CHAPTER-I

Introduction to Anti tubulin Agents
Chapter 1

Introduction

1.0. Introduction

1.1. Cancer

1.1.1. Current scenario of Cancer

The word Cancer has come from karkinos (carcinos) described by greek physician Hippocrates in 460 BC-370 BC. Later celus (roman physician) decoded karkinos (carinos) term into cancer [1]. In 2012, about 14.1 million new cases and 8.2 million deaths were estimated due to cancer globally [2]. Worldwide Cancer is second leading of deaths after cardiovascular disease [3]. According to GLOBOCAN 2018, 18.1 million new cases of cancer and 9.6 million deaths have been occurring from cancer. Over 57% of the cancer deaths were recorded in Asia in 2018. Europe shared 20% cancer death which has higher than America (15% of cancer death), Africa (7% of cancer cell) and oceania (1% of cancer death) [4] as illustrated in figure 1.

![% Death Worldwide for Both Sexes in 2018](image)

Figure 1: Worldwide cancer death percentage for both sexes.

GLOBOCAN 2018 estimated 9.8% and 9.4% of cancer incidence in india for male and female respectively from birth to 74 year. They also predicted 7.3 and 6.3 percent of mortality for male and female respectively [4] as displayed in figure 2. Indian Council of Medical Research (ICMR) has reported that 17 lakh new cases and over 8 lakh deaths may occur due to cancer by 2020 [5].

Cancer is a multigenic and multicellular disease which is stimulated by environmental factors leads to uncontrolled growth of the cell with poor clinical prognosis [6]. Medically cancer is of two types: Benign and malignant tumors [7].
Benign tumor is non-cancerous tumor in which no uncontrolled multiplication of cells takes place. This type of tumor is harmless to body. Benign tumor is converted into the malignant tumors when cells multiply at faster rate and lead to increase in cell mass. In malignant tumor, cancer spreads to other parts of body through blood. This process is called metastasis and when causes damage to adjacent tissue is called angiogenesis [8-10]. There are various factors including tobacco, obesity, infection, diet, pollution, genetic, alcohol and ionizing radiations are responsible for cancer which are illustrated in figure 3 with their percentage of causing cancer formation [11, 12].

**Figure 2**: Percentage of incidence and mortality in 2018 in India.

**Figure 3**: Various causes of cancer
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Cancer comprises of more than 200 types of cancer [13]. Among all types, lung cancer is at top with mortality percentage of 18.4% globally in 2018 followed by colorectal cancer with 9.2%, stomach cancer with 8.2 %, liver cancer with 8.2 %, breast cancer with 56.6%, esophagus cancer with 5.3 %, pancreas with 4.5 %, prostate with 3.8 %, cervix uteri with 3.3 %, leukemia with 3.2 % and other types of cancer (skin, oropharynx, testis, anus, vagina etc) with 29.3 % [4]. Graphical representation of death % by different types of cancer is demonstrated in figure 4.

![Death Percentage by Cancer Type](image)

**Figure 4:** Worldwide mobility rate of cancer in year 2018.

1.1.2. Classification of anti-cancer drugs on basis of their targets

Chemicals that are used to treat malignant cells and tissue are called anti-cancer agents. Nitrogen mustard was the first cytotoxic agents used to treat malignant tumors [14]. After sustained affords, various natural, semi-synthetic and synthetic compounds have been developed to control the growth of cancer cells or tissue [15, 16]. These anti-cancer agents are broadly classified as alkylation agents (e.g. cyclophosphamide), antimetabolites (e.g. methotrexate), antibiotics (e.g. doxorubicin), natural products (e.g. colchicines and podophyllotoxic), and hormones (e.g. aminoglutethimide) [17]. Unfortunately these drugs are associated with severe side effects like hair loss, severe pain, nausea, vomiting, bone marrow toxicity, anemia, and infertility etc. These side effects are mainly due to non-selectivities of the anti-cancer agents toward the cancer cell line [18]. Cancer cell specificity is an important aspect to reduce the toxicity whereas it is
difficult to obtain because cancer cells are very much similar to normal cells [19]. Various studies are carried out to find potent anti-cancer agents. Anti-cancer drugs mainly arrest cell division by blocking various site of action and inhibiting various enzymes release. So based on their targets, anti-cancer agents are classified into Tubulin interactors and non-tubulin interactors as shown in figure 5.

**Figure 5:** Different targets for anti-cancer agents.

1.1.3. Targets for non-tubulin interactors

Cell division is process in which a cell undergoes into a series of events to form its identical copies. There are various types of enzymes, gene, polymers, and processes which are actively participated in cell division [20]. Overproduction of any enzyme, over expression of any gene, change in structure of any polymer leads to the formation of uncontrolled cell division. So, various compounds have been synthesized to control cancer cell proliferation [21]. These compounds are classified on the basis of their targets. Apart from tubulin interactors, there are various non-tubulin interactors such as Kinase inhibitors [22], Phosphatase inhibitor [23], Proteosomes inhibitor [24], Topoisomerases Inhibitors [25], Actin inhibitors [26], HDAC inhibitors [27], Kinesins inhibitors [28] and Maps inhibitor [29]. Their mode of action to control the cancer cell division is different from that of tubulin interactors. So function and examples of non-tubulin interactors are illustrated in table 1. These interactors have maintained their valuable place in blocking cancer cell proliferation.
<table>
<thead>
<tr>
<th>Category</th>
<th>Function</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinase inhibitors</td>
<td>Inhibit protein phosphorylation by preventing transferring of phosphate group from ATP to a serine, threonine or tyrosine residue in a protein.</td>
<td><img src="image" alt="Staurosporine" /></td>
</tr>
<tr>
<td>Phosphatase inhibitor</td>
<td>Stop phosphorylation by inhibiting removal of phosphate group from the ester bond of the phosphorylated amino acids. It acts opposite to kinase inhibitor for reversible phosphorylation.</td>
<td><img src="image" alt="Okadiac acid" /></td>
</tr>
<tr>
<td>Proteosomes inhibitor</td>
<td>Causes cell death by inhibiting protein breakdown into ATP dependent proteosome complex due to Accumulation of ubiquitinated proteins.</td>
<td><img src="image" alt="Marizomib" /></td>
</tr>
<tr>
<td>Topoisomerases Inhibitors</td>
<td>Inhibit DNA replication by disrupting uncoiling and recoiling of phosphodiester backbone of DNA strands.</td>
<td><img src="image" alt="Etoposide" /></td>
</tr>
<tr>
<td>Actin inhibitors</td>
<td>Inhibit actin polymerization by influence polymer assembly, disassembly, and network rearrangement (Interfere with actin dynamics) lead to block cell proliferation.</td>
<td><img src="image" alt="Cytochalastin D" /></td>
</tr>
</tbody>
</table>
1.1.4. Overview of microtubules and its function

Tubulin is a globular protein which is made up of α- and β-heterodimer [30]. These tubulin dimers polymerize to form microtubules, which generally consist of 12 and 17 linear protofilaments assembled around a hollow core into a regular helical lattice [31]. Microtubules are the third major component of cytoskeleton with diameter of 25 nm and length vary from 200 nm to 25 μm. Genes which are responsible for tubulin production undergo into transcription to release mRNA. This mRNA further undergoes into translation process to produce α-tubulin and β-tubulin. These α- tubulin binds to GTP (guanine triphosphate) at N site (non-exchangeable site) and β-tubulin binds to GTP at E site (exchangeable site) which hydrolyzed to GDP to form α- and β- heterodimer (tubulin heterodimer). Multiple units of these heterodimers attached to each other to form linear protofilaments. These linear protofilaments assemble themselves in a parallel way to form microtubules. This whole process was illustrated in figure 6.
Microtubules lie in the state of dynamic equilibrium in which alternative cycling of polymerization and depolymerization take place. It has two ends positive and negative end. Positively charged end exposed to β-subunit in which growth and shrinkage take place at slower rate and negatively charged end bound to α-subunit in which growth polymerization and depolymerization take place at faster rate. This polymerization and depolymerization process involves in two phases. Phase one catastrophe lead to shortening of microtubules (depolymerization) and phase two rescue causes polymerization of microtubules [32-35]. Microtubules are one of the important components of cell division which produce mitotic spindle.
at anaphase to form new daughter cell [36]. Apart from cell division it has many other functions also such as:

- Cell shape: Microtubule is one of the main components of cytoskeleton. So, it resists various forces and compression to support and shape the cell. Internal organization was also sustained by it [37].
- Cell movement: Microtubules combine in specific bundle to give structure like cilia and flagella. These structures help to move cell from one place to other by crawling and expanding [38].
- Intra cellular motility: Microtubules helps various organelles of cell to transport within a cell except nucleus [39].

1.1.5. Role of microtubule in cell division

In the process of cell division, cell has two checkpoints one of them is attachment to microtubule to the chromosomes through kinetochore. Microtubules play a vital role at each stage of Mitosis (M-phase) [21] as shown in figure 7.

![Prophase](image)

**Prophase**
Centrosomes move to opposite poles of cell and form spindle

![Metaphase](image)

**Metaphase**
Polymerization of the microtubules pushes chromosomes from pole toward centre of cell and place the chromosomes at the equatorial plane which binds at kinetochore

![Anaphase](image)

**Anaphase**
Microtubules connected to the chromatids shorten, lead to pulling the chromosomes to opposite poles

![Telophase](image)

**Telophase**
Spindle fibre contract and break down

**Figure 7:** Stepwise role of tubulin in various stages for cell division.

During prophase chromosomes have been condensed and form its identical copy called sister chromatids. Centrosome consists of two centrioles from where spindle formation originated. These centrosomes move to opposite direction to form spindle pole. At metaphase,
polymerization of microtubules take place which pushes chromosomes (sister chromatid) towards the centre and lie all the chromosomes (sister chromatid) at the equator. Mitotic spindles attach to centromeres of sister chromatid through kinetochore and those spindles are called kinetochore spindle as shown in figure 8. At anaphase, mitotic spindle contract which lead to pulling of sister chromatid toward opposite pole. This pulling ultimately leads to separation of chromosome. At telophase, mitotic spindle disappears and nuclear envelope develops around each set of chromosomes [37].

Cell division is completed with aid of cytokinesis which leads to replication of cytoplasm and other organelles to form daughter cells.

**Figure 8:** Separation of chromosomes by mitotic spindle at metaphase

### 1.2. Tubulin targeting interactors

Drugs which interfere with dynamic equilibrium of polymerization and depolymerization of microtubules are called tubulin interactors [40]. On the basis of their interference action, they are classified into two categories i.e. tubulin stabilizing agents and tubulin destabilizing agents [41] as illustrated in figure 5. These agents cause shortening (destabilizing agents) and lengthening (stabilizing agents) of microtubules which disturb the equilibrium process [42]. As a result, ultimately no microtubules are available to produce mitotic spindle for cell division. These stabilizing and destabilizing agents are further classified on the basis of their binding domains. There are various binding domains where drugs bind to the tubulin causes inhibition of cell division. Basically three main binding sites has reported *i.e* colchicines binding domain, vinca binding domain and taxol binding domain [43, 44] where as colchicines binding domain
and vinca binding domain are come under polymerization inhibitor and taxol binding domain are come under depolymerization inhibitors [45]. Process of inhibition through different binding site is demonstrated in figure 10.

**Figure 9:** Different mechanism of tubulin inhibitors with their binding sites.

### 1.2.1. Tubulin stabilizing agents

Tubulin stabilizing agents inhibit depolymerization of the microtubules to tubules which lead to increase in the mass of microtubules polymer by continuous polymerization. They are also called as depolymerizing inhibitors. They mainly bind to taxol binding site which act different from that of colchicines and vinca binding domain. When GTP binds to tubulin dimer and hydrolyzed to form protofilaments. These agents bind to β-tubulin of inner surface of microtubule lumen which stimulates polymerization reaction [45]. This binding site is known as taxol binding domain. There are various tubulin stabilizing agents which enhances polymerization of microtubulin by binding and interfering with taxol binding domain. These agents are Taccalonolide (11), Epothilones (4), Discodermolide (16), Zampanolide (20) etc. There are other natural products e.g. Laulimalide (23), Peloruside A (24) Ceratamines (25), also there which binds at non-taxane site but produce same effect as that to paclitaxel (9).

These Tubulin stabilizing agents mainly attack G2/M phase of cell cycle which lead to cell death and apoptosis. There are various natural, semi-synthetic and synthetic tubulin stabilizing agents are reported. Natural tubulin stabilizing agents are obtained from plant, microorganism, and marine microorganism [46]. Some of natural tubulin stabilizing agents is shown in figure 10.
1.2.2. Tubulin destabilizing agents

Tubulin destabilizing agents inhibit polymerization of the microtubules which cause shortening of the microtubules. They are also called polymerizing inhibitors. On the basis of their binding affinities to tubulin they are further classified as vinca binding domain and colchicines binding domain [45] as mentioned in figure 5.
1.2.2.1. Vinca binding analogues

Noble and Charles Thomas Beer were the first one to identify vinca alkaloid from *Catharanthus roseus* (basionym Vinca rosea) family Apocynaceae in 1950. Earlier its putative, antidiabetic and antimalarial effects had been explored. Later on FDA approved vinca alkaloid as anti-mitotic for treating various types of cancer such as lung, breast, leukemia and hodgkin’s lymphoma etc [47, 48]. Due to its prominent anti-cancer effects, various natural and semi-synthetic analogs are obtained. These analogs are vincristine (26), vinblastine (27), vinorelbine (28), vinflumine (29) and vindesine (30). These analogs chemically made up of catharanthine nucleus having indole moiety which is attached to dihydroindole moiety of vindoline nucleus through C-C Bridge. Among all vinblastine and vincristine are used as anti-cancer agents for clinical use since last 50 years [49]. Some of the vinca targeting analogues (31-39) of natural origin are illustrated in figure 11.

![Figure 11: Tubulin destabilizing agents from natural origin targeting vinca binding site.](image-url)
1.2.2.2. Colchicine binding analogues

There are various analogs which binds to β-subunit of the tubulin same as that of colchicines (40). Colchicine interacted with Cys241 residue of β-tubulin through hydrogen bonding and showed hydrophobic interaction. These analogues act differently from that of vinca binding site analogs and taxane binding site analogs. They cause cell arrest and apoptosis by inhibiting the elongation of microtubulin. They belong to tubulin destabilizing class [50]. Various analogs (40-50) from natural origin that binds to tubulin through colchicine binding domain are reported in figure 12.

Figure 12: Tubulin destabilizing agents from natural origin targeting colchicines binding site.

1.2.2.3. Synthetic Colchicine binding analogues in clinical trial

Colchicine binding site analogues are one of the major targets in search for anti-tubulin agents. Various analogues are in clinical trial [50]. Some of them are shown in figure 13. ABT-751 (51) (E7010) is novel sulphonamide anti-mitotic agent which binds to β-tubulin at colchicine site causes cell arrest at G2/M phase and lead to apoptosis. It is an orally bioavailable anti-tubulin agent which is phase II clinical trial [51]. Herein, Indibulin (52) is another orally active anti-
tubulin agent. It was reported that it partially binds at colchicine binding site. It exhibited anti-
tumor activity against MDR1 and multi-drug resistance-associated protein (MRP). It also
demonstrated cytotoxicity against cancer cell lines with resistance to thymidylate synthase
inhibitors 5-FU and raltitrexed cisplatin, and the topoisomerase-I-inhibitor SN-38 [52]. Further
on, 2-Methoxyestradiol (53) (2-ME) is an endogenous estrogen metabolite which is produced by
hepatic cytochrome P450. In vivo studies revealed that 2-ME demonstrated potent anti-tubulin
and anti-angiogenic activity which make it for further investigation in clinical trials [53]. Due to
its adverse effect and formation of inactive conjugate after its metabolism, a metabolically stable
analog ENMD-1198 (54) was generated. It is again a colchicine binding site analog, which lead
to cell arrest at G2/M phase and apoptosis and reduce hypoxia-inducible factors factor (HIF)-1α
levels. Along with anti-cancer activity, it also causes inhibition of migration, endothelial cell
proliferation, motility, and morphogenesis [54].

EpiCepct company discovered MPI-0441138 (55) which exhibited good cytotoxicity
against T47D with GI₅₀ 2nM and also identified as a highly active apoptosis inducer with EC₅₀ 2
nM for caspase activation. It is the lead compound for MPC-6827 (56). Phase I studies revealed
that it was well tolerated at the recommended dose [55]. While, nocodazole (57) is a synthetic
tubulin-binding agent; it was first isolated by de brabander et al in 1975 as anti-helminthic agent
then in 1985 Kaczanowski et al. explored its microtubule disruption property. It prevents mitosis
by arresting cancer cell at G2/M phase and induces apoptosis in tumor cells. Now, it is used as
the reference compound to discover novel CBSIs for treating tumor cells [56].

![Figure 13: Synthetic colchicine binding site analogues](image-url)

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1.3. Indole derivatives as tubulin inhibitors

Indole (58) is an aromatic heterocyclic organic compound which consists of benzene ring fused with pyrrole ring with formula C₈H₇N. It is white crystalline solid. Naturally it occurs in human fecal matter and has fecal like smell. Chemically it is not a base due to participation of nitrogen lone electron pair in the aromatic ring [57].

![Indole (58)](image)

Indole nucleus is the core structure of many biologically active compounds which occupied a prominent position in medicinally relevant heterocyclic systems. Various indole containing naturally occurring and designed molecules exhibited broad spectrum of application in pharmaceutical, agrochemical and materials industries. Various tubulin polymerization inhibitors contain indole as the main nucleus, some of the tubulin inhibitors are Indolyl-3-glyoxamide D-24851 (59), 2-aryllindoles (60), 2-Phenylindole (61), Heterocombretastatins (62), 2,3-Diaryllindole (63), and 2-aryl-3-arylcarbonylindoles (64) are shown in figure 14 [58, 59].

While, Doris et al synthesized a series of 2-phenylindole-3-carbaldehydes with lipophilic substituents in both aromatic rings and evaluated for their anti-tumor activity against MDAMB 231 and MCF-7 breast cancer cell. Among all, compound 65 showed good anti-cancer activity against MDA-MB-231 with 6.7 nM and was found to potent inhibitor of tubulin polymerization with IC₅₀ 1.2 µM which was lower than that of colchicine (5 M) [60]. Nancy et al designed a series of 5-phenylpyrrolo [3,4-a]carbazole-1,3-dionescytotoxicity and tested against B16 melanoma cell. Compound 66 exhibited tubulin inhibition and cytotoxicity with IC₅₀ 0.82 μM and 0.6±0.1 μM respectively [61]. A series of 1-(40-Indoly1 and 60-Quinolinyl) indoles were synthesized by Mei-jungi et al. It was found that compound 67 exhibited potent activity against multiple-drug resistance MDR1 cancer cell with IC₅₀ 38 nM and also illustrated anti-tubulin activity with IC₅₀ 1.7 nM [62].

Antonio et al tested a series of arylthioindoles derivative against tubulin polymerization activity. Among all, compound 68 displayed inhibition of tubulin polymerization
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with IC$_{50}$ 0.74 µM [63]. Matthew et al discovered the series of 2-aryl-3-aroyl indole-based small-molecule as inhibitor of tubulin assembly. Among all, compound 69 illustrated anti-proliferative activity against SK-OV-3, NCI-H460, and DU-145 with GI$_{50}$±SD 1.45 ± 0.365 µM, 2.86 ± 0.104 µM, and 3.01 ± 0.0829 µM. Along with anti-proliferative activity, it was a good inhibitors of tubulin assembly (IC$_{50}$ 3.1 µM) [64]. Aleem and his group synthesized a series of fourteen N4-(substituted phenyl)-N4-alkyl/desalkyl-9H-pyrimido[4,5-b]indole-2,4-diamines as potential microtubule targeting agents. Compound 70 exhibited nanomolar GI$_{50}$ values against NCI-57 cancer cell line out of 60 panels of cell lines. Its mechanistic studies revealed that it bind to colchicine binding to tubulin lead to inhibition of tubulin polymerization with IC$_{50}$ 1.4 µM [65].

Guangchengv and his co-worker synthesized a new series of pyrano chalcone derivatives containing indole moiety and evaluated for their cytotoxicity activity. Among all, compound 71 illustrated potent cytotoxicity against tested cancer cell lines with IC$_{50}$ ranging from 0.22 to 1.80 µM. It induced cell arrest at G2/M phase and also inhibited the polymerization of tubulin [66].

Mao Cai et al designed a series of Novel hybrid molecules by connecting indole ring with N-hydroxyarylamide via alkyl substituted triazole. Hybrid molecule 72 exhibited anti-proliferative activity against HCT-116, Lovo K562, MCF-7 and HepG2 cancer cell line with IC$_{50}$ (µmol/L) 3.57, 5.01, 5.73, 6.21, and 4.11 respectively. In vitro studies revealed that compound 8 induced cell arrest at G0/G1 phase and promote the expression of the acetylation for histone H3 and tubulin [67].

Sultan and his group prepared a series of trans-indole-3-acrylamide derivatives as anti-proliferative agents. MTT assay revealed that compound 73 displayed cytotoxicity with IC$_{50}$ values of 9.5 and 5.1 µM against Raji and HL-60 cell lines with moderate anti-tubulin activity (IC$_{50}$ 17 µM). Flow cytometry shown that it lead to cell death at G2/M phase HL-60 and HeLa cells and also induced apoptosis through the activation of caspase-3 [68]. Hsueh-Yun et al developed a series of 3-aroylindole hydroxamic acids as tubulin and histone deacetylase (HDAC) inhibitors. In vitro and in vivo studies revealed that compound 74 displayed remarkable inhibitory activity against the growth of PC3 and RPMI-8226 cancer cells. It not only possessed tubulin depolymerization ability but also possesed HDAC inhibitory activity [69].
1.4. Capsaicin

Capsaicin is the major component in capsicum or chili peppers which is responsible for chili flavor of capsicum fruits [70]. It was first extracted by Christian Friedrich Bucholz in impure form in 1816 than in 1898 Micko isolated capsaicin in its pure form. E. K. Nelson in 1919, partially elucidated capsaicin’s chemical structure and its chemical composition. Capsaicin and various others structurally related secondary metabolites produced by chili peppers are also called as capsaicinoids belongs to family Solanaceae. The capsaicinoid content vary from one chili to other. Basically mild chilies contain about 0.01–0.3% and the strong chilies contain 0.3–1% of capsaicinoids [71].

Figure 14: Indole derivatives as anti-tubulin agent
Capsaicin is hydrophobic, colorless, white crystalline solid. Chemically it is 8-methyl-N-vanillyl-trans-6-nonenamide and used as a spice in many cultures worldwide. Apart from its pungency flavor, it also has several remarkable biological activities as illustrated in figure 15.

**Figure 15: Pharmacological importance of capsaicin**

It plays important roles in neuropathic pain relief, obesity, Painful bladder syndrome (hyperactive bladder), dermatological conditions (such as in Psoriasis and histamine mediated itch) cardiovascular and gastrointestinal condition [72, 73]. Besides, it has shown remarkable anti-cancer effects in pancreas, gastric, colon, breast, prostate, leukemia and hepatocellular etc carcinoma. Various multiple molecular targets responsible for the anticancer mechanism of capsaicin have been explored and some of them are shown in figure 16. It induced Apoptosis in Colon, lung Stabilizes Bladder, glioma, Stomach, lung, Colon, Nasopharynx, Glioma, Myeloma, Liver. Furthermore it induced G0/G1 phase arrest in human esophageal, colon and bladder carcinoma cells via decrease of CDK4, CDK6 and cyclin E. it also exhibited anti-anti-angiogenic property in various cancer cells [70]. Capsaicin also demonstrated anti-migratory activity and anti-invasive via modulating signaling pathways involved in cell migration and invasion which lead to suppression of advanced stages of cancer [70, 74].
1.4.1. Capsaicin analogue as anti-cancer:

A very few work has been done on the analogous derivatized from capsaicin. Paulo et al in 2013 reported one of the novel synthetic capsaicin-like analogues RPF101 as shown in figure 17. It demonstrated cytotoxic effects against MCF-7, MDA-MB-231, SK-MEL-28, Sbcl2, Mel-85 with IC_{50} 32 μM, 14.2 μM, 19.1 μM, 17.5 μM and 15.7 μM respectively whereas capsaicin exhibited IC_{50} 53 μM, 21.7 μM, 14.1 μM, 20.1 μM and 15.2 μM against MCF-7, MDA-MB-231, SK-MEL-28, Sbcl2, Mel-85 respectively. It induced cell arrest at G2/M phase and also disrupted the microtubule network [75].

![Figure 17: Novel synthetic capsaicin-like analogues RPF101.](image-url)
1.5. Conclusion

In conclusion, cancer is the leading cause of death. Various targets have been explored to treat cancer. Among all the targets, tubulin is one of the highly validated targets in cancer drug discovery as it plays a vital role in cell division. Tubulin lies in dynamic equilibrium of polymerization and depolymerization. Various interactors of natural and synthetic origin have been reported which disturb the equilibrium process of microtubule. After over viewing the vital role of tubulin in cell division and considering various indole derivatives as anti-tubulin agents (targeting colchicine binding domain).

Keeping in view of the importance of indole derivatives as colchicine binding site inhibitors, we aimed at the synthesis of indole based natural product like libraries that interact with tubulin at colchicine binding site.

Inspire by compound RPF101 as tubulin inhibitor and considering structural features of capsaicin, we aimed at the synthesis of various semi-synthetic analogues of capsaicin embedded with 1,2,3-triazole heterocycle and 1,3,4-oxadiazole Heterocycles.
1.6. References


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