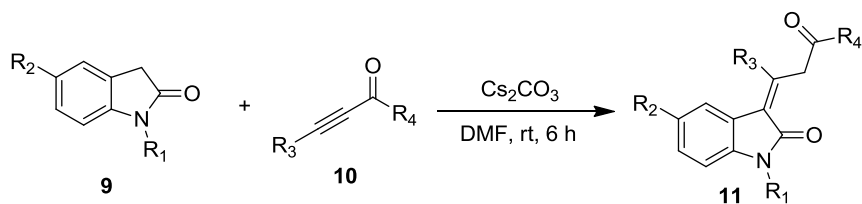


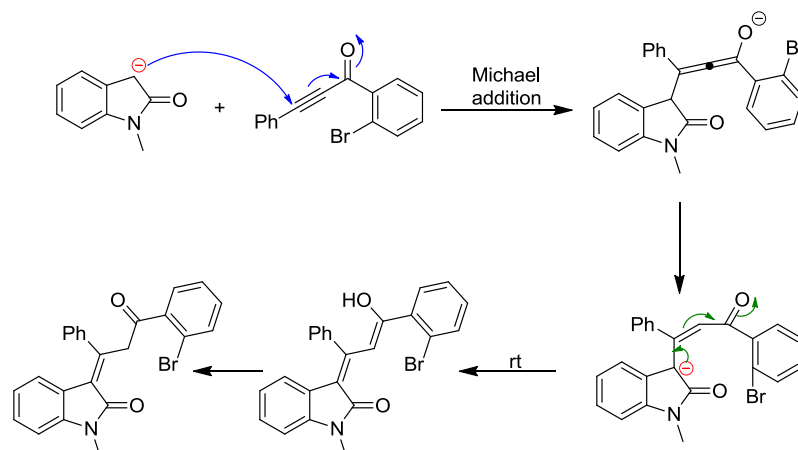
Figure 1: Natural and synthetic compounds with 3-alkylidene oxindoles

Preparation of 3-alkylidene oxindoles using ynones and oxindoles were so far not reported. We developed a novel method for the preparation of substituted 3-alkylidene oxindoles in high yields by reaction of ynones with a *N*-alkyl oxindoles at room temperature using  $\text{Cs}_2\text{CO}_3$  as a base shown in Table 1.

**Table 1:** Reaction of various substituted oxindoles with aryl ynones

Entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	time(h)	yield <sup>a</sup>
a	Me	H	Ph	Ph	6	90
b	Me	H	Ph	4-OMePh	"	85
c	Me	H	Ph	3,5-di-OMePh	"	89
d	Me	H	Ph	3,4,5-tri-OMePh	"	90
e	Me	H	Ph	4-CF <sub>3</sub> Ph	"	86
f	Me	H	Ph	3-Pyridyl	"	80
g	Me	H	Ph	3-Furyl	"	84
h	Me	H	Ph	2-thiophene	"	78
i	Me	H	Ph	2-BrPh	"	92
j	Me	H	Ph	2-Br-4,6-diOMePh	"	75
k	Me	H	Ph	6-Brbenzo[d][1,3]dioxol-5-yl	"	65
l	Boc	H	Ph	2-BrPh	"	69
m	Boc	H	Ph	3-Pyridyl	"	64
n	Me	H	4-OMePh	2-BrPh	"	72
o	Me	H	Heptyl	2-BrPh	"	74
p	Ph	H	Ph	Ph	"	90
q	Me	5-I	Ph	2-thiophene	"	76
r	Bn	5-Cl	Ph	3-Furyl	"	84
s	Me	5-Br	Ph	3,5-di-OMePh	"	82

<sup>a</sup>isolated yields. All products were characterized by <sup>1</sup>H & <sup>13</sup>C, IR and Mass spectral data.



Scheme 1: Plausible reaction mechanism

In conclusion, we have developed a novel and efficient strategy for accessing 3-alkylidene oxindoles *via* Michael addition followed by double bond migration of oxindoles & alkynones. A series of *N*-arylated,  $\alpha,\beta$ -unsaturated ynones were rearranged to 3-alkylidene oxindoles selectively by using mild base with good yields.