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*Review*

# Recent Developments on Synthetic Indoles as Potent Anticancer Agents

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**Keywords:** Synthetic indoles, indolylazoles, bis(indoles), combretastatin analogues, anticancer agents.

**Abstract:** The indole ring system is the most privileged heterocycle in nature and embedded in many biological systems. The demonstration of many indole containing alkaloids as leads for the new pharmaceutical agents, the recognition of the importance of essential amino acid tryptophan in human nutrition and the discovery of plant hormones served to bring about a massive search on indole chemistry. This led to report vast number of structurally diversified bio-active natural and synthetic indoles. The present review focuses on the structure-based drug design of variety of classes of synthetic indoles as potent anticancer agents. Particularly, the recent developments on natural-product inspired rational synthesis of functionalized indoles, indolylazoles and bis(indoles) and their anticancer activities are presented. This review also drawn the attention towards combretastatin-based structural class of indoles and well discussed their potentials as tubulin polymerization inhibitors.

## Introduction

It is observed that cancer is a major life threatening disease in the past several decades and also second largest death causing disease [1]. Although considerable advances have been made in curbing the progression of this devastating disease, till the date a complete cure for cancer is still a dream. The majority of the cancer treatment involves surgery, radiation and chemotherapy [2]. Later two therapies are conventional methods to treat metastatic cancer that are not amenable to surgical removal, with a major drawback of severe side effects. Chemotherapy involves usage removal, with a major drawback of severe side effects. Chemotherapy involves usage of chemical agents to stop the cancer cells from growing. It is observed that cancer chemotherapy is a very difficult task [3]. Despite the impressive performance of many chemotherapeutic agents present in the market such as taxanes, vinca alkaloids etc, and their potentials are somewhat restricted due to several drawbacks associated with them [4-5]. In these drugs multidrug resistance protein is amplified to enhance the drug efflux pump P-glycoprotein (Pgp)

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which led to poor bio-availability and causes low efficacy of the drugs [6-8]. Most of the anticancer drugs have limitations in clinical administration due to poor solubility, hence they always require the adjuvants and intravenous mode of administration that often cause serious side effects such as nephrotoxicity, neurotoxicity and cardiotoxicity [9]. Novel anticancer molecules with poor selectivity towards cancer cells are another major impediment to develop new generation drugs in oncology[10]. Above all these challenges, more importantly, the sky-scraping cost and limited availability of these anticancer drugs to common man leads financial burden in the health-care sector. Over several years, extensive research efforts have been made by both industry and academia to develop selective and cost-effective chemotherapeutic agents to make available to everyone in the society.

Revolutionary development in the molecular biology exploded the identification of several specific targets in tumour cells, which are vital for their replication processes [11-12]. Thus, diverse strategies have been employed to recognize new chemical scaffolds as targeted anticancer drugs [13]. The natural products such as plants, microorganism and marine products of various types have traditionally represented main source of cytotoxic anticancer agents [14]. The structural diversity and selectivity led them to consider as highly advanced lead compounds for chemotherapy [15-16]. Due to less availability and complexity of these molecules, further optimization of the activity is difficult. Hence the researchers have come up with new analogues without considerable loss of activity. Many of designer molecules in medicinal chemistry have their roots from natural products [17-19]. Structural modifications of the natural products often directed to find the key pharmacophore in the molecule and it facilitate to retain most of the activity in the modified analogues [20]. The recent developments in the medicinal chemistry led to a greater focus and appreciation for the nitrogen containing small heterocycles to interrogate biological systems [21-23]. Indole nucleus is one of such *N*-containing privileged heterocycles present in most of the naturally occurring bio-active molecules with diverse therapeutic utilities [24-26]. Over past several years, a large number of indole-based synthetic analogues has been discovered with excellent anticancer activity, which are comparable to their parent natural product counterparts [27-28]. In this review, we mainly focus on the recent discoveries of novel synthetic indoles as anticancer agents, which are rationally designed based on the natural indole alkaloids. Here we summarised the rational approach, chemical synthesis and structure-activity relationship (SAR) studies of these new chemical entities.

In late 1950's the discovery of vinca alkaloids as anticancer agents was the mile stone in the cancer chemotherapy [29-30]. Vinblastine (**1a**) and Vincristine (**1b**) are the indole-based dimeric alkaloids produced by leaves of the periwinkle plant *Catharanthus roseus* (formerly known as *Vinca rosea*) that inhibit microtubule assembly by preventing tubulin polymerization. Later, several semi-synthetic vinca alkaloids such as Vinorelbine (**2a**) and Vinflunine (**2b**) were reported for their potent anticancer activity (Figure 1) [31].

Over the years several natural and synthetic indoles have been emerged as effective chemotherapeutic agents. Based on the structural diversity of cytotoxic indole derivatives, they may be broadly divided into three groups.

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(a) Functionalized indoles as anticancer agents
(b) Indolylazoles as anticancer agents
(c) Bis(indoles) as anticancer agents

**(a) Functionalized indoles as anticancer agents**

Diverse functional groups substituted on the indole ring and subsequent enhancement in their anticancer activity was described under this category. Indole-3-carbinol (**3**) is one of the naturally occurring simple indoles, isolated from cruciferous vegetables, such as broccoli, cabbage and cauliflower [32]. Indole-3-carbinol has shown prominent anticancer properties and is in developmental clinical trials for regression of cervical and vulvar intraepithelial neoplasia (VIN) cancers [33-34]. The compound **3** prevents chemically induced and spontaneous tumorigenesis in several animal studies and also has potential therapeutic applications for the treatment of metastatic breast cancers [35]. Marconett *et al.* showed that indole-3-carbinol is most effective and tissue specific in disrupting the estrogen-dependent growth of human cancer cells such as breast cancer, that co express ERα, GATA3 and AhR. Therefore, indole-3-carbinol will have significantly reduced systemic side effects in heart and bones [36]. Ultra-violet B activated 5-hydroxyindole-3-acetic acid (5-HIAA$^{UVB}$) **4** induces apoptosis in prostate and bladder cancer cells through the stress signaling and apoptotic pathways and 5-HIAA$^{UVB}$ markedly increased the sub-G0/G1phase and resulted in cell cycle disruption [37].

**Indole-3-carboxaldehyde derivatives**

Erwin von Angerer *et al.* reported simple indole derivatives 3-formyl-2-phenylindoles (**5**) as tubulin polymerization inhibitors. The compounds **5** inhibited the polymerization of tubulin to functional microtubules by binding to the colchicine binding site and arrest cell cycle in the G2/M phase, which leads to an apoptotic cell death [38]. The preliminary *in-vivo* activity studies indicated that the 3-formyl-2-phenylindoles (**5**) do not inhibit the growth of tumours. Probably due to the presence of metabolically unstable aldehyde group and subsequently, insufficient bio-availability is another reason. Hence, several structural modifications were attempted to 3-formyl-2-phenylindoles by same authors in order to overcome the stability issues. The aldehyde group was modified by condensation with malononitrile to give corresponding methylene propionitrile **6** [39]. Even though the compounds **6** achieved the *in-vivo* stability and inhibited the growth of MXT mouse mammary tumours, but lost their antimitotic activity of inhibiting tubulin polymerization. Further, structural optimizations led to imine **7a** and oxime 7**b** with strong antimitotic activity [38]. Impressive activity of oximes encouraged the authors to extend their study by synthesizing the aroylhydrazones of 2-phenylindole-3-carbaldehydes (**8**). The resulting hydrazones inhibited the growth of MDA-MB-231 and MCF-7 breast cancer cells with $IC_{50}$ values ranging 20–30 nM for the most potent derivatives. Though the hydrazones **8** exhibited similar structure–activity relationship as the aldehydes **5**, they did not inhibit tubulin polymerization as the aldehydes but were capable of blocking the cell cycle in G2/M phase. Hydrazones **8** drive the tumor cells into apoptosis as demonstrated by the strong increase of caspase-3 activity [40]. Oncrasin-1 **9** is another indole aldehyde derivative effectively kills K-Ras mutant cancer cells [41-42]. Shuhong *et al.* have recently reported Oncrasin-1 analogues as inhibitors of the C-terminal domain of RNA polymerase II and their antitumor activities

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revealed analogues are less cytotoxic to normal cells [43].

Induced anticancer activity of simple molecule NSC-741909 (**10**) is associated with sustained Jun N-terminal kinase (JNK) activation, resulting from suppression of JNK dephosphorylation associated with decreased protein levels of MAPK phosphatase-1 [44-45]. Sulphonamide derived novel indoles including E7070 (**11**), ER-68487 (**12a**) and oxindole ER-67865 (**12b**) have exhibited anticancer activity at multiple points of cell cycle G1/S or G2/M phases [46-47]. Indole-7-sulfonamide **13** induced G2/M phase arrest in P388 cells, suggesting that the methoxy group plays a crucial role in binding to the tubulin assembly [48].

Indibulin (D-24851, **14**) displayed excellent *in-vitro* and *in-viv*o antitumor properties and currently it is undergoing advanced pre-clinical trials. Compound **14** has a mechanism of action similar to that of vincristine and paclitaxel [49-50]. It destabilizes microtubules in tumor cells as well as in a cell-free system. Recently, indole derivatives **15** (AstraZeneca) and indolyl-2-hydrazide-hydrazones (**16**) (Abbott Lab) have been approved as angiogenesis inhibitors that cause selective destruction of tumor vasculature [48, 51]. Janssen Pharmaceuticals, USA recently, patented several tryptamine derivatives **17** as potent anticancer agents. Compounds **17** discussed in the patent have excellent *in-vitro* and *in-vivo* antitumor effects. Moreover, the compounds have low affinity for the P450 enzymes which reduces the risk of adverse drug-drug interactions allowing for a wider safety margin. The current invention also noticed the low drug induced neurological effects and have an improved cardiovascular profile which may favorably influence the dose limiting toxicity of the compounds [52].

P. Singh *et al.* reported [53] anticancer activities of simple indole derivatives **20** by synthesizing from the reaction of indole-3-carboxaldehydes (**18**) and barbituric acids (**19**) under microwave irradiation (Scheme 1). Structure-activity relationship of indole-barbituric acid derivatives **20** led to two potent compounds **20a** and **20b** with the $GI_{50}$ values of 7.5 μM and 13.8 μM, respectively. Interestingly, the $GI_{50}$ values of both these compounds were found to be better than indomethacin ($GI_{50}$ = 64.3 μM) and 5-fluorouracil ($GI_{50}$ = 17.7 μM). The correlation of experimental data and docking studies in the active sites of COX-2, TS and RNS indicated the probable mode of action of compounds **20a** and **20b** for their cytotoxicities [53].

## Functionalized indoles as combretastatin A-4 (CA-4) analogues

Bioisosterism is a strategy of medicinal chemistry for the rational design of new drugs, applied to a lead compound for molecular modification. The role of bioisosterism in rational drug design as well as in the molecular modifications is to improve pharmacodynamic and pharmacokinetic properties of a lead compound [54-55]. Many of the synthetic indole-based scaffolds have been designed by utilizing the concepts of bioisosterism. Varieties of functional groups are tailored at C-2 and C-3 positions of the indole ring and evaluated for their anticancer activity; these structural modifications are in rational to the naturally occurring anticancer agents [56]. Majority of indole-based drugs are able to modulate the microtubule assembly either by inhibition of tubulin polymerization or by blocking microtubule disassembly [27, 57]. In the present review we limit our discussion

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to rational approach of designing functional indoles by considering one of the prominent tubulin binding natural agents, Combretastatin A-4 (CA-4, **21**). The trimethoxyphenyl group ('A' ring) and "*cis*" conformation in CA-4 are retained in the synthetic analogues. Historically, it was believed that ring B was the only structured moiety amenable to modifications yielding potent compounds, and therefore, this ring has received greater attention from medicinal chemists.

## 1-Aroyl, 2-aroyl and 3-aroylindoles

Rational approach for the synthesis of aroylindoles is shown in figure 3. J-P. Liou *et al.* reported the general method for the synthesis of 1-or 3-aroylindoles which involve the reaction of various mono or polymethoxy substituted benzoyl chlorides with variety of indoles as mentioned in scheme 2 [58]. The indoles were treated with EtMgBr, $ZnCl_2$, and $AlCl_3$ followed by the addition of a benzoyl chloride at room temperature led to 3-aroylindoles (**22a-p**). On the other hand, 1-aroylindoles (**23a-p**) were obtained by reacting indole with the base NaOBu-t and followed by addition of an appropriate aroyl chloride. The detailed SAR was studied by introducing methoxy substituent at various positions of indole ring and also replacing a methoxy group to fluoro and hydroxyl groups. The overall study indicated that in 3-aroylindole series the presence of a methoxy group at position C-6 of the indole nucleus (BPR0L075, **22a**) greatly contributed to the anti-tumor activity, whereas the shifting of the methoxy group from C-6 to other positions led to less active (C-5 and C-7) or inactive (C-4) compound. Also noticed introduction of fluoro and hydroxyl groups at C-5 position of indole led to dramatic loss in activity. In case of 1-aroylindoles **23a-p**, the methoxy group at C-5 position of the indole (BPR0L081 **23a**) exhibited stronger cytotoxic activity than the corresponding indoles bearing methoxy at position 4, 6, or 7 [58]. The aroylindoles inhibited the tubulin polymerization at micromolar concentration, suggesting a correlation between cytotoxic activity and the microtubule system. Compound BPR0L075 (**22a**) inhibited tubulin polymerization and induced mitochondrial-dependent apoptosis in various human cancer cells and effective in suppressing cell growth of both MDR-positive and negative tumor cells both *in-vitro* and *in-vivo* [59-60]. More recently, L. Liu *et al.* reported that **22a** induced vascular disruption in human breast cancer mammary fat pad xenografts [61]. The findings from X. Liu research group revealed that **22a** overcomes the multidrug resistance and triggers the alternative cell death by mitotic catastrophe in Paclitaxel resistance ovarian cancer cells [62].

2-Aroylindoles are another class of combretastatin derivatives with potent anticancer activity. The synthesis of 2-aroylindoles was achieved in good yields by reacting 2-lithioindoles (**24**) with aroyl chlorides in THF at -78 °C and subsequent alkaline hydrolysis of the resulting *N*-phenylsulfonyl ketone (**26**). The 2-aroylindoles **27** were prepared by the reaction of 2-lithio indoles **24** with aldehydes and the resulted intermediate carbinol (**25**) was subjected to PDC oxidation as shown in scheme 3 [63]. The most active aroylindole derivative D-64131 (**27a**) exhibited good activity against the human HeLa/KB cervical, SK-OV-3 ovarian, and U373 astrocytoma carcinoma cell lines ($IC_{50}$ = 20-75 nM). 2-Aroylindoles **27** were proved to be specific β-tubulin binders and microtubule destabilizer, and some of these derivatives were found as active as paclitaxel. Further studies on compound D-64131 (**27a)** suggested that it

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competitively binds with [$^3$H]colchicine to α,β-tubulin and inhibited microtubule formation in the G2/M phase of the cell division cycle. In [$^3$H]colchicine experiments **27a** ($IC_{50}$ = 0.51 μm) bound β-tubulin with the same potency as paclitaxel ($IC_{50}$ = 0.53 μm) [64].

## Arylthioindoles

Arylthioindoles **31** and arylsulphonylindoles **32** were designed based on the structural modifications of 3-aroylindoles **23** by replacing its keto functionality with sulphur or sulfide groups and introducing an ester or heterocyclic rings at C-2 position of the indole ring as shown in figure 4.

R. Silvestri research group has reported the optimized synthetic protocol for the preparation of arylthioindoles, involving the reaction of substituted indoles **30** with *N*-phenyl-thiosuccinamides in presence of $BF_3.Et_2O$ or diarylsulfides in presence of NaH. Intermediate arylthioindoles **31** were oxidized using *m*-CPBA to accomplish the final sulfones **32** (Scheme 4) [65].

The authors have studied the detailed SAR of these scaffolds by introducing a methoxy group at different positions of indole ring and phenyl ring. The study concluded that methoxy group at C-5 position, trimethoxyphenylthio group at C-3 position of the indole ring (compound **28**) and sulfur in sulfide state enhanced the anticancer activity. Compound **28** ($IC_{50}$ = 2.0 $\mu$M) was 1.6 times more active than colchicine and about as active as CA-4 as an inhibitor of tubulin polymerization. It has the potent growth inhibition of MCF-7 cells ($IC_{50}$ = 13 nM) which is comparable to the activity of colchicine and CA-4 ($IC_{50}$ = 17 nM) [65]. Further, docking these arylthioindoles in colchicine binding site of tubulin clearly indicate that the trimethoxy ring is well situated in proximity to Cys241. Also, methoxy substituent of the indole moiety is very close to the corresponding group on ring-C of colchicine, leading to a very similar general binding of the two inhibitors. Additionally, indole ring establishes the hydrogen bond between N-H and back bone of Thr179 [66]. These observations are consistent with the highly efficient inhibition of [$^3$H]colchicine binding that occurs with compound **28**. Subsequently, in order to improve the potency of the molecules, the same research group has attempted further structure optimization to arylthioindole scaffold. These changes included the replacement of sulfur with carbonyl and methylene unit, which led to the comparable results with arylthioindoles as tubulin inhibitors but substituent at C-2 position plays a key role in case of these analogues.

More recently, series of arylthioindoles were reported by incorporating various cyclic substituents such as aryl/heteroaryl rings at C-2 position of the indole ring (Figure 5). Of these, initial compounds with the thiophene and pyrrole substituents at C-2 of indole (**34**) were found to be most active analogues. These compounds showed higher metabolic stability as compared to their parent ester derivative **33** and were more effective than vinorelbine, vinblastine, and paclitaxel as growth inhibitors of the P-glycoprotein-over expressing cell line NCI/ADR-RES [67]. In most recent study, thiophene has been replaced with several heterocycles to achieve the most potent arylthioindoles. Compound **35** with an imidazole substituent showed highest anticancer activity ($IC_{50}$ = 1.0 nM, MCF-7) and it was found to be uniformly active in the whole panel of cancer cells and superior to colchicine and CA-4 [68].

## Diarylindoles

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The substituents on both C-2 and C-3 positions of indole ring led to another class of combretastatin analogues. The *cis* restricted five- or six-membered fused heteroatomic bridgehead analogues with two or three atom distance are reported with improved anticancer activity (Figure 6). Medarde *et al.* reported several diarylindoles with trimethoxyphenyl at C-3 and aryl/heteroaryl at C-2 of indole ring [69]. The furan substituted compound **36** was found to have best inhibitory activity against cancer cell lines; displayed a remarkable cytostatic activity with log$IC_{50}$ values ranging from -7.48 to -7.64 for T-47D breast cancer cells to NB-10CNS cancer cells [69].

Synthesis of **36** was carried out by the Fischer indolization of proper 1-furyl-2-(3,4,5-trimethoxphenyl)ethanone (**39**) with 4-methoxyphenylhydrazine (**40**) in refluxing acetic acid/ethanol as exemplified in scheme 5 [69].

Fynn *et al.* reported the benzo-fused heterocycles as combretastatin A-4 analogues, this elaborated study led to two different series of compounds with potent tubulin polymerization inhibition activity. 2-(4-Methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-6-methoxyindole (**37a**) was prepared by the reaction of 2-iodo-5-methoxyacetanilide (**41**) with 4-methoxyphenylethyne (**42**) and 3,4,5-trimethoxyiodobenzene (**44**) through a multi-component reaction. Initially intermediate 1,2-diarylethyne **43** formed by the reaction of 2-iodo-5-methoxyacetanilide with 4-methoxy-phenylethyne in the presence of a catalytic amount of $Pd(PPh_3)_2Cl_2$. Heating of **43** with 3,4,5-trimethoxyiodobenzene (**44**) in DMSO caused the oxidative-addition of Pd(0) followed by Pd(II)-cyclization and reductive elimination, with subsequent loss of the acyl group to afford **37a** (Scheme 6) [70].

Cacchi *et al.* described the synthesis of compounds **37b** and **38** in a multi-step synthetic protocol as shown in scheme 7. 2-Iodo-5-methoxytrifluoroacetanilide (**45**) was coupled to 4-methoxy-3-iso-propyloxyphenylethyne (**46**) under Sonogashira conditions to give the corresponding ethyne intermediate **A**. Subsequent reaction with 3,4,5-trimethoxyiodobenzene (**44**) followed by deprotection using $AlCl_3$ afforded the corresponding phenols **37b** and **38** [71]. Compounds **37a** ($IC_{50}$ > 40 μM) and **37b** ($IC_{50}$ = 4.1 μM) showed less to moderate activity as tubulin polymerization inhibitors. Insertion of keto functionality led to compound **38** with 1.3 times ($IC_{50}$ = 1.6 μM) more active than CA-4 ($IC_{50}$ = 2.1 μM) as a tubulin polymerization inhibitor. Compounds **37b** and **38** were less potent (18 % and 54 %) than CA-4 (91 %) as inhibitors of [$^3$H]colchicine binding to tubulin and are cytotoxic against the MCF-7 breast carcinoma cells. The most potent indole **38** ($IC_{50}$ = 45 μM) was 4.1 times less active than CA-4 (**21**, $IC_{50}$ = 11 μM) on the MCF-7 cells [70].

Most recently, Rafael Pelaez research group reported the synthesis of novel series of indolephenstatins and indoleisocombretastatins (**47**) as potent tubulin inhibitors (Figure 7). Diverse varieties of functional groups at C-3 position of indole ring were evaluated for their cytotoxic potentials against several human cancer cell lines. The compound with cyano and hydroxyiminomethyl substituents showed highest potency with tubulin polymerization inhibition values in submicromolar range and cytotoxicity in subnanomolar range. Further, detailed studies revealed that the highest activity is

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due to the inhibition of tubulin and induce apoptotic death by caspase-3 activation. Molecular modelling studies suggest the indole derivatives bind to colchicine site of the tubulin [72].

## Indolyl chalcones

Chalcone is a generic term for the compounds bearing the 1,3-diphenyl-2-en-1-one. Large number of synthetic and natural chalcones has been tested for their potential anticancer activities [73-74]. Initially, Edward *et al.* demonstrated that the diphenyl derivatives of chalcones as potent tubulin binding agents [75]. Most of these synthetic chalcones share the structural analogy as well as mode of action similar to CA-4 [76]. Over the years, several attempts have been made to improve the anticancer activity of chalcone scaffold by incorporating *N*-heterocycles such as indole [77]. More recently, our research group reported synthesis and anticancer activity of two series of indolyl chalcones **49** and **50**. These chalcones were synthesized in analogy to indolylazoles **48** by replacing the five-membered heterocyclic ring with an enone moiety and this change has been proved to be beneficial for the biological activity (Figure 8). The synthesis of **49** and **50** was accomplished by the Claisen-Schmidt reaction of either indole-3-carboxaldehydes (**51**) with an appropriate acetophenone **52** in presence of piperidine or 3-acetylindoles (**53**) with appropriate aldehydes in presence of sodium hydroxide in ethanol as shown in scheme 8 [78].

The *in-vitro* anticancer activity studies of **49** and **50** against three human cancer cell lines including epithelial (A-549), pancreatic carcinoma (PaCa-2) and androgen-independent human prostatic adenocarcinoma (PC-3) indicated that these compounds are the most potent and selective anticancer agents. The highest cytotoxicity was observed for the compounds (**49a** and **49b**) having a 3,4,5-trimethoxyphenyl substituent ($IC_{50}$ = 0.03-0.09 μM PaCa2). This study revealed that 3,4,5-trimethoxyphenyl, 4-pyridyl and *N,N′*-dimethyl-aminophenyl groups are crucial for the anticancer activity [78].

Recently, W A Maltese research group demonstrated novel indolyl chalcones 3-(2-methyl-1*H*-indol-3-yl)-1-(4-pyridinyl)-2-propen-1-one (MIPP, **55a**) and 3-(5-methoxy-2-methyl-1*H*-indol-3-yl)-1-(4-pyridinyl)-2-propen-1-one (MOMIPP, **55b**) induced cell death with the hallmarks of methuosis; a novel caspase-independent form of cell death in which massive accumulation of vacuoles derived from macropinosomes. MIPP and MOMIPP effectively reduced the growth and viability of Temozolomide-resistant glioblastoma and doxorubicin-resistant breast cancer cells. Thus, these molecules serve as prototype for new drugs that could trigger the death by methuosis in cancers that are resistance to apoptosis [79]. Gurkan-Alp *et al.* reported the synthesis of chalcone type of novel indole-retinoid derivatives and studied their cytotoxic properties in different type of cancer cell lines. These compounds have effective anti-proliferative capacity in liver, breast and colon cancer cell lines. More particularly, the most potent derivative **56** against several breast cancer cell lines showed apoptosis induced anti-proliferative effect. The molecular docking studies indicated that compound **56** binds to retinoid receptors RXRα and RXRγ sites (Figure 9) [80].

## (b) Indolylazoles as anticancer agents

Indoles attached to any nitrogen containing heterocycles are classified under this category. The following discussion

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describes anticancer activity of natural and synthetic indolylazoles. Indolyloxazoles, Labradorin 1 (**57a**) and Labradorin 2 (**57b**), isolated of from *Pseudomonas syringae* pv. *Coronafaciens*, were found to be cytotoxic against NCI–H 460 (lung-NSC) human cancer cell lines with $GI_{50}$ values of 9.8 µg/mL and 9.6 µg/mL, respectively [81]. Indolylthiazole Camalexin (**58**), isolated from phytoalexin of *Arabidopsis thaliana* induced apoptosis in T-leukemia Jurkat cells [82]. Pyrimidine class of marine alkaloids indolylpyrimidines (Meridianins A-E, **59**) isolated from the tunicate *Aplidium meridianum*, displayed cytotoxicity towards murine tumor cell lines and are known as kinase inhibitors. Here we limit our discussion to the most recent cytotoxic synthetic indolylazoles **60** which were rationally designed in analogy with natural indolyl alkaloids (Figure 10).

For the past several years, our research group intensely working on the rational design of novel synthetic indolylazoles in analogy to naturally occurring indolyloxazoles **57**. We introduced several five-membered heterocyclic rings and synthesized diverse variety of indolylazoles (**60**) and evaluated their anticancer activity. Our initial efforts included the solvent-free synthesis and anticancer activity studies of novel indolyl-1,3,4-oxadiazoles (**63**). The expeditious synthesis of **63** required the initial [bis(trifluoroacetoxy)iodo]benzene (1.2 mmol) mediated oxidation of indolyl-3-aldehyde-*N*-acylhydrazones (**61**, 1.0 mmol) to obtain indolyl-1,3,4-oxadiazoles **62** in good yields. Further, removal of benzenesulfonyl group and alkylation afforded a series of indolyl-1,3,4-oxadiazoles **63** (Scheme 9) [83].

The *in-vitro* anticancer activity of compounds **63** against three human cancer cell lines and their structure–activity relationship (SAR) study revealed that the compounds with 4-pyridyl ($IC_{50}$ = 1.6 µM) or 3-pyridyl ($IC_{50}$ = 0.9 µM) substituent (**63a** or **63b**) were potent and selective against PaCa2 cancer cell lines. Also, the *N*-methylation of indole nitrogen in **63** led to dramatically improved cytotoxicity against cancer cells ($IC_{50}$ = 1.4 µM, PaCa2) [83]. The encouraging anticancer activity results of **63** prompted us to further evaluate structural modifications to enhance the cytotoxic potentials of indolylazoles. In this regard, 4-(3′-indolyl)oxazoles (**67**) were synthesized as bioisosteric structural analogues to the naturally occurring 4-(3′-indolyl)oxazoles (**57**). The synthesis was initiated by the preparation of an intermediate 3-tosyloxyacetyl-1-benzenesulfonyl indole (**65**) from the reaction of acetylindole (**64**) with [hydroxy(tosyloxy)-iodo]benzene. The key step of the protocol involves the solvent-free microwave irradiation of **65** with appropriate amides for the exclusive formation of 4-(3′-indolyl)oxazoles **66** in good yields. Finally, the desulfonation followed by *N*-alkylation of indolyloxazoles **66** produced 4-(3′-indolyl)oxazoles **67** in good yields (Scheme 10) [84].

The *in-vitro* anticancer activity studies of 4-(3′-indolyl)oxazoles (**67**) found to be moderate when compared to indolyl-1,3,4-oxadiazoles. The most active compound (**67a**) in this series has the anticancer activity with $IC_{50}$ value of 14.1 µM against MCF7 breast cancer cell lines. In order to improve the anticancer potentials of indolylazoles, indolyl-1,3,4-oxadiazoles **63** were further optimized by replacing central 1,3,4-oxadiazole ring to 1,3,4-thiadiazloe ring and synthesized a novel series of 5-(3′-indolyl)-1,3,4-thiadiazoles (**70**). The synthetic protocol involves the reaction of indole-3-carboxylic acids (**68**) with corresponding aryl/heteroaryl hydrazides to

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afford *N,N′*-diacylhydrazines (**69**) which upon treatment with Lawesson's reagent produced **70** in good yields (Scheme 11) [85].

The SAR of indolyl-1,3,4-thiadiazoles **70** revealed the importance of substituents at C-2 and C-5 positions of 1,3,4-thiadiazole. The compound with 4-benzyloxy-3-methoxyphenyl and 5-bromo indolyl substituents (**70a**) is the most active in suppressing the growth of cancer cells ($IC_{50}$ = 1.5 μM, PaCa2). The compounds bearing C-2 substituent as benzyl, 3,4-dimethoxyphenyl and 4-benzyloxy-3-methoxyphenyl have shown significant cytotoxicity against multiple cancer cell lines ($IC_{50}$<10 μM). Introduction of 4-*N*-*N*-dimethylaminophenyl and 3,4,5-trimethoxyphenyl at C-2 induced selectivity against MCF-7 and MDA-MB-231 cancer cell lines [85]. In continuation of our efforts next we incorporated biologically significant 1,2,4-triazole linker and prepared a novel series of indolyl-1,2,4-triazoles **73** and **74**. The facile synthesis of novel indoly-1,2,4-triazoles **73** and **74** employed the reaction of indole-3-carbonitriles (**72**) with aryl/heteroaryl hydrazides in presence of potassium carbonate in good yields as shown in scheme 12 [86].

The detailed SAR study indicated that most of the compounds in the series showed improvement in anticancer activity results as compared to previously prepared indolylazoles and this specifies the significance of 1,2,4-triazole linker. The study also revealed that substituents including 3,4,5-trimethoxyphenyl, 3,4-dimethoxyphenyl, 4-benzyloxy-3-methoxyphenyl, 4-piperidinyl, 4-fluorophenyl and *N*-methylindole are beneficial for the activity of indolyl-1,2,4-triazoles. In particular, 3-(3′,4′,5′-trimethoxyphenyl)-5-(*N*-methyl-3′-indolyl)-1,2,4-triazole (**74a**) ($IC_{50}$ = 0.8 μM, PaCa2) and 3-(4′-piperidinyl)-5-(*N*-methyl-3′-indolyl)-1,2,4-triazole (**74b**) ($IC_{50}$ = 1.6 μM, MCF-7) were the most promising and broadly active compounds against the tested cell lines [86]. Further, preliminary molecular target identification studies showed that the most potent compounds **70b** and **74a** disrupted the microtubule network at 10 μM, indicating these compounds exhibit anticancer activities via interacting with tubulin assembly [87].

Most recently, A.D. Westwell research group reported novel indolylazoles containing 1,2,4-oxadiazole and isoxazole rings substituted at C-2 position of the indole ring as pro-apoptotic antitumour agents. The synthesis of 5-(indol-2-yl)-1,2,4-oxadiazoles (**77**) was carried out by base-catalysed condensation reaction between substituted amidoximes **75** and indole-2-esters (**76**), using sodium ethoxide in refluxing ethanol in low to moderate yields (Scheme 13) [88]. The anticancer activity of synthesized 5-(indol-2-yl)-1,2,4-oxadiazoles (**77**) against various cancer cell lines resulted in two most potent compounds **77a** and **77b** on COLO320 cancer cell lines with $IC_{50}$ = 7.7 μM and $IC_{50}$ = 9.1 μM, respectively [88]. Selected compounds were able to trigger apoptosis in sensitive cell lines, such as *via* activation of caspase-3/7 or caspase independent pathway, demonstrating that indole-based oxadiazoles **77** possess *in-vitro* antitumor and pro-apoptotic activity.

In later study, the regiochemical controlled synthesis of two series 3-(indol-2-yl)-5-phenylisoxazoles and 5-(indol-2-yl)-3-phenylisoxazoles has been developed. Initially, 3-(indol-2-yl)-5-phenylisoxazoles (**80**) were prepared by the palladium-catalyzed reactions of indole-2- carbonyl chlorides (**78**) with phenylacetylenes to give

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intermediate alkynyl ketones (**79**) which upon condensation with hydroxylamine hydrochloride under refluxing conditions. In another series, 5-(indol-2-yl)-3-phenylisoxazoles (**83**) were prepared by dipolar cycloaddition of 2-ethynyl-1-methylindole (**81**) and aldoximes (**82**) promoted by sodium hypochlorite solution and triethylamine (Scheme 14). In the similar way the synthesis of 5-(indol-5-yl)-3-phenylisoxazoles (**85**) was carried out by the dipolar cycloaddition of 5-ethynylindole (**84**) with aldoximes **82**. The *in-vitro* growth inhibitory activities of the new isoxazoles against the (colon) and Calu-3 (lung) human cancer cell lines revealed preferential antiproliferative activity within the 5-(indol-5-yl)-3-phenylisoxazole series. The most active compounds **85a** and **85b** showed $IC_{50}$ values 13.5 μM and 9.0 μM against COLO320 cancer cells. Further analysis revealed the ability of the indol-5-yl series to induce expression of effector caspases-3 and -7, and retention of viability of the human bronchial smooth muscle cell (BSMC) control cell population, suggesting selective pro-apoptotic antitumour effects [89].

Our recent study on exploring novel heterocyclic linkers for indolylazoles led to a facile synthesis of various 2-arylaminoindolyl-1,3,4-thiadiazoles (**89**). Synthesis of **89** was achieved from the acetyl chloride mediated cyclization of thiosemicarbazide **88**, which in turn was obtained by the reaction of indolyl-2(3)-carbohydrazides **86** with aryl isothiocyanates **87** as shown in scheme 15 [90].

The structure-activity relationship study of synthesized 2-arylamino-5-(indolyl)-1,3,4-thiadiazoles (**89**) showed that all the compounds were selectively cytotoxic against tested breast cancer cell line MDA-MB-231 ($IC_{50}$ <1 μM). Compound **89a** with 3,4,5-trimethoxyphenylamino substituent showed high activity profile against multiple cancer cell lines, particularly promising results against prostate cancer cell line ($IC_{50}$ = 0.15 μM, LnCaP). Also these 5-(indolyl)-1,3,4-thiadiazoles were more potent than the control Doxorubicin (Figure 11) [90].

In Zhang and co-workers have reported 1,2,4-triazole substituted indoles (**90**) as potent tubulin polymerization inhibitors. Compounds **90a-c** having structural similarity to combretastatin A-4, retained the *cis* configuration required for bioactivity. The introduction of *N*-methyl-5-indolyl group in place of B ring of CA-4 led to compounds **90a** and **90a** which exhibited potent cytotoxicity against a variety of cancer cells including multi-drug-resistant (MDR) cells (KB VI cells, $IC_{50}$ = 21 and 32 nM). The inhibition potency of **90a** and **90a** was similar to that of CA-4. Loss of double bond in the indole ring of **90a** resulted loss of activity (compound **90c**) indicating aromaticity and/or planarity of B ring is critical for activity. Computer docking and molecular simulations of **90a** inside the colchicine binding site of tubulin enabled identification of residues most likely to interact strongly with these inhibitors and explain their potent anti-tubulin activity and cytotoxicity (Figure 12) [91].

One of the major problems for current tubulin inhibitors is the development of drug resistance in cancer patients. P-Glycoprotein (Pgp)-mediated multidrug resistance is one foremost reason for the failure of treatment by paclitaxel and vinblastine. In order to address these issues D.A James *et al.* proposed a series of indole-imidazole derivatives **91** that demonstrated substantial *in-vitro* anti-proliferative activities against cancer cell lines, including multidrug resistance (MDR) phenotype [92].

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More recently, Wei Lu *et al.* reported the novel 2‑indolyl-4-benzoyl-imidazole (ABI-III) analogues as potent tubulin polymerization agents. The equal potency ($IC_{50}$ = 3.7 nM) on both a paclitaxel resistant cancer cell line (PC-3/TxR) and its matching parental cell line PC-3 of analogue **92** indicated that the ABI-IIIs were not substrates of Pgp and can effectively overcome Pgp-mediated multidrug resistance and paclitaxel resistance [93]. C-M. Li *et al.* demonstrated the compound **92** is orally active tubulin antagonist. This bind to the colchicine-binding site on tubulin and inhibited tubulin polymerization, induced cell apoptosis, and retained potency in P-glycoprotein-over expressing cell lines [94]. Pyrimidine class of marine alkaloids indolylpyrimidines (Meridianins A-E) (**93**) isolated from the tunicate *Aplidium meridianum* displayed potent cytotoxicity towards murine tumor cell lines and are known as kinase inhibitors [95]. Recently, P. Moreau research group has synthesized diversely substituted analogues of Meridianins (**94**) and studied for their *in-vitro* anticancer potencies against various cancer cell lines [96]. Fuchun Xie *et al.* reported that the pyrimidine substituted indoles displayed high antiproliferative activities against several cancer cell lines with $IC_{50}$ values ranging from 16 to 62 nM and **95** showed the tubulin binding ability with $IC_{50}$ = 0.79 μM (Figure 13) [97].

**(c) Bis(indoles) as anticancer agents**

Bis(indoles) are one of the important class of indole containing natural products, in which two indole nuclei are separated by a heterocyclic ring spacer or any functional group. Bis(indole) alkaloids played significant role in anticancer research, for example, Nortopsentins (**96**) and Topsentins (**97**), isolated from marine sponge *spongsorites ruetzleri*, are well known anticancer agents of this category [98]. Nortopsentins A–C, with its 2,4-bis(3′-indolyl)imidazole skeleton exhibited *in-vitro* cytotoxicity against P388 cells and antifungal activity against *Candida albicans*. Their *N*-methylated derivatives improved P388 activity as compared to the activity of parent compounds [99]. Similarly, Topsentins (**97**) inhibited the growth of P388 mouse leukemia cells and Herpes simplex virus, type 1 (HSV-1) [100]. Piperazine containing bis(indole), Dragmacidin (**98**) from a deep water marine sponge *Dragmacidin* sp. exhibited *in-vitro* cytotoxicity with $IC_{50}$ values of 15 μg/mL against P-388 cell lines and 1-10 μg/mL against A-549 (human lung), HCT-8 (human colon) and MDA-MB-231 (human mammary) cancer cell lines [101-102]. Rhopaladins A-D (**99**) from Okinawan marine tunicate *Rhopa/aea sp* exhibited inhibitory activity against cyclin dependent kinase 4 (CDK4) and *c-erbB-2* kinase ($IC_{50}$ = 12.5 and 7.4 μg/mL, respectively) (Figure 14) [103]. Similarly, several diverse classes of natural bis(indoles) have been isolated and studied for their potential cytotoxic effects [104-106].

Of these several natural bis(indoles), more particularly, Nortopsentin **96** gained the attention of researchers due to its structural simplicity and broad anticancer activity. In recent years, a large number of synthetic Nortopsentin analogues were reported by replacing imidazole ring spacer of **96** with variety of five-or six-membered heterocyclic rings and evaluated for their anticancer activity. The thiazole containing analogues, bis(indolyl)thiazoles **100** have shown anticancer activity against a panel of NCI-60 human cancer cell lines in sub micromolar concentrations. The same authors have reported bis(indolyl)pyrazines (**101**) and bis(indolyl)pyrazinones (**102**) and found that the bis(indoles) with 6-membered

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heterocyclic spacers exhibited excellent *in-vitro* cytotoxicity against multiple cancer cell lines [107-108].

Bis(indolyl)pyrimidines (**103**) with *N*-tosylindoles as substituents exhibited significant inhibitory activities against leukemia SR, CNS Cancer (SF-539) and breast cancer (MDA-MB-435) cell lines with the $GI_{50}$ values of 0.22, 0.16 and 0.22 μM, respectively. 3,5-Bis(indolyl)pyrazine (**104**) demonstrated good inhibitory effects against a variety of tumor cell lines with the $GI_{50}$ values less than 10 μM [109]. Bis(indolyl)-4-trifluoromethylpyridines (**105**) exhibited weak cytotoxicity towards murine leukemia cells (P388), and some compounds in this series displayed moderate inhibitory activity against A-549 cancer cells [110]. Diana and co-workers reported bis(indolyl)thiophenes (**106**) as effective bis(indoles) anticancer agents against the leukemia sub-panel of cancer cell lines having $GI_{50}$ in the range 0.34-3.54 μM [111]. Bis(indolyl)furans (**107**) with methoxy and methyl groups at C-5 and N-1 positions of indole ring have shown selectivity towards multiple cancer lines in a panel of NCI-60 human cancer cell lines. Cytotoxicity studies of compounds **106** and **107** revealed that the methoxy group at C-5 position of indole is critical for their anti-cancer activity. Pyrazole and isoxazole heterocyclic spacers provided analogues bis(indolyl)isoxazoles (**108**) and bis(indolyl)pyrazoles (**109**) with good cytotoxicity against NCI-60 human cancer cell lines. The DNA-intercalating assay of **109** revealed that DNA cannot be main cause for cell death and anticancer activity is due to some other mechanism (Figure15) [112-113].

Sunjoo *et al.* reported the topsentin analogue 3-(2′-indolyl)phenyl methanone (**110**) as micro-tubule destabilizing agent (Figure 16). Compound **110** inhibited tubulin action and exhibited potent antitumor activity in various preclinical models. Nanomolar concentrations of compound **110** caused down-regulation of bcl-2, induced PARP cleavage and apoptosis in both LnCaP and PC-3 prostate cancer cells. Bis(indole) **110** inhibited polymerization of purified tubulin and induced a strong and concentration-dependent G2/M arrest in PC-3 cells [114].

Recently, our research group also reported rational design, synthesis and anticancer activity of some Nortopsentin (**96**) analogues having 1,2,4-thiadiazole and 1,3,4-oxadiazole rings as central heterocyclic spacers in place of parent imidazole ring in **96**. A facile and high yielding synthesis of bis(indolyl)-1,2,4-thiadiazoles (**115**) and bis(indolyl)-1,3,4-oxadiazoles (**117**) were carried out using a relatively benign iodobenzene diacetate (IBD) reagent. A rapid synthesis of bis(indolyl)-1,2,4-thiadiazoles (**115**) involved the oxidative dimerization of variety of indolyl thioamides (**112** and **113**) using IBD at room temperature [115]. Bis(indolyl)-1,3,4-oxadiazoles (**117**) were synthesized in good yields by the IBD mediated oxidative-cyclizations of intermediate bis(indolyl)hydrazide-hydrazones (**116**) [116]. The scope of the reaction was studied by reacting variety of substituted indoles (Scheme 16).

The detailed SAR studies of these two series of compounds have revealed that the introduction of 1,2,4-thiadiazole ring led to moderate anticancer activity. Bis(indole)derivative **115a** showed selective cytotoxicity against prostate cancer cell lines ($IC_{50}$ = 14.6 μM, LnCaP cells). In the later series of bis(indolyl)-1,3,4-oxadiazoles (**117**), anticancer activity was dramatically increased several folds as compared to previous series of bis(indoles) **115**. Most of the bis(indolyl)-1,3,4-oxadiazoles showed

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anticancer activity at sub-micromolar concentrations. The SAR of **117** indicated that the substituent at C-5 position of the indole ring play a crucial role in imparting the anticancer activity. Also, *N*-alkylation of indole ring was found to be beneficial for selective cytotoxicity. Bromo-substituted **117a** was the most active compound in the series, with $IC_{50}$ values of 20 nM against prostate (DU145) and cervical (HeLa) cancer cell lines. Compounds **117b-d** were found to be selective cytotoxic against tested cancer cell lines (Figure 17). Preliminary mechanism of action studies in MDA-MB-231 breast cancer cells indicated that bis(indolyl)-1,3,4-oxadiazoles **117** induced apoptosis and promoted cell death [116].

In searching novel spacers for synthetic bis(indoles) and to enhance the anticancer activity, our research group has come up with a new series of bis(indolyl)hydrazide-hydrazones (**121**) by replacing the heterocyclic ring with a hydrazide-hydrazone functionality (–CO–NH–N=CH–). Synthesis of **121** was carried out by reacting various indole-2(3)-carbohydrazides (**118** and **119**) with indole-3-carboxaldehydes (**120**) in presence of acetic acid (Scheme 17) [117].

*In-vitro* anticancer activity evaluation of all the synthesized bis(indolyl)hydrazide-hydrazones (**121**) against various human cancer cell lines showed that hydrazide-hydrazones were selectively cytotoxic against breast cancer cell line (MDA-MB-231). Among the synthesized compounds, **121a** with indole-2-carboxylic acid hydrazide and 6-methoxyindole moieties is the most potent compound of this series ($IC_{50}$ = 0.7 µM, MDA-MB-231). In *N*-alkylated series, compound **121b** having *N*-(*p*-chlorobenzyl) and bromo substituents was found to be the most potent against multiple cancer cell lines ($IC_{50}$ = 10.0-1.0 µM). Compound **121c** (Figure 17) exhibited selective cytotoxicity against breast cancer cell line ($IC_{50}$ = 3.1 µM, MCF-7) [117]. Further, preliminary mechanistic studies indicated that the present series of compounds could be a new class of potent apoptosis inducers which can open a new strategic approach to design novel bis(indole) analogues as potent anticancer agents.

More recently, A. Carbone *et al.* synthesized a series of novel 2,5-bis(3′-indolyl)pyrroles (**124**) by replacing imidazole ring of Nortopsentin (**96**) with pyrrole ring. Synthesis of **124** involved the initial preparation of intermediate **123** from Vilsmeier-Haack reaction of *N*-methylindole (**122**) followed by the treatment of **123** with ammonium acetate as shown in scheme 18.

All the synthesized 2,5-bis(3′-indolyl)pyrroles (**124**) exhibited potent cytotoxicity against various cancer cell lines with mean $IC_{50}$ values ranging from 4.4 µg/mL to 0.37 µg/mL. Further, the most active compounds in this series showed tumour selectivity as indicated by *ex-vivo* clonogenic assay [118].

In the latest reports on designing the novel anticancer agents based on Topsentin-class of marine alkaloids included the synthesis of 4-amino-2-arylamino-5-indoloylthiazoles (**125a-c**) (Figure 18). Synthesized diaminoindolylthiazoles (DIT) were tested against HeLa cancer cells and compound **125c** showed highest cytotoxicity with an $IC_{50}$ value of 1 µM.

The further study revealed that the 4-amino-2-arylamino-5-indoloylthiazoles **125a-c** induced apoptosis through the intrinsic pathway by reducing the mitochondrial membrane potential and activating caspases 3 and 9. The active compound **125c**

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effectively arrested the cell cycle at $G_2$/M phase, which is followed by accumulation of the cells in the Sub G0 phase. Compound **125a** was effective in downregulating TNF-induced NF-κB activation [119].

## Conclusion

Indole containing compounds have been playing a crucial role in the anticancer drug discovery research. Many of the simple and complex indoles derived from nature and their synthetic analogues demonstrated their ability in both *in-vitro* and *in-vivo* biological assays. The most promising molecules of several structural classes such as indolylazoles and bis(indoles) showed their mechanism of action mostly via the inhibition of tubulin polymerization. Some of these molecules are in pre-clinical to advanced clinical stages. Further, thorough understanding of diverse structural classes of existing indoles and their anticancer effects will give a clear insight to develop most potent and selective anticancer agents, and overcome the drawbacks associated with existing anticancer drugs.

## Acknowledgements

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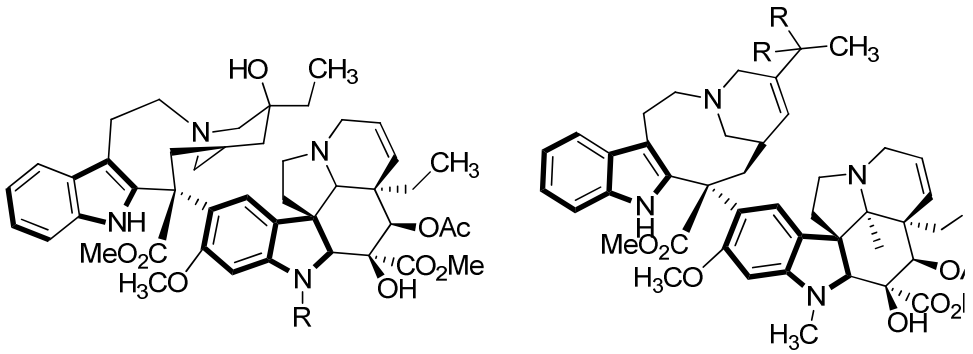


Vinblastine (R = $CH_3$) (**1a**)
Vincristine (R = CHO) (**1b**)

Vinorelbine (R = H) (**2a**)
Vinflunine (R = F) (**2b**)

**Figure 1** Natural and synthetic Vinca alkaloids

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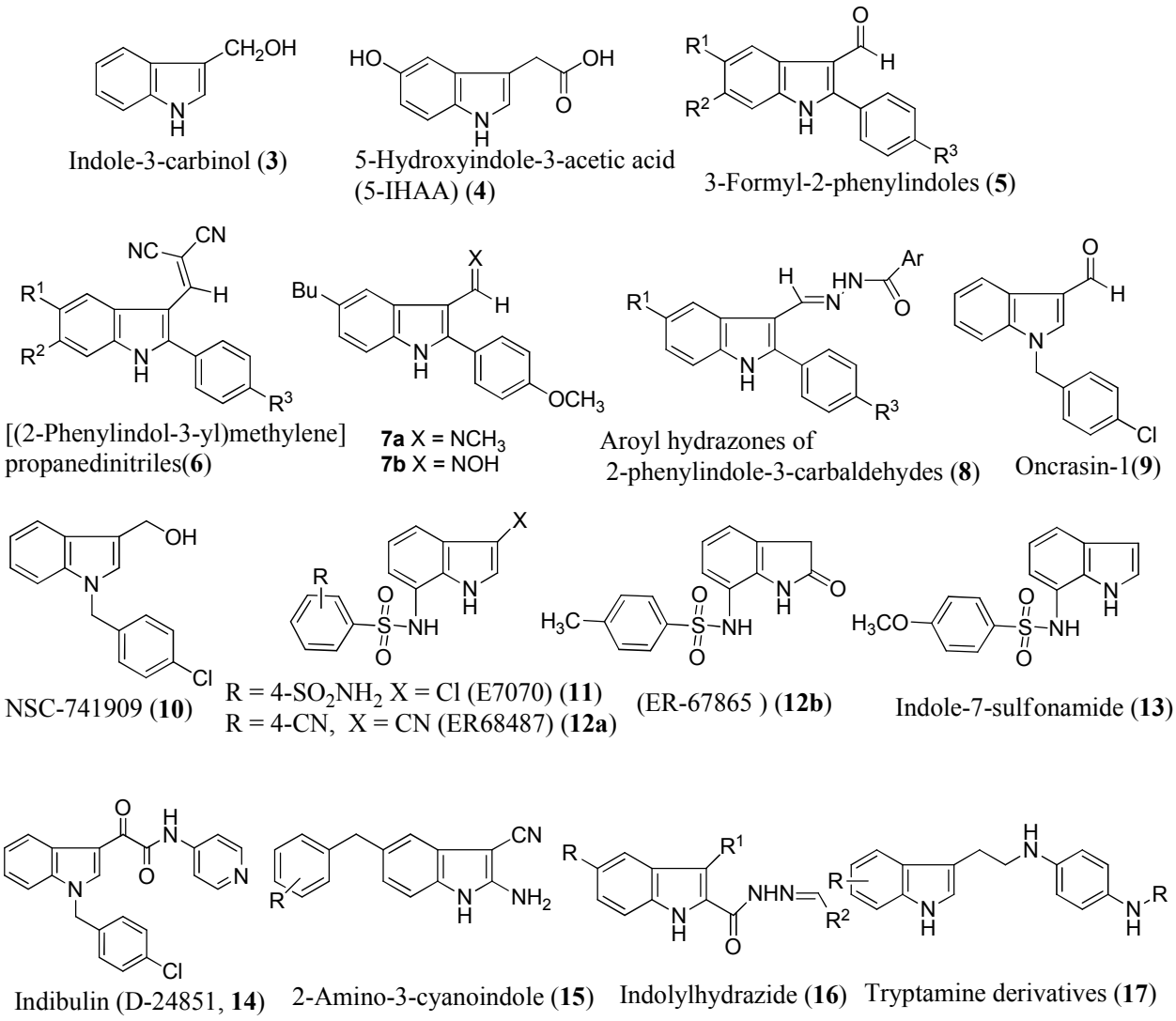
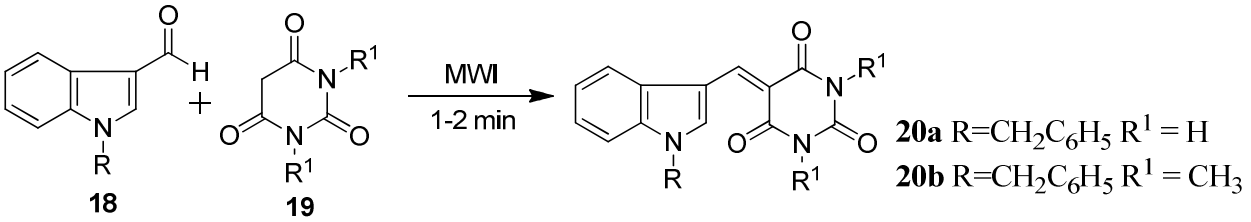



**Figure 2** Functionalized indoles as potent anticancer agents




**Scheme 1** Synthesis of indole-barbituric acid derivatives

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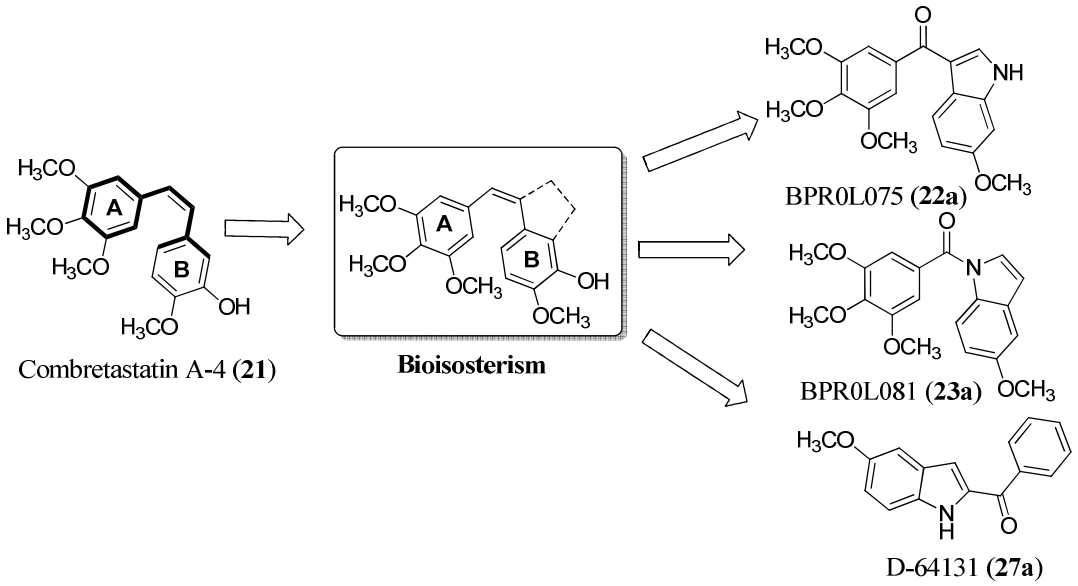
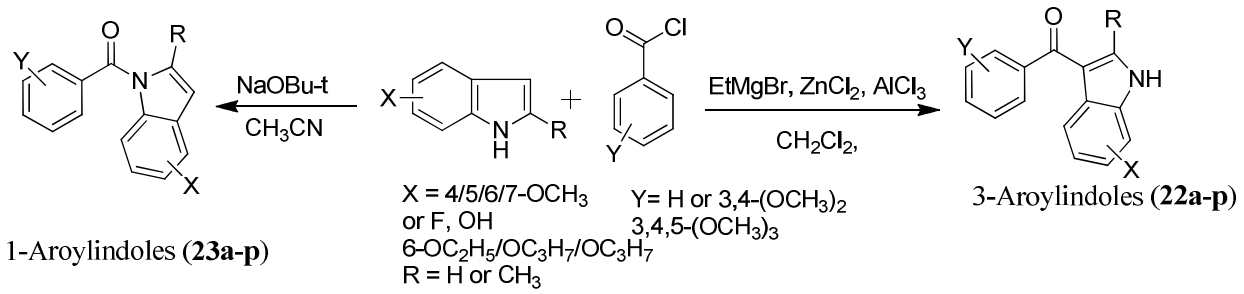
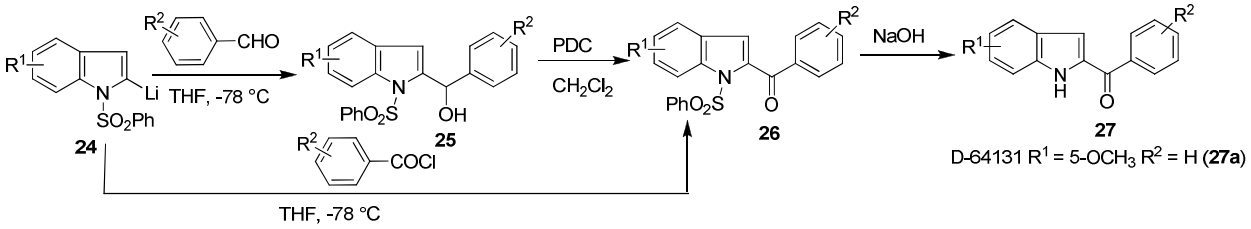



**Figure 3** Rational approach for aroylindoles




**Scheme 2** Synthesis of 1-or 3-aroylindoles




**Scheme 3** Synthesis of 2-aroylindoles

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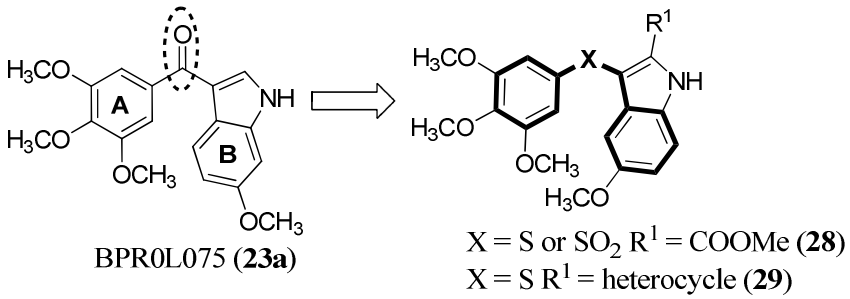
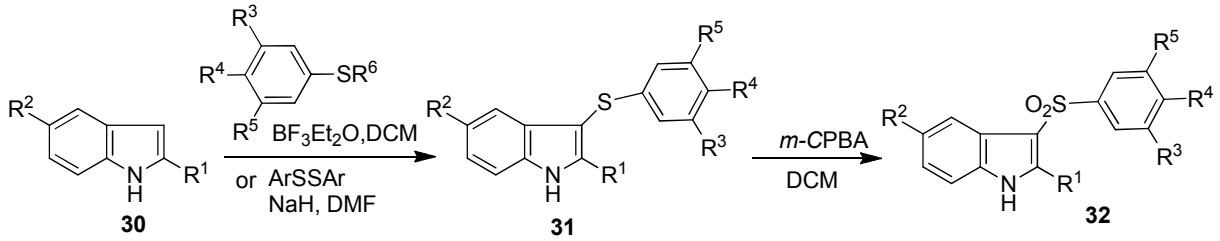



**Figure 4** Rational design of arylthioindoles




**Scheme 4** Preparation of arylthio/arylsulphonylindoles

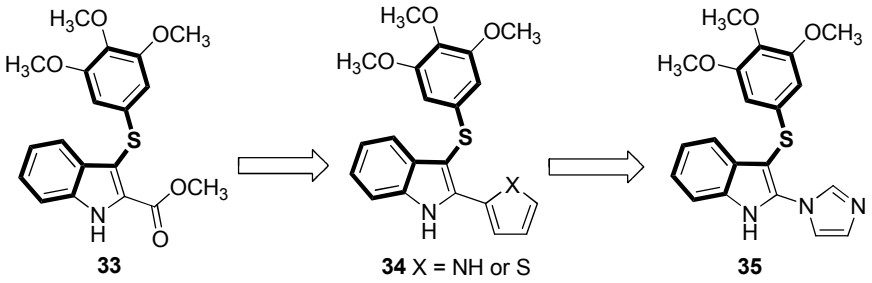



**Figure 5** Variations at C-2 position of arylthioindoles

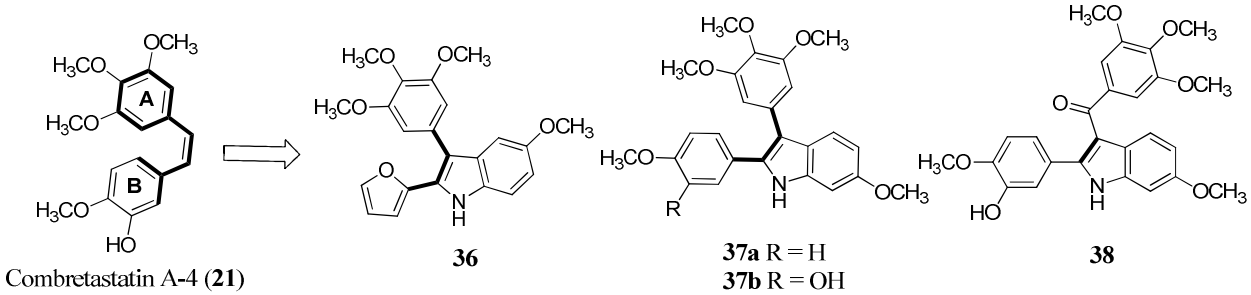



**Figure 6** Diarylindoles as combretastatin A-4 derivatives

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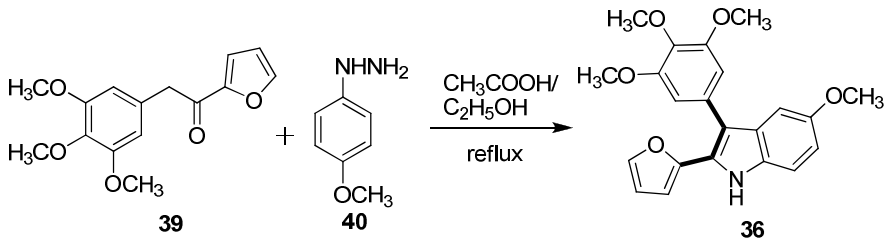
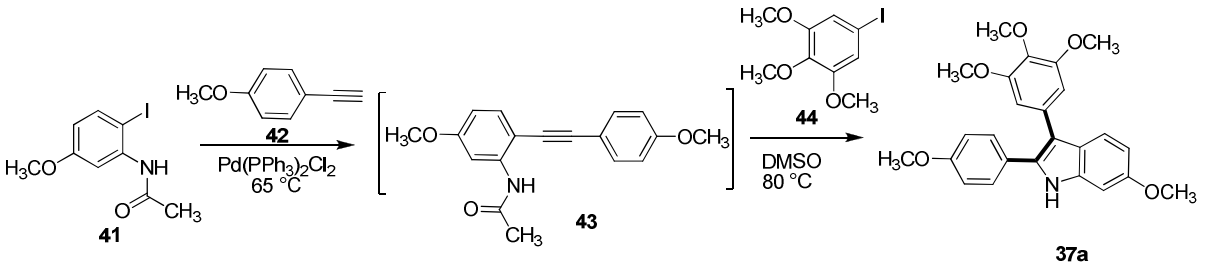
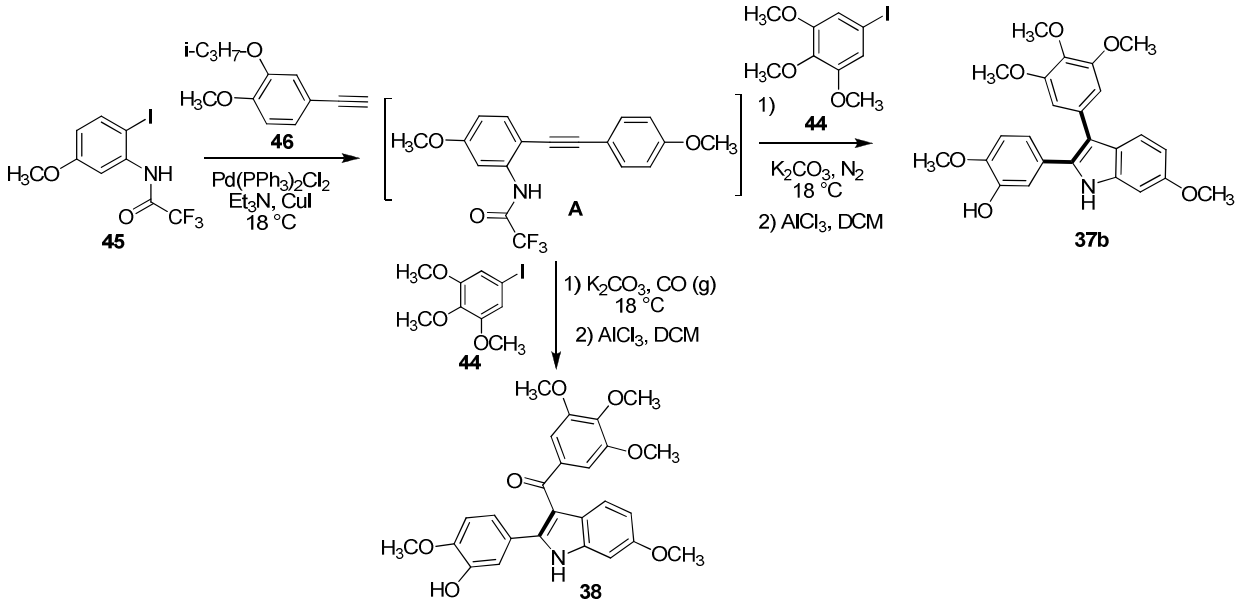



**Scheme 5** Synthesis of 2-furyl-indole derivatives




**Scheme 6** Preparation of 2,3-diarylindoles




**Scheme 7** Synthesis of compound **37b** and **38**

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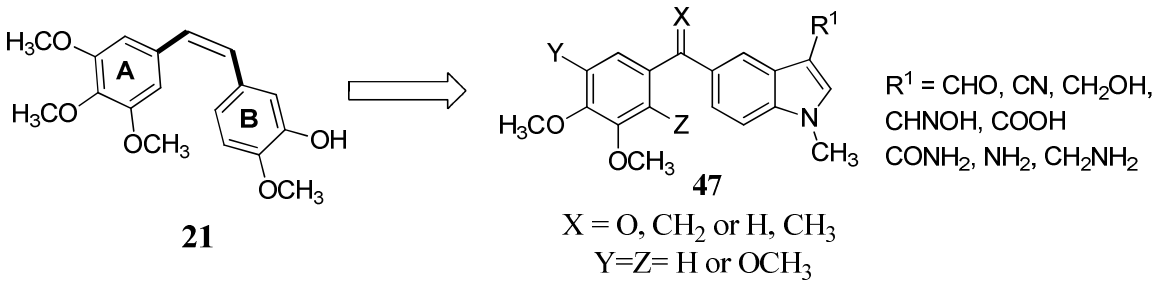



**Figure 7** Indolephenstatins and Indoleisocombretastatins (**47**) as potent tubulin inhibitors

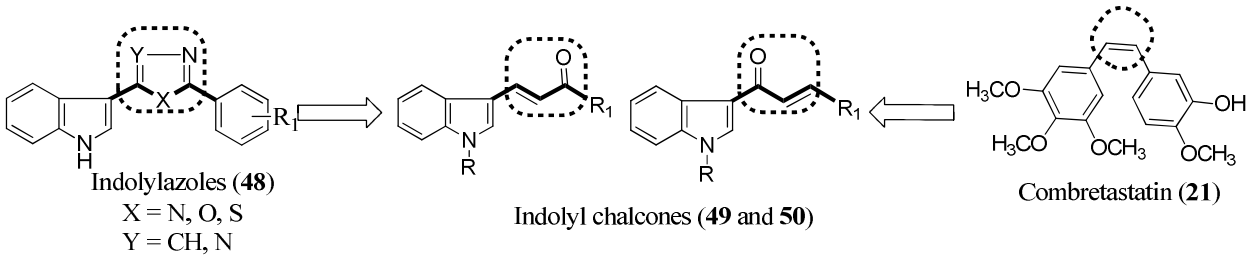
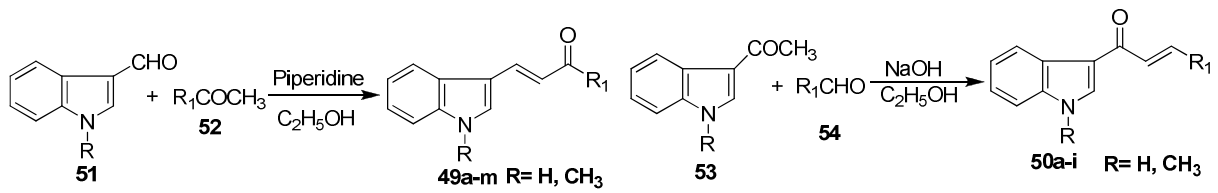



**Figure 8** Rational approach for indolyl chalcones




**Scheme 8** Base-catalyzed synthesis of indolyl chalcones

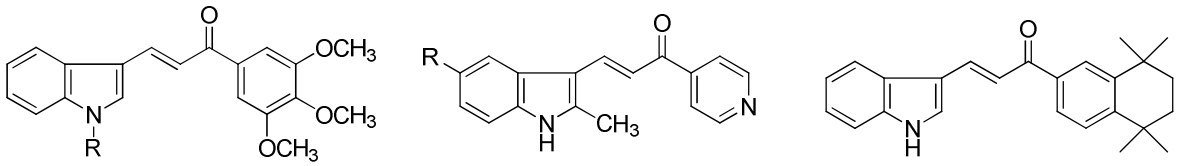



**Figure 9** Indolyl chalcones as anticancer agents

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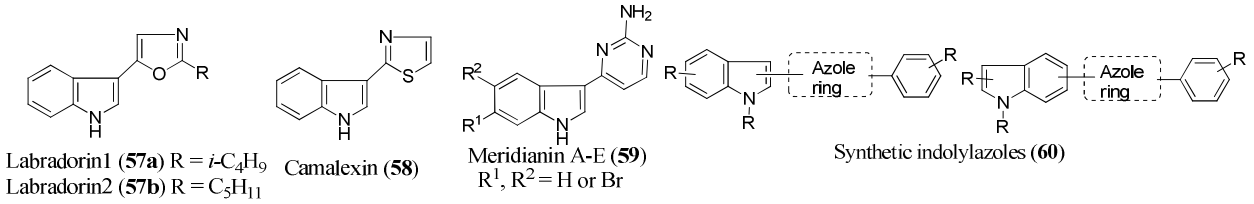
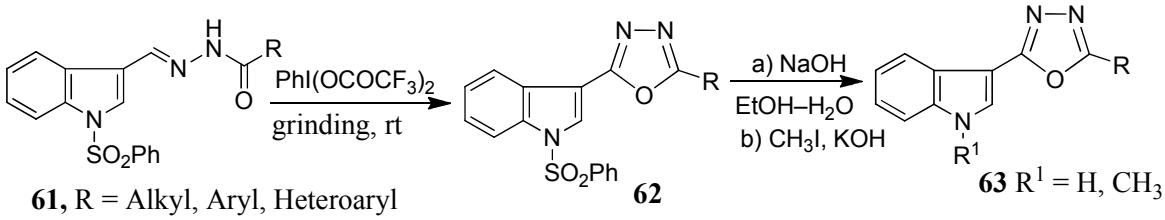
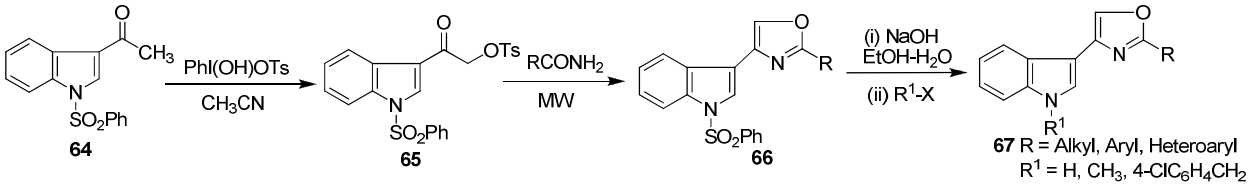


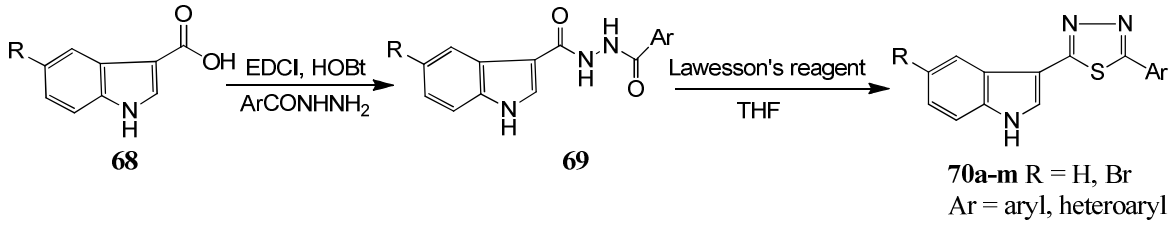

**Figure 10** Design of synthetic indolylazoles as anticancer agents




**Scheme 9** Synthesis of indolyl-1,3,4-oxadiazoles




**Scheme 10** Synthesis of 4-(3′-indolyl)oxazoles (**67**)




**Scheme 11** Preparation of 5-(3′-indolyl)-1,3,4-thiadiazoles

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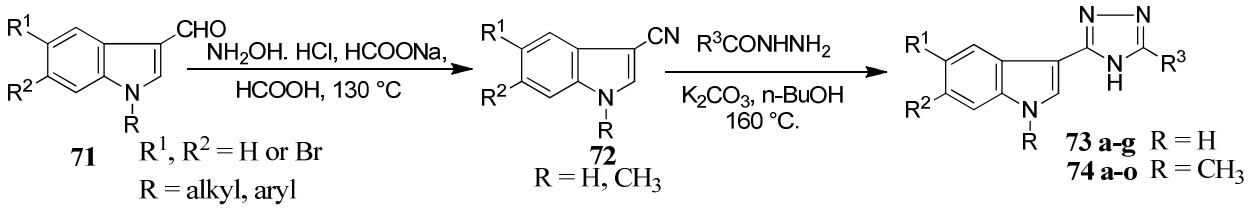
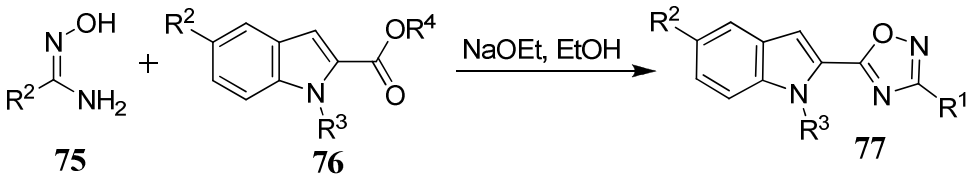



**Scheme 12** Facile synthesis of indolyl-1,2,4-triazoles




**Scheme 13** One-step synthesis of 5-(indol-2-yl)-1,2,4-oxadiazoles

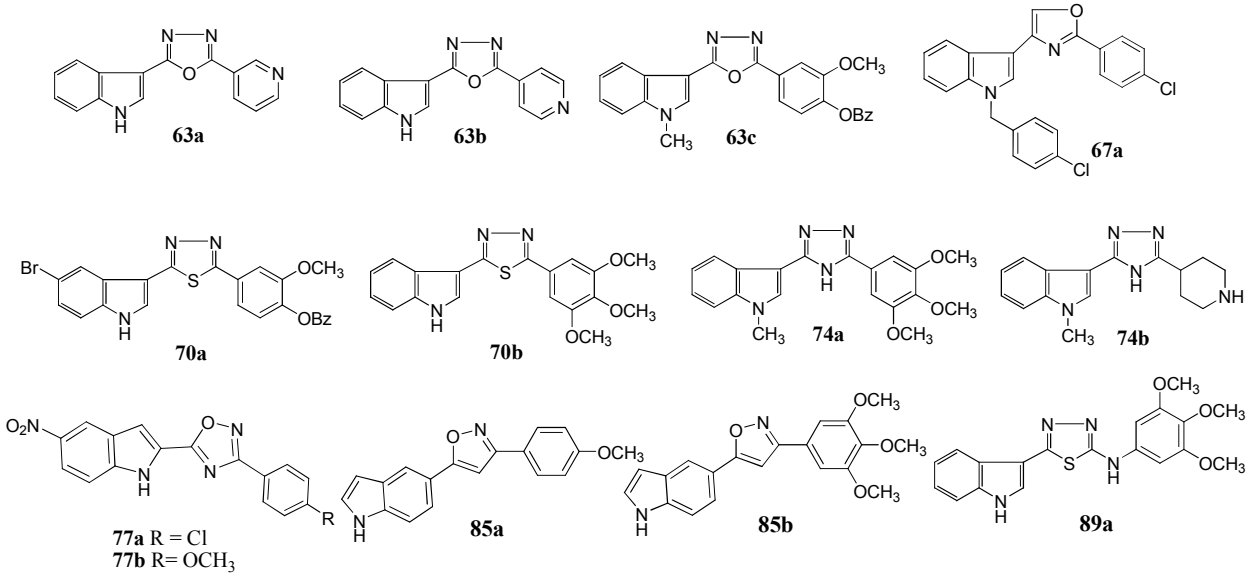



**Figure 11** Synthetic indolylazoles as most potent anticancer agents

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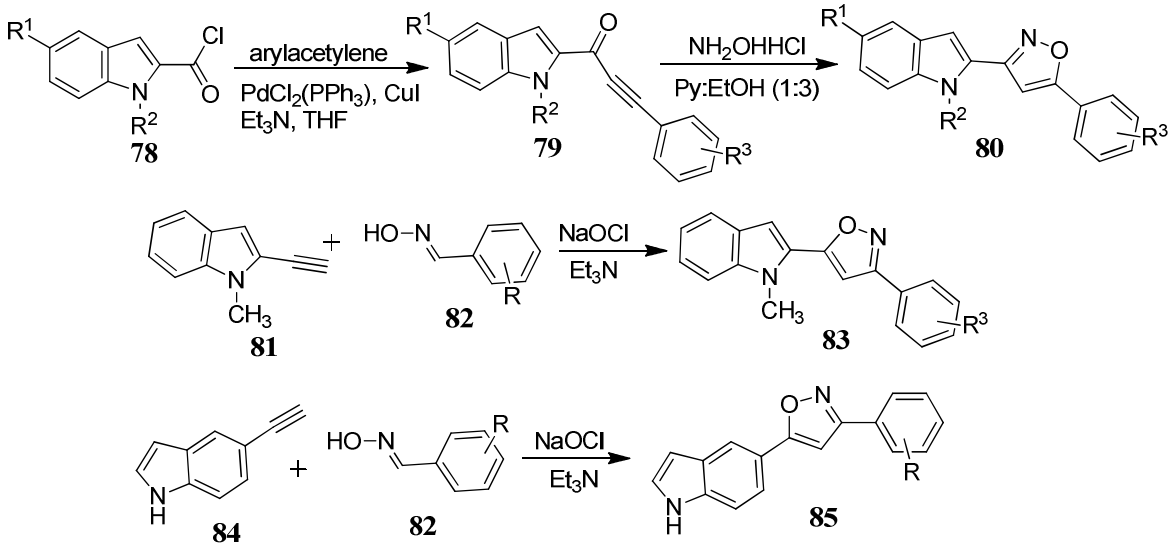
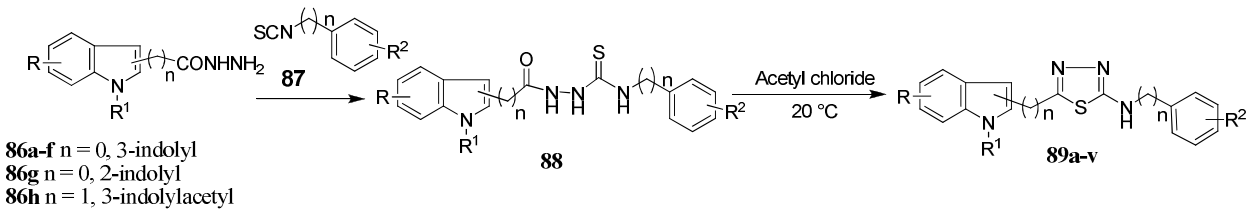



**Scheme 14** Synthesis of diverse indolylisoxazoles




**Scheme 15** Preparation of 2-arylamino-5-(indolyl)-1,3,4-thiadiazoles

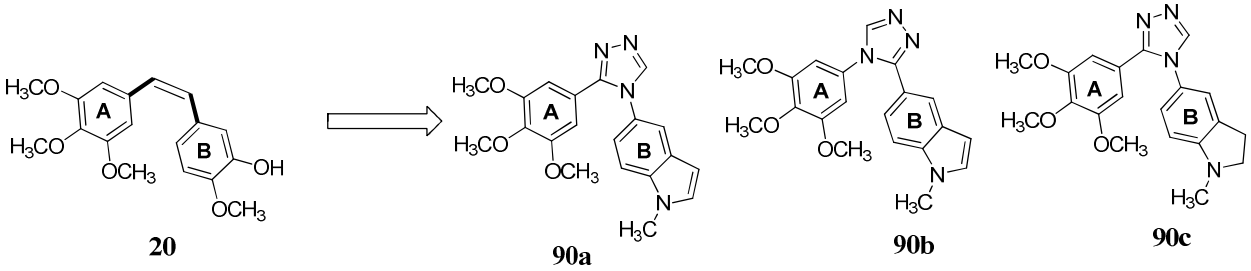



**Figure 12** Indolyl-1,2,4-triazoles as potent tubulin polymerization inhibitors

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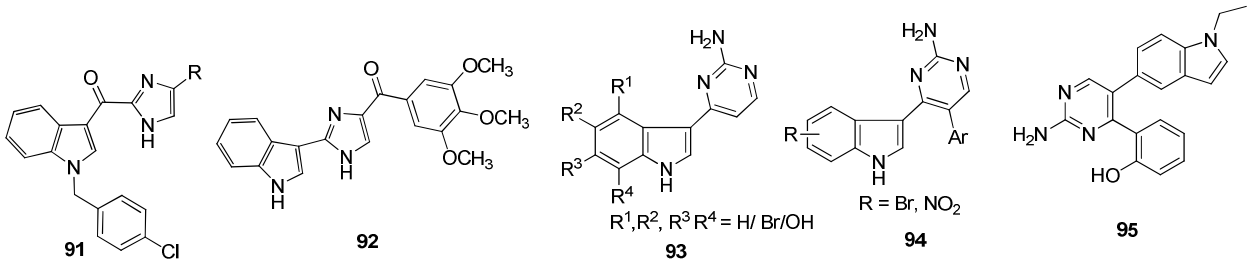


**Figure 13** Indolyl imidazoles and pyrimidines as anticancer agents

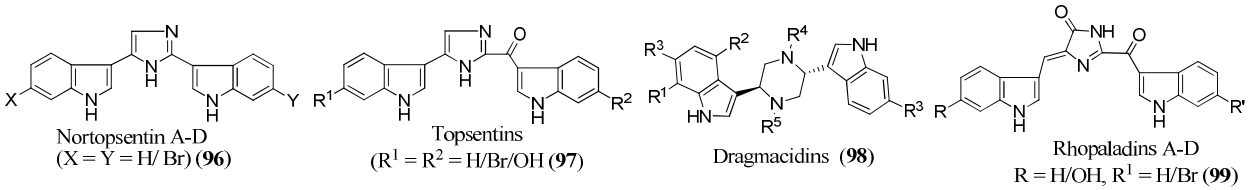


**Figure 14** Some naturally occurring cytotoxic bis(indolyl)heterocycles

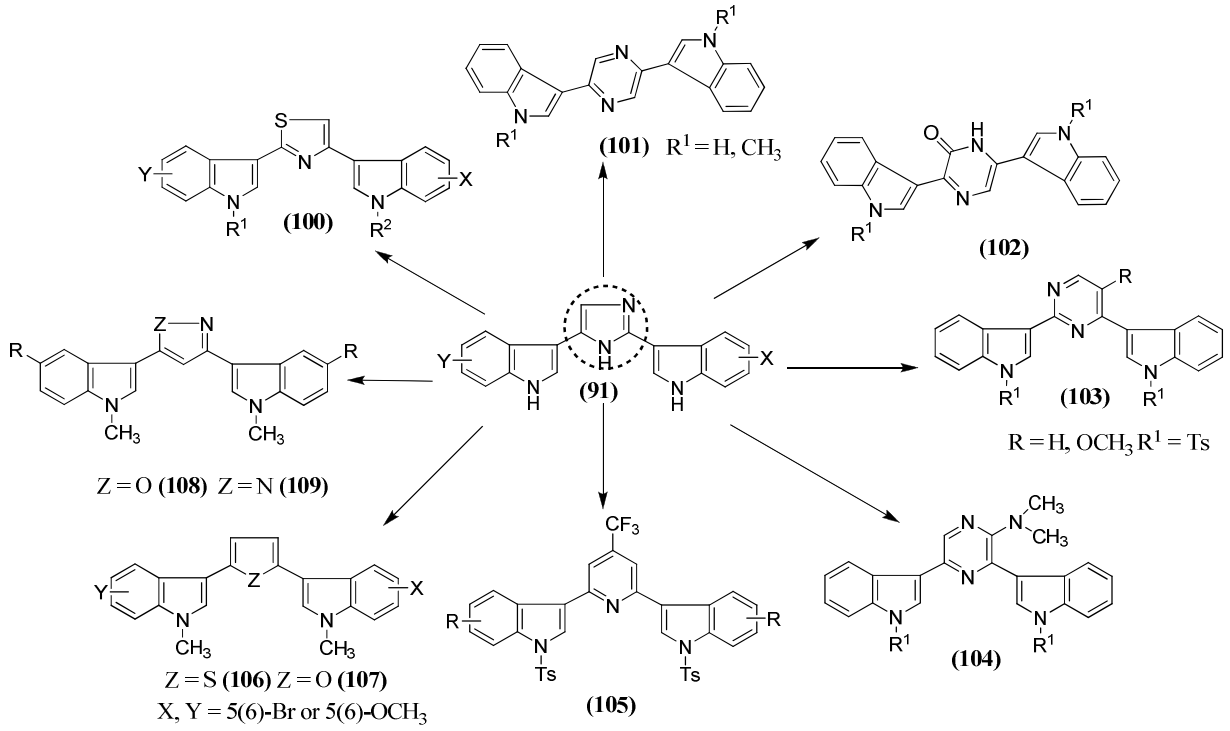


**Figure 15** Synthetic bis(indolyl)heterocycles as Nortopsentin analogues

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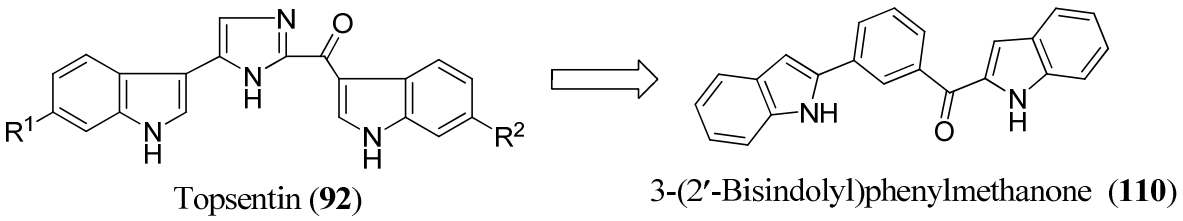
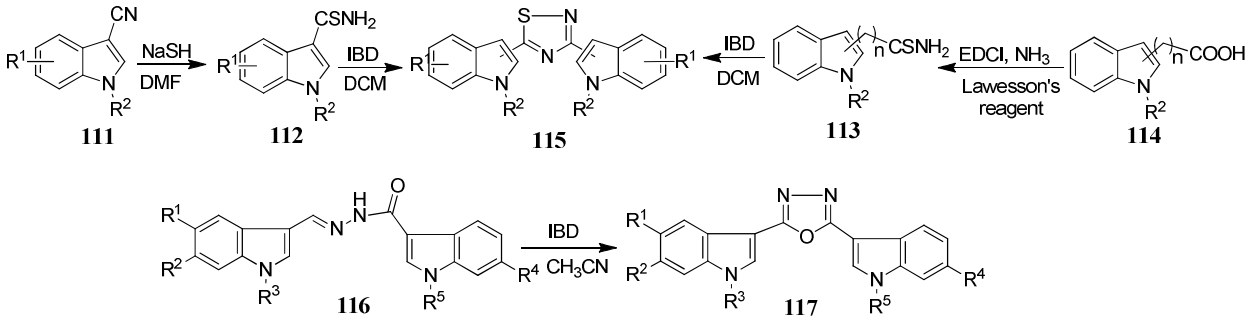
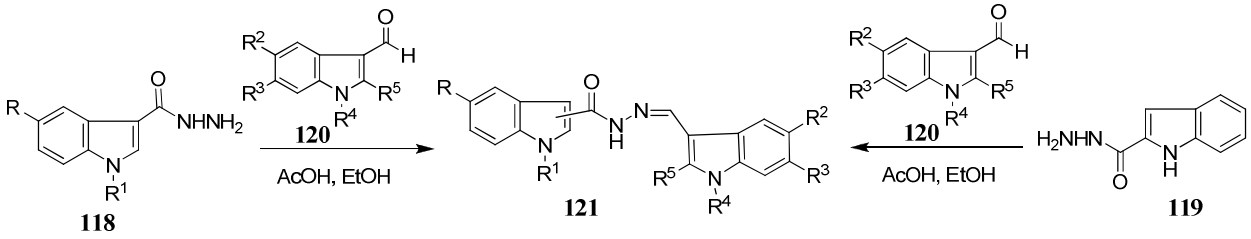



**Figure 16** Synthetic Topsentin analogue **110** as an anticancer agent




**Scheme 16** Synthesis of bis(indolyl)-1,2,4-thiadiazoles and bis(indolyl)-1,3,4-oxadiazoles




**Scheme 17** Synthesis of bis(indolyl)hydrazide-hydrazones

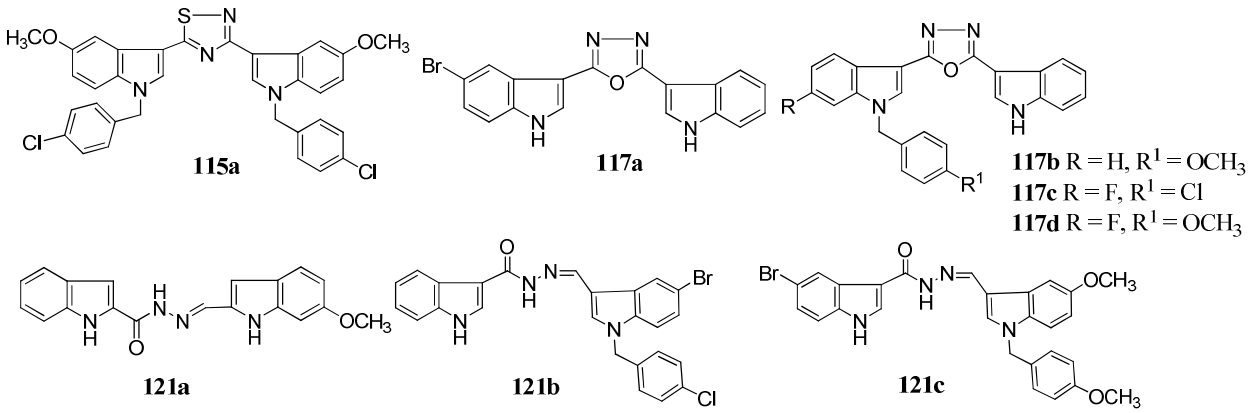



**Figure 17** Cytotoxic synthetic bis(indole) derivatives

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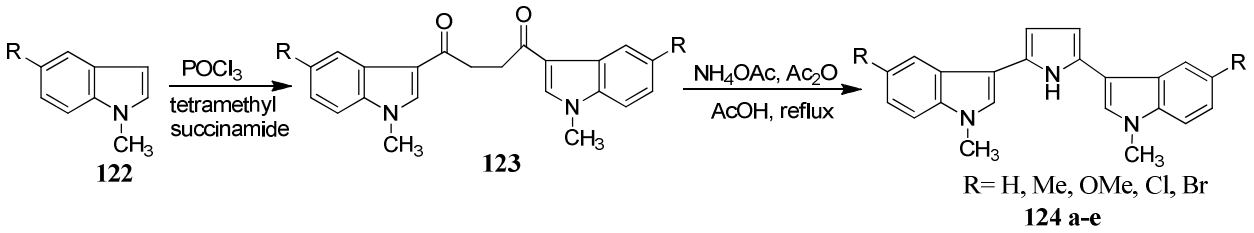


**Scheme 18** Synthesis of 2,5-bis(3′-indolyl)pyrroles (**124**)

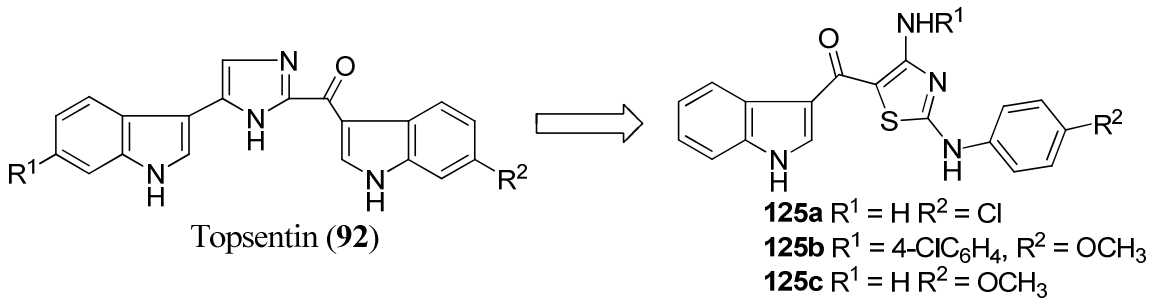


**Figure 18** 4-Amino-2-arylamino-5-indoloylthiazoles (**125a-c**) as potent anticancer agents

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