A REVIEW ON DOCKING STUDIES OF INDOLE MOIETY AS POTENT INHIBITOR OF TUBULIN POLYMERIZATION

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Aromatic heterocycles especially indole plays an important part in treatment of cancer. This review highlights compounds in development bearing indole moiety in their scaffold for the treatment of cancers. This review also highlights the utilization of colchicine binding site in order to inhibit tubulin polymerization. Docking studies shows that colchicine binding site is used by various indole derivatives to exert their action. Vincristine and vinblastine are the natural compounds which have the anticancer activity but they act on the vinca domain of the tubulin protein. Vinca domain can be too large for small ligands, so small molecules can utilize colchicines binding site to inhibit microtubule polymerization.

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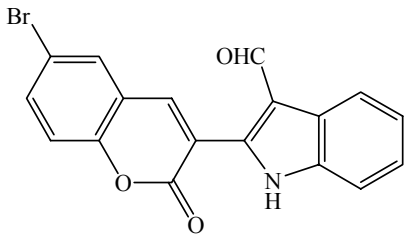
Introduction

The design and discovery of more effective and safer anticancer drug candidates are of interest in contemporary medicinal chemistry. Despite continued research efforts, cancer remains as a death cause of a large population of the world. There is enough scope to develop new compounds which can possess good antiproliferative action with different site of binding. When we talk about the anticancer agents, microtubules can be a good target in order to achieve cell cycle arrest. Microtubules are important in mitosis and have been recognized as an important target for the development of novel anticancer drugs. Microtubule formation involves polymerization as well as depolymerization of α and β tubulin dimers. Regulation of this process is strictly done by different regulatory proteins after expressing various tubulin forms (6 types of α-tubulin and 7 types of β-tubulin).[1] Therefore if tubulin is targeted, it would have been important route to anticancer therapy. A vast number of natural products like Paclitaxel, Vincristine, Combretastatin A-4 and Colchicines are there which can induce cell apoptosis through interference with polymerization and depolymerization of tubulin. Colchicine is a naturally occurring antimitotic agent, it resembles cis-stilbene and acts at same binding site of microtubule.[2,3,4] The microtubules have three ligand binding sites-vinca domain,[5] colchicine domain[6] and taxol domain.[7]

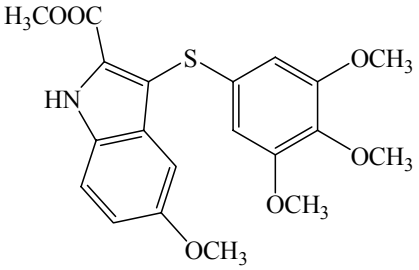
Indole as Tubulin Polymerization Inhibitor

Sunil et al reported the synthesis of three types of indole derivatives, 3-(1-benzyl-1*H*-indol-2-yl)-2*H*-chromen -2-ones,[8] 2-(2-oxo-2H-chromen-3-yl)-1*H*-indol-3-carbaldehydes[9] and 2-(2-oxo-2*H*-chromen-3-yl)-1*H*-indol-3-carboxylicacid.[10] Docking studies (Figure 1) were performed on BCl-2 (B-Cell lymphoma-2) which is an apoptosis related gene. Cytotoxic effect in a dose dependent manner was observed when tested on human breast adenocarcinoma (MCF-7).[11] Vincristine was taken as a standard drug. Compound (**1**) was found to be most potent.[12]



(**1**)

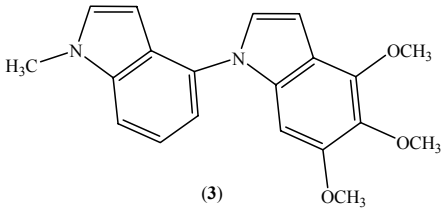
Docking studies of novel arylthioindoles (ATIs) with tubulin protein have been reported. All studies were performed on a MacPro dual 2.66 GHz Xeon by Ubuntu 9. The tubulin structure was downloaded from PDB data bank (http://www.rcsb.org)-PDBID:1SAO,[13] 3KHC and 3KHE.[14] Compound (**2**) was found to be the most potent candidate.[15]



(**2**)

1-(4'-Indolyl and 6'-quinolyl)indoles were synthesized and evaluated for biological activity by Lai et al.[16] Docking was performed on colchicine binding site with Gold 4.0 software to evaluate inhibition of microtubule polymerization. Compounds (**3**) and (**4**) (Figure 3) were found to be most potent among the synthesized derivatives.[16]

Huang et al established the SARs of 2,4-disubstituted furo [3,2-*b*] indole derivatives. They synthesized the compounds and anticancer activity was evaluated against NCI-60 (National Cancer Institute-60) and A498 renal cancer cell lines.[17,18] Compound (**5**) (figure 4) was found to be most potent.[19]



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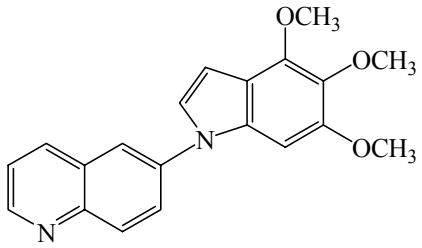

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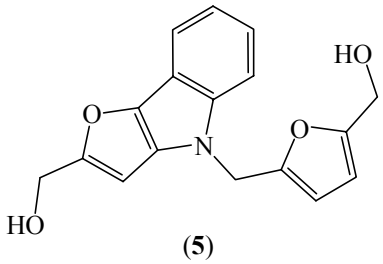
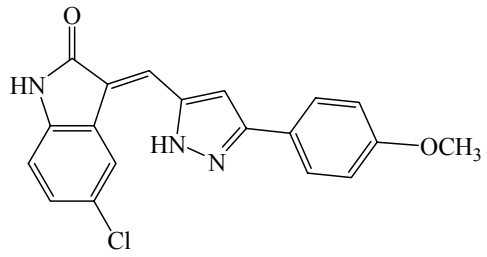


(**5**)

Design and synthesis of some pyrazole-oxindole conjugates has been reported for targeting tubulin polymerization. Twenty-one compounds were synthesized through Knoevenagel condensation reaction and their activity against different cancer cell lines was investigating.[20,21,22] Docking studies were performed on three lead compounds. They were docked against tubulin structure (PDB code: 3E22) and they showed the disruption of microtubule network via colchicine binding site.[23,24,25] Compounds (**6**) and (**7**) were found to be most potent.[26]

Pyrano-chalcone derivatives containing indole moiety have been designed, synthesized and evaluated for ant-tubulin activity. A molecular docking study was performed by Genetic Optimization of Ligand Docking (GOLD). They induced cell cycle arrest in G2/M phase and inhibited tubulin polymerization in colchicine binding site and anticancer activity was exerted against HepG2 human liver carcinoma.[27] Compound (**8**) was having the best activity amongst all the derivatives.[28]



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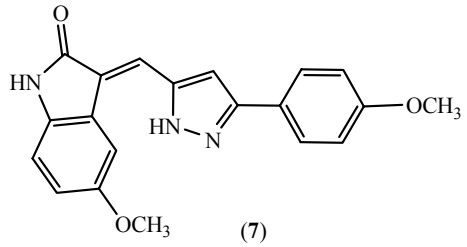

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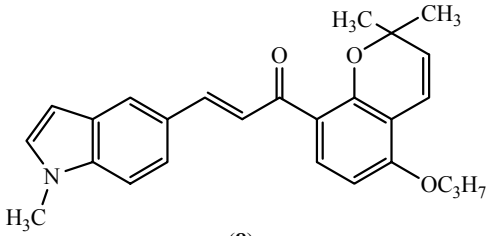
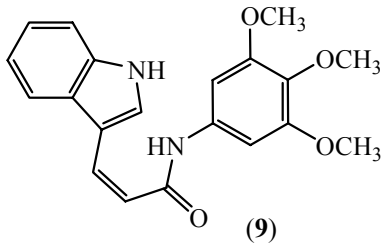


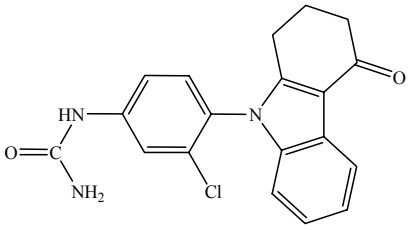
(**8**)

Synthesis of trans-indole-3-acrylamide derivatives and their activity was investigated against proliferation of human cancer cell lines (HeLa, MCF-7, MDA-MB-231, Raji and HL-60) by MTT assay. Compound (**9**) was found to be most active against both Raji and HL-60 cell lines. IC_{50} values were 9.5 & 5.1 μM. Docking studies were performed with tubulin/DAMA colchicine complex (PDB ID: 1SA0).[13,29]



(**9**)

Docking and synthesis of indole and carbazole analogues has been done. It has been mentioned that the tubulin has three sites, taxane, vincamycin and colchicines sites. Vincamycin and taxane are complex molecules whereas colchicine is less complex so it attracts the scientists.[30-34] High content Cellular Analysis (HCA) of compound (**10**) (carbazole urea analogue) with cells shown that it causes cell apoptosis by blocking G2/M progression and shows similar effects as that of Paclitaxel and Vinblastine.[35] Compound (**11**) was found to be most potent among indole derivatives.[36]



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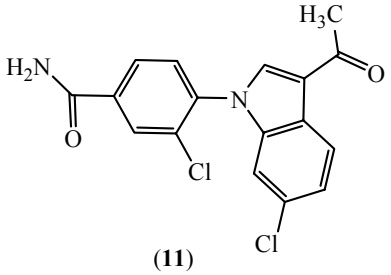
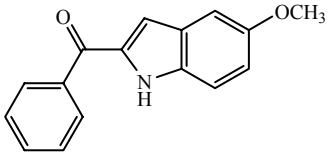


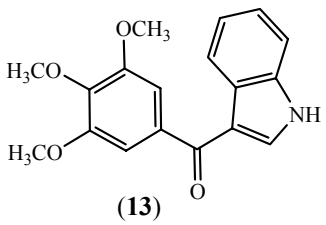
(**11**)

About 160 indole derivatives have been synthesized. 2-Aroylindoles were found orally active tubulin inhibitors. Tubulin binding assay was carried out according to Tahit et al.[37] Tubulin GTP assay was carried out according to the modifications done by Roychowdhury et al.[38] Compound (**12**) was found to be most potent against all tested cell lines.[39]



(**12**)

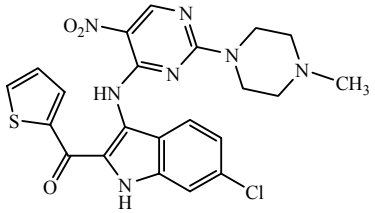
Antimitotic and antitumor activity of novel indole compounds has been reported. Many 3-aroylindoles have been designed and synthesized as combretastatin A-4 (CA-4) analogs for evaluation of biological activity.[40] In-vitro assay of microtubule assembly was performed according to the procedure discussed by Bollag et al.[41] In vivo assay of microtubule assembly was performed according to the Blagosklommy et al.[42] Among all derivatives, 6-methoxy-3-(3',4',5'-trimethoxy-benzoyl)-1*H*-indole (**13**) was found to be best lead compound in a concentration dependent manner.[43]



(**13**)

Synthesis and molecular docking of indole-pyrimidine derivatives have been described. The inhibition of tubulin polymerization has been related with colchicine binding site. For *in-vitro* tubulin polymerization assay, tubulin was taken from pig brain which was isolated by the method given by Shelanski et al.[44]The molecular modeling studies were performed with surflex-dock module and the tubulin protein structure was downloaded from protein data bank (PDB). Energy minimization of molecules was done by using tripos force field.[45] It was found that compound (**14**) was having best binding characteristics with colchicine binding site[46] and it occupies the same pocket as that of CA 224.[47]

Synthesis and biological activity of stable inhibitors of colchicine binding site of tubulin heterodimer have been reported. The importance of TMP (3,4,5,-trimethoxyphenyl) moiety for the growth inhibition of tumor cells have been ascertained.[48,49,50] It was found that 4-substituted methoxybenzoyl-aryl-thiazole (SMART)[51], 2-aryl-4-benzoyl-imidazole (ABI)[52], and phenylaminothiazole (PAT)[53] are good anticancer agents. These agents are active even at the nanomolar concentrations on many cell lines but their pharmacokinetics showed that their bioavailability is poor. It was due to the two major metabolic reactions in the microsomes of the liver i.e. carbonyl reduction and demethylation of TMP ring.[54] Three sets of new analogs were synthesized by the modifications at carbonyl linker of preexisting potent compounds, which were originally having short half life (17 minutes) or which were metabolically labile. Compounds (**15**) and (**16**) were found to be most potent with enhanced half life.[55]



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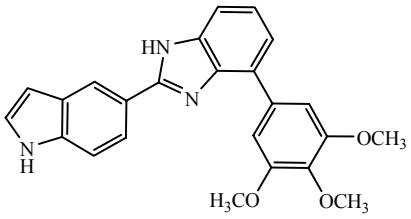
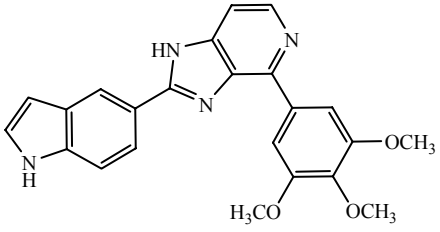


(**15**)



(**16**)

Mechanism of qction

All the papers show that the compounds inhibited the tubulin polymerization after binding with the colchicine domain of the tubulin. Taxanes act by stabilizing the microtubule whereas vinca and colchicines act by destabilizing the microtubules. The inhibition of tubulin polymerization results in the cell cycle arrest in G2/M phase and causes apoptosis.

Conclusion

It has been shown in this review that indole moiety is present in structure of various antimitotic agents. Colchicine binding site itself captured the interest of the researchers in recent time. Complexity of vinca and taxane domain resulted in the enhancement of the optimization of colchicines binding analogues. Advantages due to which colchicines binding site got attention are high potency, relatively simple compounds for optimization, toxicity is selective for tumor vasculature and their ability to withstand with the P-glycoprotein efflux pump mediated multidrug resistance. It also shows that the colchicine binding site is the preferred site for the binding for indole derivatives to exert anticancer activity.

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