Isoindoloindolones - biological activities and syntheses

Hari K. Kadam[a,b] and Santosh G. Tilve*[a]

[a] Department of Chemistry, Goa University, Taleigao Plateau, Goa - 403 206, India
[b] Present address: Department of Chemistry, St. Xavier's College, Goa - 403 507, India
E-mail: stilve@unigoa.ac.in

Abstract

This review describes the biological activity and synthesis of structurally and biologically significant isoindoloindolone compounds. The various synthetic reports are mainly described under two headings based on use of palladium chemistry or the Wittig reaction as the key step for the construction of the indole or isoindole ring. Other methods are included in the miscellaneous approaches.

Keywords: Isoindoloindolones, bioactivity, synthesis, Wittig reaction, cyclisation
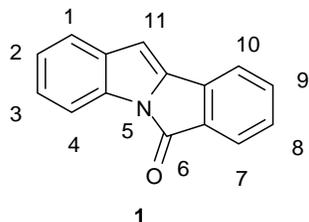
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1. Introduction

Indole based compounds are frequently encountered in bioactive substrates. 6*H*-Isoindolo[2,1-*a*]-indol-6-one **1** is a predominant candidate of such type. Structurally it is a tetracyclic system having an indole ring fused to an isoindoline moiety with tethered (bridgehead) nitrogen (Figure 1).

Figure 1. 6*H*-Isoindolo[2,1-*a*]indol-6-one.

Although this heterocyclic structural motif is yet to be revealed in any natural product, it has already received a position of major importance as a bioactive compound.[1-4]

2. Biological Activity

The derivatives of isoindoloindolone are well known for their specific bioactivity profiles. Isoindoloindolone derivatives are reported as potent ligands of MT_3.[5] The third melatonin binding site, MT_3, is an enzyme, quinone reductase-2 and not a usual seven transmembrane domains receptor. Hydroxyisoindoloindolone derivative **2a** has subnanomolar affinity for the melatonin binding site MT_3.
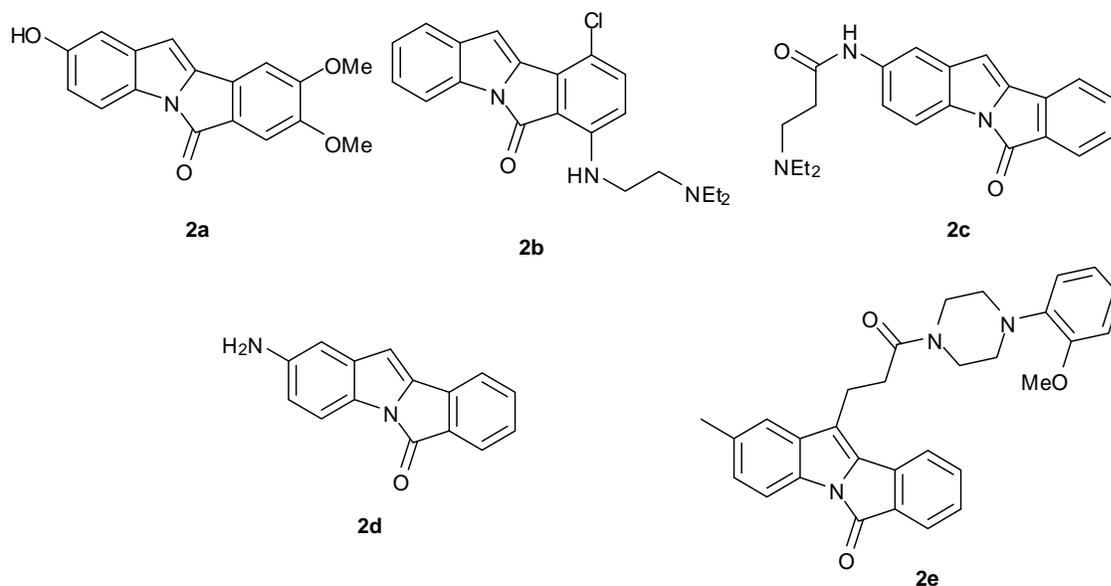
Figure 2. Biologically important isoindoloindolones.

Chloroisoindoloindolone derivative **2b**, amidoisoindoloindolone derivative **2c**, and aminoisoindoloindolone **2d** show DNA binding ability and non-specific interference with the topoisomerase-I catalytic cycle (Figure 2). Compound **2b** also has an antiproliferative effect

against HT-29 and L1210 cell lines. Compounds **2c** and **2d** exhibit inhibitory potency for topoisomerase-II comparable to that of etoposide.[6,7] Compound **2e** shows moderate binding affinity towards human neurokinin-1 (hNK$_1$) receptors in the central nervous system.[1]

The NorA protein is a multidrug resistant efflux in the bacterium *Staphylococcus aureus*. This has resulted in resistance towards numerous structurally dissimilar antibiotics such as norfloxacin, ethidium bromide, berberine, etc. Isoindoloindolone **1** is used as a precursor in the synthesis of 2-aryl-5-nitroindoles as NorA efflux pump inhibitors.[8,9] Isoindoloindolone **1** also exhibit charge-transfer fluorescence with high quantum yields in non polar solvents.[10]

3. Synthetic Strategies

Synthetic strategies of isoindoloindolones have been explored by research groups all over the world for decades (1979-2014) due to their diverse applications. Some of these efficient and remarkable achievements are discussed below.

3.1. Palladium catalyzed coupling reactions
Palladium acetate promoted intramolecular-dehydrogenative cyclisation of 1-benzoylindole is a short and simple method for the synthesis of isoindoloindolones (Scheme 1).[11-18] It was first explored by Itahara in 1979[11-14] and was further developed by many other research groups.
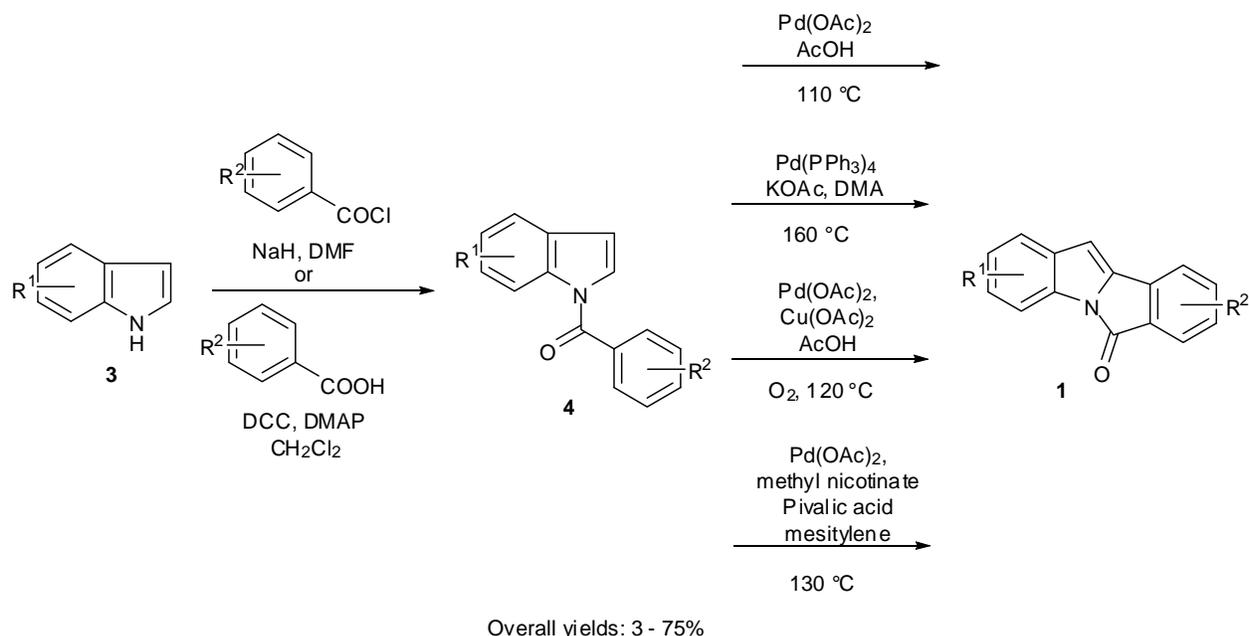

**Scheme 1.** Intramolecular-dehydrogenative cyclisation approach.

Bremner and his group[8] prepared 1-benzoylindole **4** and reacted with palladium acetate in refluxing acetic acid to give isoindoloindolone **1**. Dinnell *et al*. used Pd(PPh$_3$)$_4$ as catalyst and

KOAc as a base in refluxing DMA for the synthesis of isoindoloindolones.[1] DeBoef and co-workers used Cu(OAc)$_2$ along with Pd(OAc)$_2$ in refluxing acetic acid in O$_2$ atmosphere for intramolecular aerobic oxidative coupling of 1-benzoylindoles to give isoindoloindolones.[15] Electron rich tethered arenes gave better yields than unsubstituted arenes. Kandukuri and Oestreich used methyl nicotinate as ligand for Pd(OAc)$_2$ in mesitylene and pivalic acid in O$_2$ atmosphere for aerobic dehydrogenative double C-H coupling in 1-benzoylindoles to give isoindoloindolones.[16]

Hibino and co-workers prepared isoindoloindolone by employing Suzuki–Miyaura reaction of *N*-Boc-indole-boronic acid **5** and methyl-*o*-iodobenzoate **6** to give *N*-Boc-indole esters **7** followed by deprotection to give prominent precursor **8** and finally base mediated cyclisation to isoindoloindolones (Scheme 2).[19] The method was further modified to complete the total synthesis of indoloquinoline alkaloid isocryptolepine.
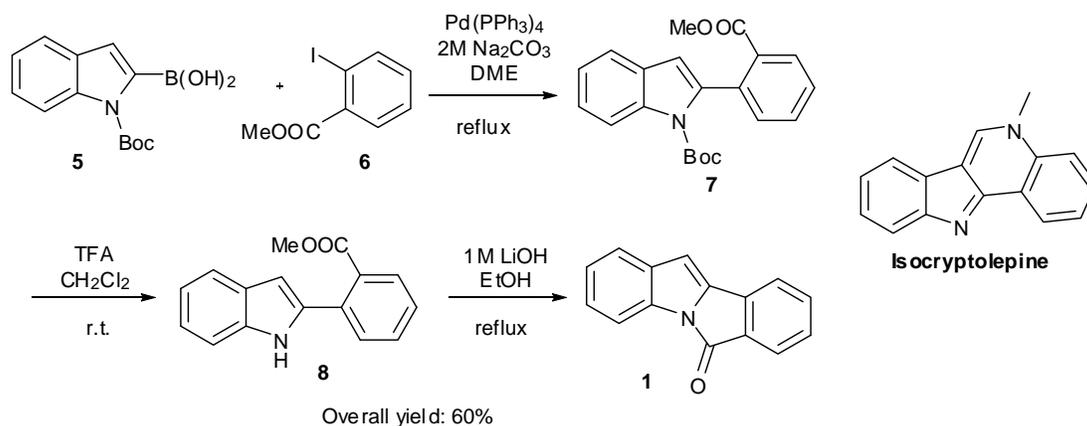
Scheme 2. Hibino's method.
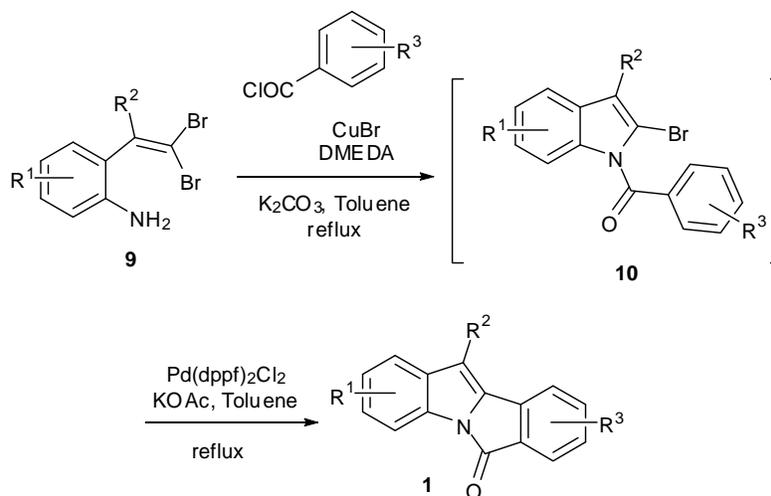
Scheme 3. Bao's method.

Bao's group[20] reported a synthesis of isoindoloindolones through one-pot sequential Cu catalyzed

C-N coupling and Pd catalyzed C-H activation reaction (Scheme 3). This two-step one-pot synthesis uses *o*-gem-dibromovinylanilines **9** as a starting material for benzoylation with benzoyl chloride and simultaneous intramolecular Buchwald-Hartwig C-N coupling with CuBr catalyst to give *N*-benzoylated 2-bromoindole **10**. Finally Pd catalyzed intramolecular Heck C-C coupling gave isoindoloindolones. Various derivatives with substituents on both aryl rings were prepared efficiently (Table 1) in moderate to good yields. The yields of 7-methyl and 10-chloro-11-methyl derivatives of **1** were somewhat low.

Table 1. Bao's method for isoindoloindolones

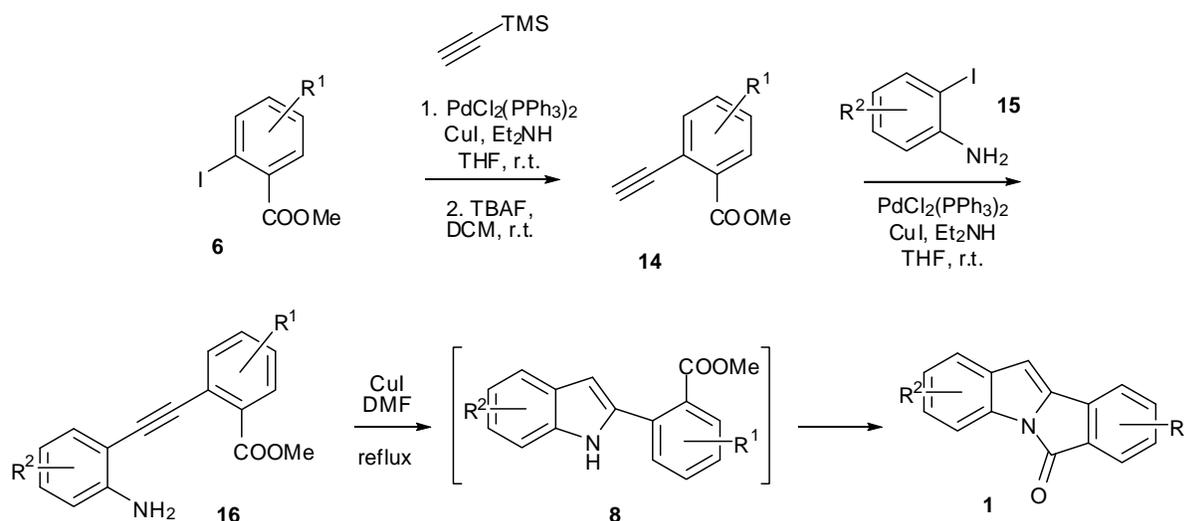| Entry	Product **1**	Yield %[a]	Entry	Product **1**	Yield %[a]
a		62	i		58
b		56	j		58
c		54	k		60
d		61	l		57
e		43	m		62
f		67	n		52
g		75	o		57
h		62			

[a] Isolated yields.

Cyclisation of dihalo-*N*-vinylbenzamide **13** to isoindoloindolone by tandem intramolecular Heck reaction is demonstrated by Dominguez's group taking advantage of difference in reactivity between two halo groups (Scheme 4).[21] The required dihalo-*N*-vinylbenzamide **13** was obtained by condensation of *o*-bromoarylamine **11** with acetaldehyde followed by benzoylation with *o*-iodobenzoyl chloride **12**. Chemoselective palladation with the iodo group of benzamide **13** to form methylene phthalimide intermediate via 5-*exo*-trig cyclisation followed by *endo* cyclisation furnished the isoindoloindolone. The overall yield of the sequence was 35%.
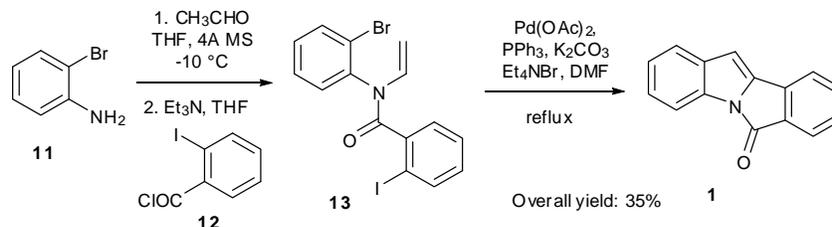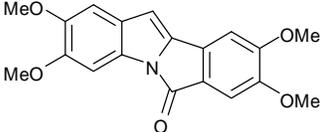

Scheme 4. Dominguez's method.

Estevez's laboratory reported a copper-mediated intramolecular cyclisation of methyl 2-(2-aminophenylethynyl)benzoates **16** to isoindoloindolones (Scheme 5, Table 2).[22] This precursor was prepared by double Sonogashira coupling reactions initially between trimethylsilylacetylene and methyl-*o*-iodobenzoate **6** then subsequently with *o*-iodoaniline **15**. Though the chemistry involved in the synthesis is quite interesting, the low overall yields (6-38%) discourage its application on a larger scale.

Scheme 5. Estevez's method.

Table 2. Estevez's method for isoindoloindolones
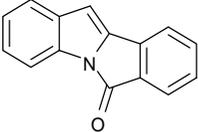
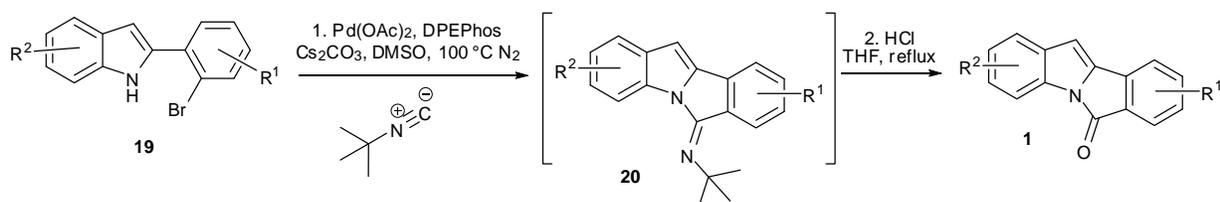| Entry	Product **1**	Overall yield %[a]	Entry	Product **1**	Overall yield %[a]
a		16	c		6
b		38			
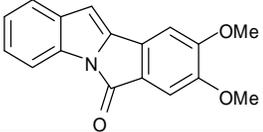
[a] Calculated over 3 steps.

Ponpandian and Muthusubramanian achieved isoindoloindolone synthesis using copper catalyzed domino sp-sp^2 decarboxylative cross coupling reaction of arylpropiolic acids **17** with *o*-iodotrifluoroacetanilide **18** and subsequent cyclisation (Scheme 6) in excellent yield.[23] However, the scope of this method to prepare other derivatives was not studied.
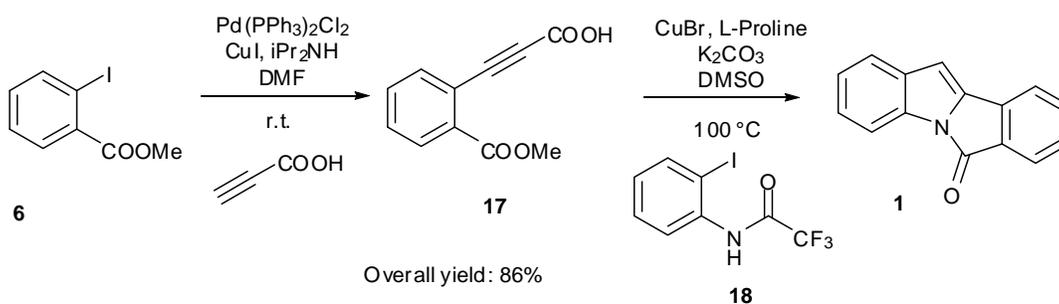
Scheme 6. Muthusubramanian's method.

Zhu and co-workers developed synthesis of isoindoloindolones with Pd-catalyzed intramolecular cyclization *via tert*-butyl isocyanide insertion on 2-(2-bromophenyl)-1*H*-indoles **19** (Scheme 7, Table 3).[24] This method efficiently demonstrates the utility of isocyanides in C-N or C-C bond construction with *N-tert*-butyl intermediate **20**. Using this method a library of twelve compounds was prepared in good to excellent yield.

Scheme 7. Zhu's method.

Table 3. Zhu's method for isoindoloindolones

Entry	Product **1**	Yield % [a]	Entry	Product **1**	Yield % [a]
a		86	g		76
b		93	h		86
c		87	i		81
d		86	j		66
e		84	k		96
f		97	l		76

[a] Isolated yields.

3.2. Wittig reactions

Boutin and co-workers have developed a sequence involving Wittig olefination of *o*-nitrobenzaldehyde **21** with *in situ* phosphorane formed from the phosphonium salt **22** to give nitroarene **23**.[5] The nitro group was reduced by catalytic hydrogenation in the presence of Raney Ni followed by base hydrolysis of the amino-lactone **24** to give the indole acid **25** (Scheme 8). The acid was then converted into isoindoloindolones by refluxing in toluene in presence of *p*-TSA. Six isoindoloindolone derivatives with substituents on both the rings were prepared using this four-step protocol in overall yields of 32-58% (Table 4).
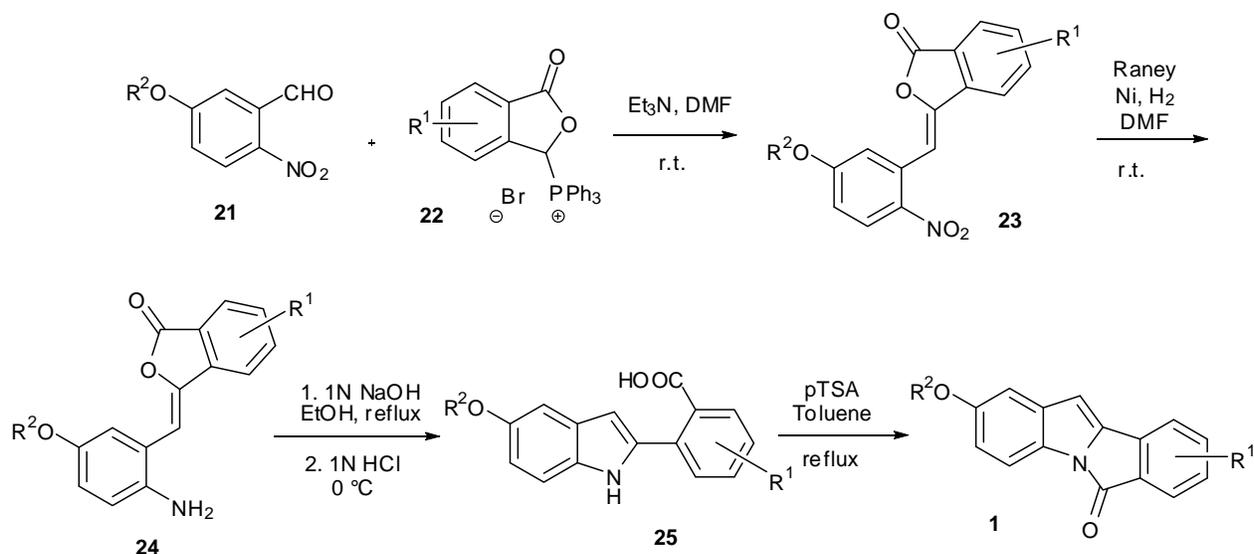
Scheme 8. Boutin's method.

Table 4. Boutin's method for isoindoloindolones

Entry	Product **1**	Overall yield %[a]	Entry	Product **1**	Overall yield %[a]
a		32	d		25
b		42	e		31
c		52	f		28

[a] Calculated over 4 steps

Our group has developed a two-step route to 6*H*-Isoindolo[2,1-*a*]indol-6-ones starting from *o*-nitrobenzaldehydes **26**.[25] The methodology involves Wittig reaction followed by tandem reductive cyclization–lactamization (Scheme 9).
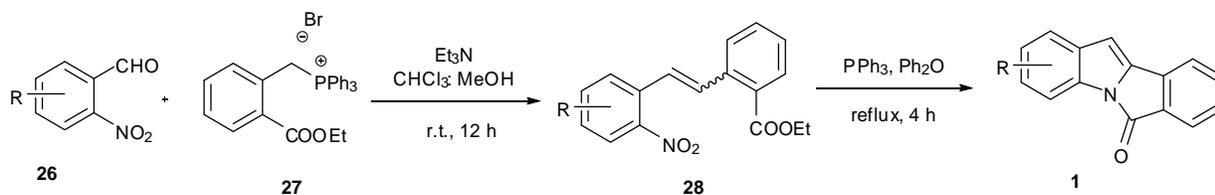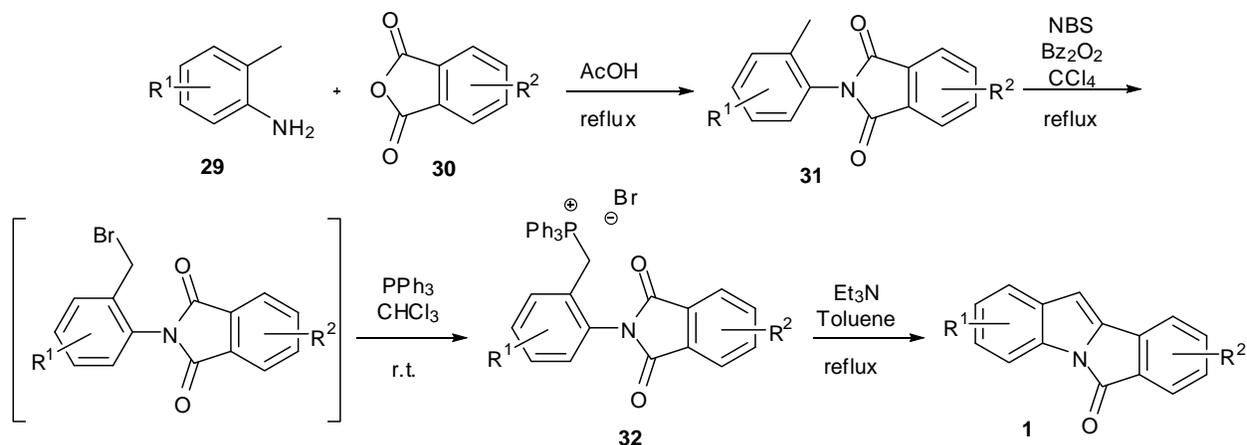
Scheme 9. Tilve's method.

Table 5. Tilve's method for isoindoloindolones

Entry	Product **1**	Overall yield %[a]	Entry	Product **1**	Overall yield %[a]
a		64	d		47
b		54	e		58
c		56	f		56

[a] Calculated over 2 steps.

Various substituted *o*-nitrobenzaldehydes were subjected to Wittig reaction with the phosphorane formed from the benzylic phosphorus salt **27** to obtain the corresponding substituted ethyl 2-(2-nitrostyryl)benzoates **28.** These were then subjected to tandem reductive cyclisation – lactamization using PPh$_3$ in refluxing diphenyl ether. The corresponding isoindoloindolones were obtained in good overall yields. (Table 5) The flexibility of this method was demonstrated by synthesizing a series of isoindoloindolones with electron-donating groups like methoxy, dimethoxy, trimethoxy, and methylenedioxy, as well as electron-withdrawing groups like chloro.

Intramolecular Wittig reaction is employed as a key step by Monneret and his group[6-7] to synthesize isoindoloindolones (Scheme 10, Table 6). The Wittig salt **32** was prepared by benzylic bromination of *N*-(*o*-tolyl)-phthalimides **31** followed by reaction with PPh$_3$. The overall yield of the four compounds ranges from 28-55%.
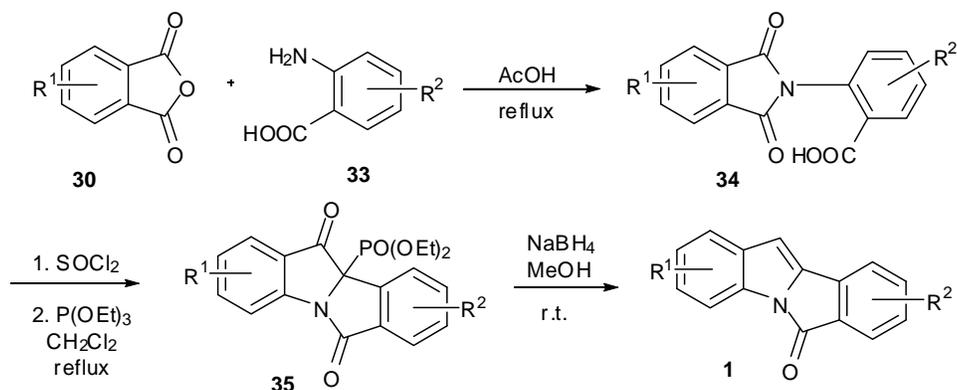
Scheme 10. Monneret's method.

Table 6. Monneret's method for isoindoloindolones

Entry	Product **1**	Overall yield %[a]	Entry	Product **1**	Overall yield %[a]
a		28	c		46
b		55	d		38

[a] Calculated over 3 steps.

3.3. Miscellaneous approaches

Griffiths and his group[26] developed a novel route to isoindoloindolones using *o*-(*N*-phthaloyl)benzoic acids **34** (Scheme 11, Table 7). The process involves formation of acid chlorides followed by reaction with triethyl phosphite to give tetracyclic-β-keto phosphonates **35** via a carbon-carbon bond forming reaction involving phosphonate anion. This ketoamide phosphonate **35** on reduction with NaBH$_4$ furnished the required isoindoloindolones in 31-44 % overall yields.

Scheme 11. Griffiths's method.

**Table 7**. Griffiths's method for isoindoloindolones

Entry	Product **1**	Overall yield %[a]	Entry	Product **1**	Overall yield %[a]
a		31	c		42
b		37	d		44

[a] Calculated over 3 steps.

Flash vacuum pyrolysis of methyl-2-(indol-1-yl)-benzoate **37** to isoindoindolone was developed by McNab *et al.*[27,28] (Scheme 12). Here high temperature cascade reaction involving sigmatropic shift-elimination-cyclisation provided isoindoloindolone. Methyl 2-(indol-1-yl)-benzoate **37** was prepared by C-N coupling of indole and *o*-iodobenzoic acid followed by esterification.
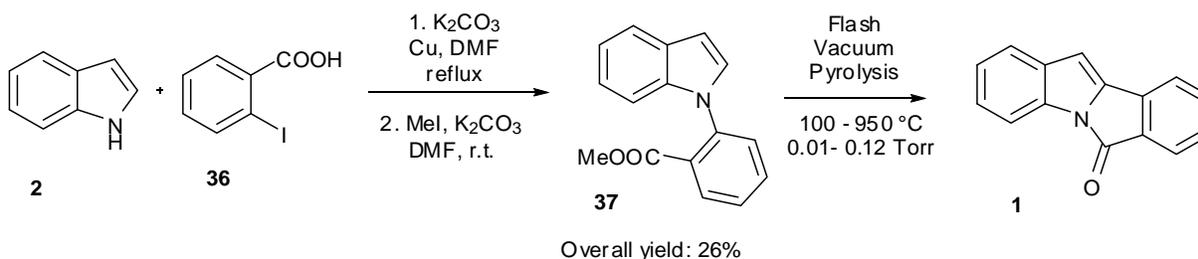

Scheme 12. McNab's method.

Kanaoka's group[29-31] has developed a photochemical isoindoloindolone synthesis. UV irradiation of *N*-(*o*-tolyl)tetrachlorophthalimide **38** resulted in photocyclisation to give the tetracyclic alcohol **39**. Further dehydration in presence of acid gave tetrachloroisoindoloindolone **40** (Scheme 13).
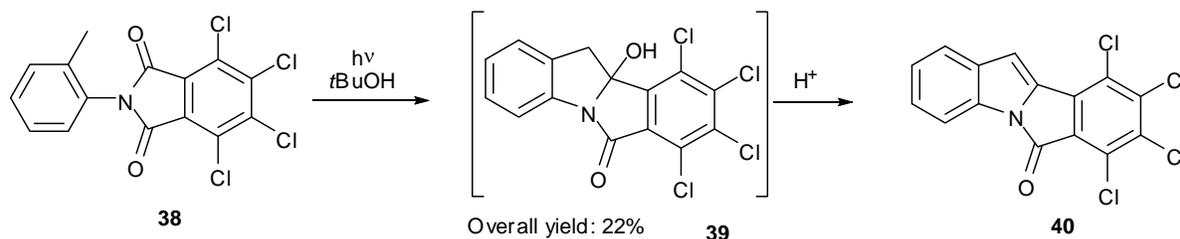
Scheme 13. Kanaoka's method.

A metal free synthesis of isoindoloindolone was reported by Wang's group using dibenzocyclohepten-5-one **41** as starting material (Scheme 14).[32] This method involves Beckmann rearrangement of the oxime **42** to the lactam **43** using TFA, followed by bromination and intramolecular cyclisation of dibromodihydrodibenzoazocin-6-one **44** to yield isoindoloindolone.
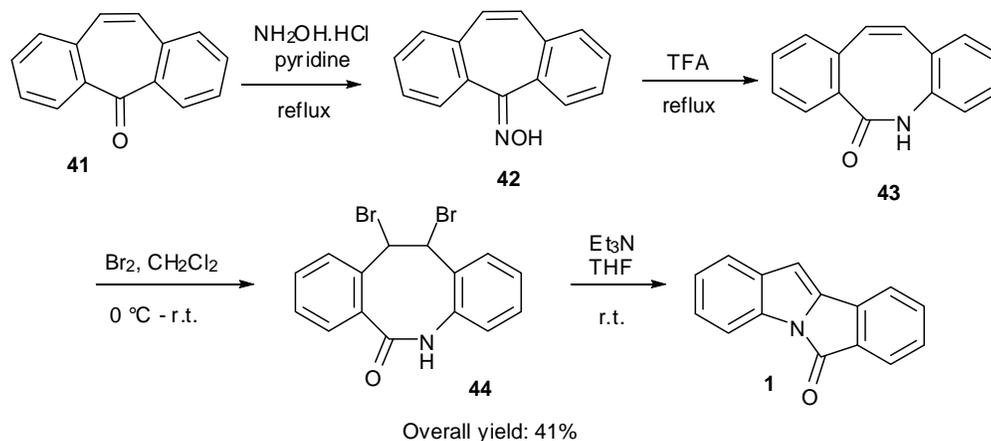
Scheme 14. Wang's method.

4. Conclusions

The synthesis of isoindoloindolones has been extensively studied on account of their diverse biological applications. The methods use different approaches for constructing the indole or isoindole ring. Palladium-catalyzed cyclisation to the indole C-2 is widely used in assembling the isoindole ring. The Wittig reaction was also explored in a few approaches for assembling the

indole ring. Clean and high yielding general strategies are required for making newer analogues for biological testing.

Acknowledgements

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Authors' Biographies

Dr. Hari K. Kadam (born in Goa, India) completed his M.Sc. (Organic Chemistry) with Gold Medal in 2009 from Goa University and simultaneously cleared the CSIR-UGC NET JRF exam. He received his Ph.D. degree in 2015 from Goa University under the supervision of Prof. S. G. Tilve. Presently, he is employed in St. Xavier's College, Goa as Assistant Professor in Chemistry. His current research interests include the synthesis of bioactive heterocyclic compounds and cross coupling reactions.

Prof. Santosh G. Tilve is a Professor of Organic Chemistry at the Dept. of Chemistry, Goa University. He received his Ph.D. degree in 1989 from Pune University under the supervision of Prof. R. S. Mali. After working in the chemical industry for six months, he started his academic career as a Lecturer at Goa University. He was promoted to Associate Professor in 1999 and to full Professor in 2007. He also worked as a Visiting Fellow with Prof. I. Blair at the Pennsylvania University, USA in 2000-2002. His current research interests include asymmetric synthesis, heterocycles, green chemistry, domino reactions and nano composites as catalyst.