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Review on Combretastatin based Heterocycles as Antitubulin Anticancer Agents.

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ABSTRACT
Combretastatin (CA-4) and its analogues are undergoing several clinical trials for treating different types of tumors. Combretastatin is a naturally occurring well known tubulin polymerization inhibitor. CA-4, a natural product isolated by Pettit and coworkers in 1988 from the South African bush willow tree Combretumcaffrum, strongly inhibits the polymerization of tubulin by binding to the colchicine-binding site. Unlucky, poor solubility of CA-4 impinged its clinical development and required the preparation of more soluble derivatives such as CA-4P. However, cardiovascular toxicity and neurotoxicity were dose limiting for CA-4. These significant side effects currently represent the main obstacles to broad clinical application of CA-4. For this reason, it is important to develop other CA-4 structurally related compounds Combretastatin and its analogues have been discussed in this review in detail. For better understanding,

Keywords: Anticancer, antiproliferative, combretastatin analogues, combretastatin, microtubule binding agents, tubulin binding agents.

I. INTRODUCTION

Cancer

Cancer is the uncontrolled growth and spread of cells (Adopted from WHO website http://www.who.int/topics/cancer/en/ accessed on 06/05/2018). Not all tumors are cancerous in the starting phase and do not spread to other parts of the body. The sign and symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss abdominal pain, diarrhea, and constipation etc these symptoms may indicate cancer (Koo, Hamilton, Walter, Rubin, & Lyratzopoulos, 2018). But with time it spread all over body. This problem is so serious which may cause millions of deaths and numbers of patients increasing with time. In US 1688780 new cancer cases and 600,920 deaths reported during 2017 (Siegel, Miller, & Jemal, 2017). In India, according to National Institute of cancer over more than 2.5 million peoples are living with this disease, over 7 lakh new patients registered with cancer and more than 5 lakh deaths are related with cancer (National Institute of cancer adopted from website http://cancerindia.org.in/statistics/accessed on 10/05/2018). Whereas the other the body National registry cancer program of Indian council of medical research register estimate 13,88,397 patents by their 27 active centers in 2015 (Jagathnath Krishna & Sebastian, 2017). These facts showed that cancer in its most drastic conditions. The treatment therapies like radiotherapy(H. H. Chen & Kuo, 2017), immunotherapy (Emens et al., 2017), hormonal therapy (Abraham & Staffurth, 2016), surgery (Coffey et al., 2003)etc are used to target cancer cells and chemotherapy is one of them.

Chemotherapy for Cancer

Chemotherapy is defined as the treatment of any specific infection or diseases with specific the drug which may have specific toxicity to cell or microorganism with no or less toxicity to the patient (Tripathi, 2013). The cancer chemotherapy is the treatment of cancerous cells by using specific drugs which may bind to the factors or hallmarks of cancer and stop the proliferation of cancer cells and promote them to cell death. These drugs act on the particular target and showed there effect on the cells. The chemotherapy drugs like Cisplatin, Chlorambucil, Cyclophosphamide (alkylating agents) Gemcitabine, 5-flourouracil, Methotrexate (antimetabolites) Doxorubicin, Epirubicin (anti-tumor antibiotics) Irinotecan, Topotecan, Etoposide (topoisomerase Inhibitors), Vincristine, Peclitexel, Docetaxel (anti-tubulin Drugs) etc are used in the treatment of cancer (Dickens & Ahmed, 2018).

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Nowadays, combination of these drugs is prescribe to the patient in a way that the drugs can target different phase of the cell cycle and achieve maximum cell killing. The chemotherapy is given with the combination with immunotherapy (Mahoney, Rennert, & Freeman, 2015)radiotherapy (W. Cao, Gu, Meineck, & Xu, 2014)etc to achieve maximal effect over cancer. The combination of therapies may help to solve some problem associated with chemotherapy and others. In chemotherapy, the drug molecules are designed in a way that the molecule binds specifically over the target. These targets are found during cell division or present in their active form in cancer cells. The topoisomerase (Ross, 1985), epidermal growth factors receptors (Baselga, 2001), vascular endothelial growth factor (Ferrara, 2005), cyclin-dependent kinase (Musgrove, Caldon, Barraclough, Stone, & Sutherland, 2011), poly ADP ribose polymerase (Lord & Ashworth, 2008)etc are found inactive in cancer cells which are considered as a target for the cancer therapy and targeting microtubules are one of them.

Main Text

1.2Microtubules as a drug target

Microtubules are associated from dimers of α- and β-tubulin. Microtubules are the key components of the cytoskeleton which are structurally long, filamentous, tube-shaped protein polymers that are essential in all eukaryotic cells. They are the key component during development and maintenance of cell shape, in the transport of vesicles, mitochondria and other components throughout cells, in cell signaling, and in cell division and mitosis. Microtubules are the heterodimers of α-tubulin and β-tubulin which belongs to the family of globular proteins. It classified into five distinct families ie alpha, beta, delta, gamma, epsilon-tubulins and the sixth family is zeta-tubulin which was found only in kinetoplast of protozoa. The most commonly known family members of the tubulin are α-tubulin and β-tubulin, which are the key component of microtubules. (Hadfield, Ducki, Hirst, & McGown, 2003). Microtubules composed of α-tubulin and β-tubulin heterodimers with dimensions of 4 nm ×5 nm ×8 nm and having the mass of 100,000 daltons, arranged in the form of slender filamentous tubes that can be many micrometers long structures formed by 13 parallel protofilaments which can be assembled and dissembled using α, β-tubulin. The arrangement of subunits α and β in a form of head to the tail arrangement shown in fig: 1.1

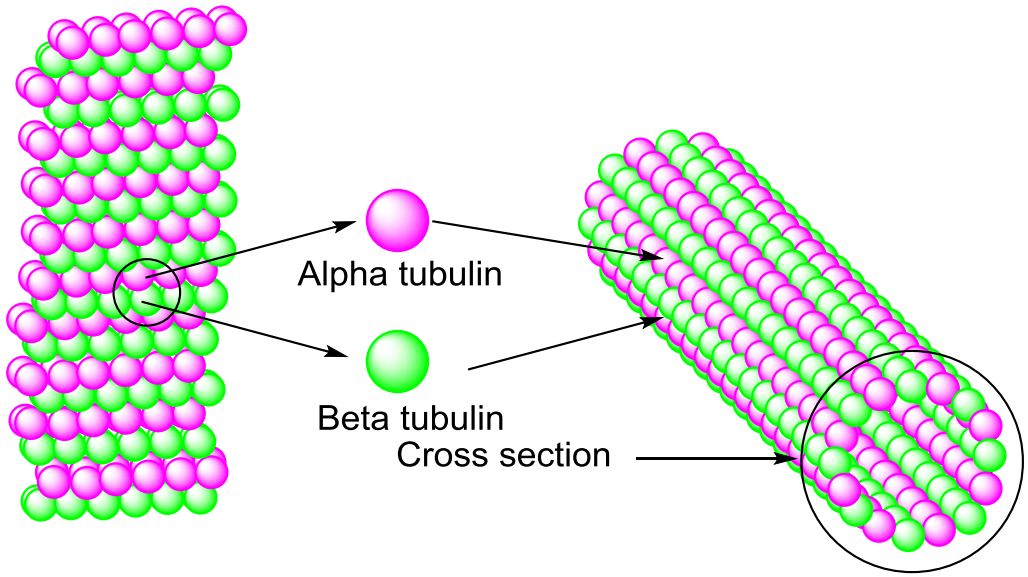

Fig:1.1Structure of microtubules and its arrangement

(O'Donnell & O'Bryan, 2014)

The polymerization of the microtubules from tubulin proceeds via nucleation elongation mechanism. To maintain their structure the microtubules show polymerization as well as its degradation and maintain its equilibrium by obtained the energy from GTP hydrolysis. This

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process is also known as dynamics of microtubules (M. A. Jordan & Wilson, 2004).

1.3.1 Dynamics of microtubules

Dynamic instability is the switching between phases of microtubule growth and shrinkage is driven by the binding and hydrolysis of GTP by the αβ-tubulin dimer. The microtubules polymerized from the plus or positive end with faster growth as compared to its other end. Suddenly the growth is also interrupted by destabilization or de-polymerization which makes its length constant. This Dynamic instability is described by four variables: the rate of growth, the rate of shortening, switch from microtubule growth or pause to shortening (catastrophe) and the switch from shortening to growth or pause also known as rescue(Alushin et al., 2014). This process helps to maintain the structure of microtubules as well as help in the regulation of cellular functions, cell division, shape changes, and cell differentiation (Hadfield et al., 2003).

The structure of the tubulin is shown in fig:1.2 which revealed that the tubulin is a heterodimer of α and β subunits.They continuously assembled and de-assembled by which they maintain their state.

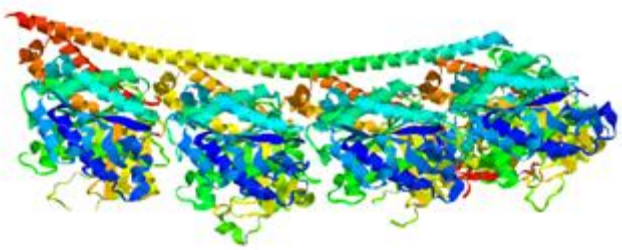

Fig:1.2 Tubulin proteins: The rainbow color showing its alpha- and beta- subunits (Adapted from PDB: 5LYJ, https://www.rcsb.org)

There are some natural compounds that inhibit the formation spindle which forms due to the tubulin units by bind to the pockets which presents in between the tubules and the destruct the microtubules formation also known as the binding sites of tubulin. There are four main binding sites present in the tubulin in which the natural legend binds and distract the microtubules formation. The binding sites are:

1. Vinca site
2. Taxane site
3. Colchicines site
4. Laulimalide site. (Rajak et al., 2013)

The vinca domain is located at the plus end interface on the exchangeable GTP binding site in b-tubulin. The taxane binding site resides within the lumen of the microtubule. It is located in a deep hydrophobic pocket at the lateral interface between adjacent proto-filaments. The third binding site is colchicine, which situated at the intra-dimer interface between beta-tubulin and alpha-tubulin. However the fourth binding site on b-tubulin that is occupied by laulimalide known as the Laulimalide site (Kaur, Kaur, Gill, Soni, & Bariwal, 2014).

1.3.2 Mechanism of Microtubules targeting drugs

The microtubule-targeting drugs bind to the binding site over tubulin and showed their effect on cell proliferation by disrupting the microtubule, which induces cell cycle arrest in G2-M phase and produces abnormal mitotic spindles. Microtubule-targeting drugs are also known as the anti-mitotic drugs, which differ in their actions on microtubule stability and dynamic parameters. At their higher concentrations, these drugs may act by two mechanisms either by inhibiting microtubule polymerization, which destabilizing microtubules and decreasing microtubule polymer mass and in a second way it promotes microtubule polymerization which stabilizing microtubules and increasing the polymer mass (M. Jordan, 2002).
Based on their mechanism, the microtubule-targeting agents are classified into two classes:
1. Microtubule destabilizing agents like vinca alkaloids vinblastine, vincristine, etc and colchicine and their analogue.
2. Microtubule stabilizing agents like taxanes derivative like paclitaxel and docetaxel(Pellegrini & Budman, 2005).

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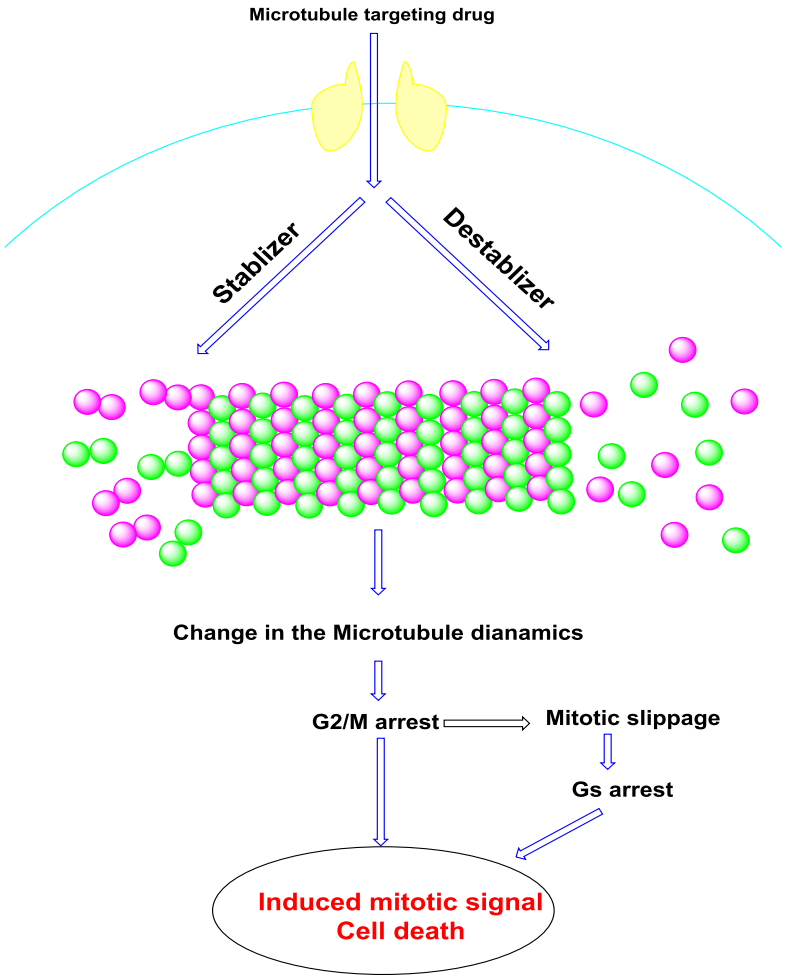

Fig: 1.3 Mechanism of microtubule-targeting drugs (Bhat & Setaluri, 2007)

At low concentrations, both microtubules stabilizing and destabilizing drugs show their effect only by interfering with the microtubule dynamics instead of microtubule polymer mass, but they hang on to their ability to block mitotic progression and induce apoptosis also shown in fig: 2.3 (M. A. Jordan & Wilson, 2004). On the other side, some antimitotic agents or some microtubule-targeted drugs can act as vascular-targeting agents (combretastatin analogue). They rapidly depolymerize microtubules and stop the newly formed vasculature to shut down the blood supply to tumors (Kanthou & Tozer, 2009). So that the targeting microtubules a good approach against cancer. The microtubules targeting agents bind to the sites presents on the tubulin proteins and arrest the cell proliferation. There is a large number of molecules are designed and synthesized which target these sites. Here we are focused on one of these site i.e. colchicine binding site.

1.4 Colchicine binding site

The tubulin binding with the N-deacetyl-N-(2- mercaptoacetyl) colchicine (DAMA colchicine) (PDB ID 1SA0) clarifies that the colchicineexerts its position in between α and β tubulin proteins and destabilize the microtubules (Ravelli et al., 2004). This site is known as colchicine binding site. This binding site is present on the face of α tubulin ring and another part is present on β tubulin. Recently Li and group divided colchicinebinding site into three zones: Zone 1, Zone 2 and Zone 3. The zone 1 present in between in the junction of α and β tubulin which surrounded with Serα178, Val α181, Metβ259, and Asnβ258. The Zone 2 is present in β tubulin which is surrounded with a crowd of amino acids while zone 3 is presented deeper in β tubulin which is shown in fig 2.4. These zones help us to understand colchicine binding pocket and help to design new/novel inhibitors. The inhibitors which bind to this site were also divided into two classes: classic

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colchicine binding inhibitors and non-classical colchicine site inhibitors. The classical inhibitor contains a bridged molecule with a butterfly-like shape which touches Zone 1 and 2 of binding site whereas in non-classical inhibitors are extended chain molecules which are designed to touch the zone 3 also which is present deeper in β tubulin. (Li, Sun, Xu, Zhu, & Xu, 2017)

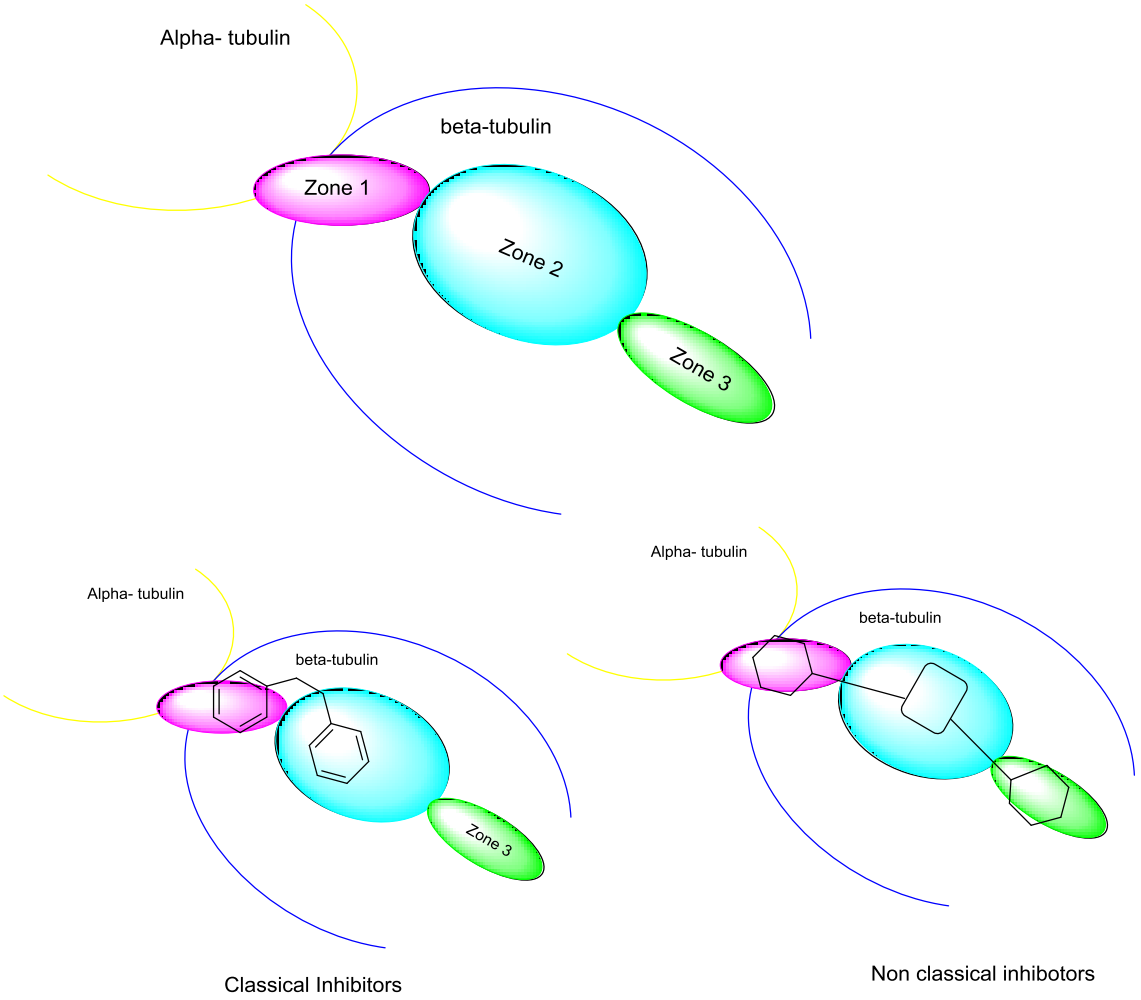

Fig:1.4 Binding zone over colchicine binding site, classical inhibitors and non-classical inhibitors (Li et al., 2017)

In past decade, there are numbers of molecules designed, synthesized and evaluated for the colchicine binding site and some under clinical trials but none of them was approved by FDA. The clinical trials molecules like colchicine, combretastatin-4, etc are under clinical trials.

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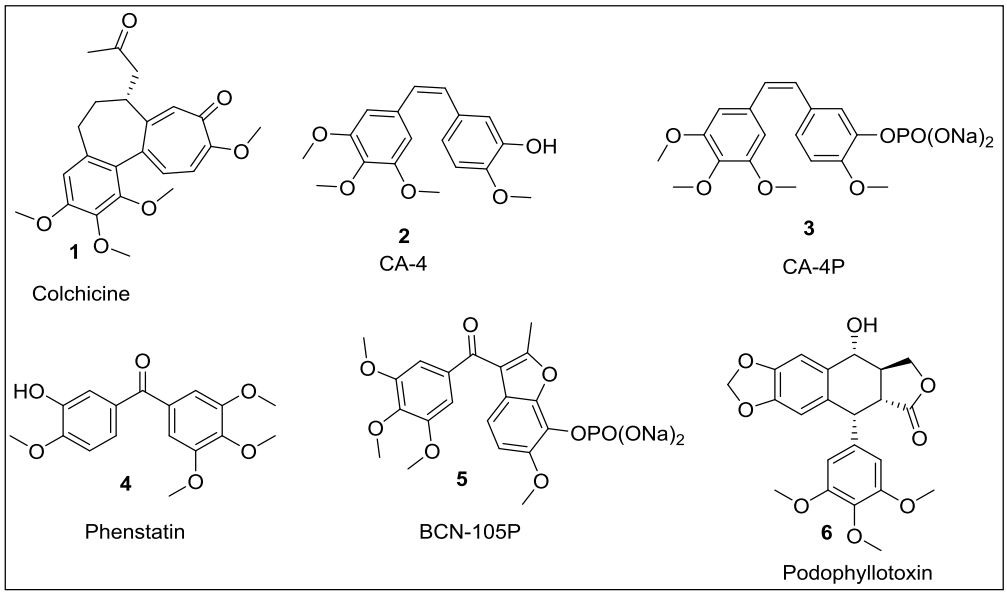

Fig:1.5 Drugs under clinical trials

1.4.1 Colchicine

Colchicine **1**is a natural alkaloid of the plant Colchicum autumnale L. also known as meadow saffron plant which is geographically present in Asia, Europe and some parts of America (A. Kumar, Sharma, & Mondhe, 2017). This compound was firstly isolated by Pelletier and Caventon in 1820. This structure constituted with three fused ring system in which ring A containstrimethoxy group in a phenyl ring system, a seven-member ring with a substituted acetamide group at seventh positions and whereas ring C is tropolonic ring. (Dasgeb et al., 2018). The anti-tumor activity of this compound was firstly studied in 1935. This compound showed good antitumor activity but due to some unsafely measure like high toxicity, muscular dystrophy, hemorrhagic gastroenteritis, nephrotoxicity, cardiovascular damage, extramedullary hematopoiesis and multiple visceral organ dysfunctions found in its clinical trials. Therefore the other derivatives are designed and evaluated to overcome such problems with good activity against cancer (Dubey, Kumar, Labrou, & Shukla, 2017).

1.4.2 Combretastatin-4 phosphate (CA_4P)

The modified version of combretastatin**2** is combreastatin-4P **3** whichhave a biaryl system in which the Ring A contains three trimethoxy groups while in the second ring there is a methoxy and a hydroxy group in a phenyl ring. Some other modification was done to maintain thecis form and to improve other pharmacokinetic property. The analogue of combretastatin-4 phosphate (CA-4P) (3) a prodrug of combretastatin-4 which is water soluble and having good anticancer activity and vascular disrupting potency over large number of cancer cell lines and also under clinical trials phase III for various solid tumor (M. Zhang, Liang, Li, Liu, & Wang, 2017).

1.4.3 Phenstatin and BCN-105P

The phenstatin**4** and BCN105 **5** are the benzophenone which was reported by Pettit and coworkers which have good microtubules destabilizing capability (G. B. Kumar et al., 2016). Structurally the phenstatin and BCN-105P have biphenyl ring system in which ring A have trimethoxy group while B ring is different and cis conformation is restricted with the keto group (Hsieh et al., 2003). These compounds have good anticancer activity against various cell lines. Some another analogue of these molecules is also under clinical trials.

1.4.4 Podophyllotoxins

Podophyllotoxin**6**is a naturally occurring aryltetralincyclolignan which is obtained from Podophyllumhexandrum and from other species that contains four fused rings named as A–D with four chiral centers which are almost planar. Podophyllotoxins was firstly obtained in 1880 (Yu, Che, & Xu, 2017). Structurally it contains four fused rings, ABCD out of them ringA is dioxolane ring which is optimal for activity, B and C are fused benzene and hexane which provide structural framework for structure, the D is a lactone ring which is essential for biological inhibition, while the fifth ring is not fused which is a phenyl ring

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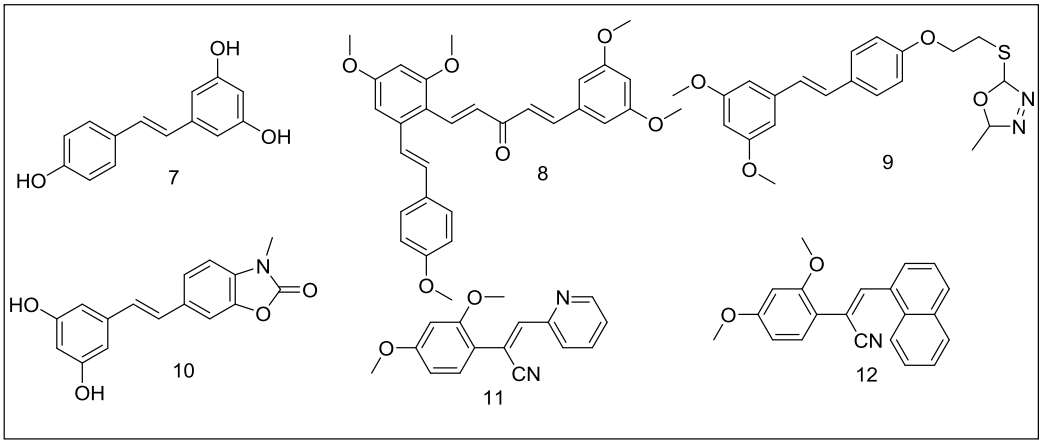
with three trimethoxy group which help to form hydrophobic interaction with binding pocket (X. Zhang et al., 2017). There were some problems faced during clinical trials like solubility, lack of specific selectivity for healthy tissues and other side effects like gastrointestinal reactions. Besides these problems, the good activity of compounds attract researcher towards this and some other analogues are also under clinical trials (Ling et al., 2017). The molecules which are under clinical trials having the biaryl system and antiproliferativepotential. Some other biaryls also having good antiproliferative activity over various cell lines. These molecules also target cancer cells via targeting tubulin proteins.

1.5 Recently reported biaryls as antiproliferative agents

1.5.1 Resveratrol

Resveratrol **7** is a constituent of the human diet that has been shown to inhibit cellular processes associated with tumor initiation, promotion, and progression. It is obtained or found in the grapes species and it has good antiproliferative activity **(Mgbonyebi, Russo, & Russo, 1998)**. Schneider and group found that the resveratrol has good antiproliferative activity against cancer cell lines (Schneider et al., 2000).Recently many analogs were synthesized and evaluated their antiprolifrative activity. Ruan and group a series of resveratrol derivatives possessing curcumin**8** were synthesized and checkedtheir antiproliferative potential over various cancer cell lines including murine melanoma B16-F10, human hepatoma HepG2 and human lung carcinoma A549. Among them, compound displayed good in vitroantiproliferative activity against B16-F10 with an IC_{50} value of 0.71 lg/mL (Ruan et al., 2012).



Murtey and group synthesized and evaluated the novel class of resveratrol-oxadiazole hybrid compounds **9**and screened there in vitro antiproliferative activity against three human cancer cell lines. All the compounds showed superior antiproliferative activity than the reference compound resveratrol (Murty, Penthala, Polepalli, & Jain, 2016). Gerova and group introduced abezoxazole ring with the ring B **10** which also showed good antiproliferative activity against MCf-7, HL-60cell lines in nanomolar concentration(Gerova et al., 2017). On other hand, mu and group synthesized a series of novel derivatives of 2,3-diaryl acrylonitrile derivative **11,12** and the synthesized compounds have antiproliferativepotential which was checked over human cancer cell lines, such as BEL-7402, HeLa, and HCT116 with IC_{50} values in the range of 0.13–60.23(Ma, Li, & Tian, 2017).

1.5.2 Curcumin and its derivatives

Curcumin**13** is a major constituent obtained from Turmeric (Curcumalonga Linn) is a member of the Zingiberaceae family and is cultivated in tropical and subtropical regions around the world and it originates from India, Southeast Asia and, Indonesia. The curcumin has abiaryl system and reported antiproliferative activity (Amalraj, Pius, Gopi, & Gopi, 2017).

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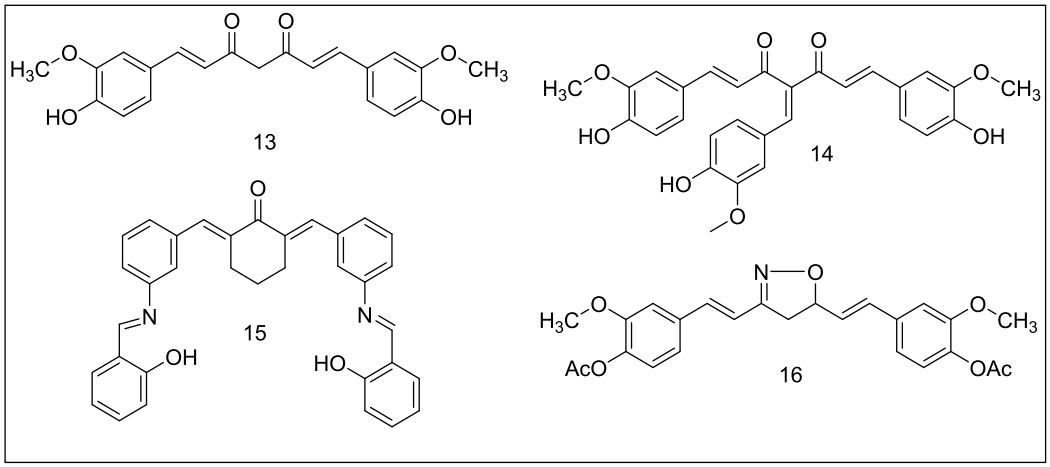

Chakarborti and group synthesized a derivative **14** of the curcumin which showed good antiproliferative activity. They introduce benzlidine molecule which attains a binding site on tubulin or target tubulin (Chakraborti et al., 2011). The other group Chen et al designed and synthesized of two series of novel double Schiff-base substituted 4-piperidone/cyclohexanone derivatives of curcumin**15** which also showed good antiproliferative activity (Q. Chen et al., 2016). Lozada and group also utilized the property of the curcumin and synthesized some derivatives **16** which has biarylssystem and showed good anti-proliferative activity over HCT-15, U-251 in micromolar concentration. (Lozada-García et al., 2017)

1.5.3 Chalcone and its derivatives

Chalcones are the flavone precursorswhich is known for wide range of biological activities such as anti-diabetic, anti-neoplastic, anti-hypertensive, anti-retroviral, anti-inflammatory, anti-parasitic, anti-histaminic, anti-malarial, antioxidant, anti-fungal, anti-obesity, antiplatelet, anti-tubercular, immunosuppressant, anti-arrhythmic, hypnotic, anti-gout, anxiolytic, anti-spasmodic, anti-nociceptive, hypolipidemic, anti-filarial, anti-angiogenic, antiprotozoal, anti-bacterial, anti-steroidal, cardioprotectiveetc(Boumendjel et al., 2008). The chalconeisbiaryls which are also used as antiproliferativeagents. Recently many chalcone derivatives were synthesized and their potentials were checked over various cancer cell lines.Peyrot and group synthesized trans-1-(2,5-dimethoxyphenyl)-3-[4-(dimethylamino)pheny1]-2-methyl-2-propen-1-one derivative**17** which have the ability to bind with purified porcine brain tubulin and inhibits the microtubule assembly in vitro and cause de-polymerization. (Peyrot et al., 1989). Salum and group synthesized a series of 3, 4, 5-trimethoxychalcones and evaluated their cell mitosis inhibitory activity. Here they utilized the trimehoxy group in their structure and found active against human leukemia cell line. Compound **18** was exhibited most potent inhibitor of tubulin (Kerr, Hamel, Jung, & Flynn, 2007)

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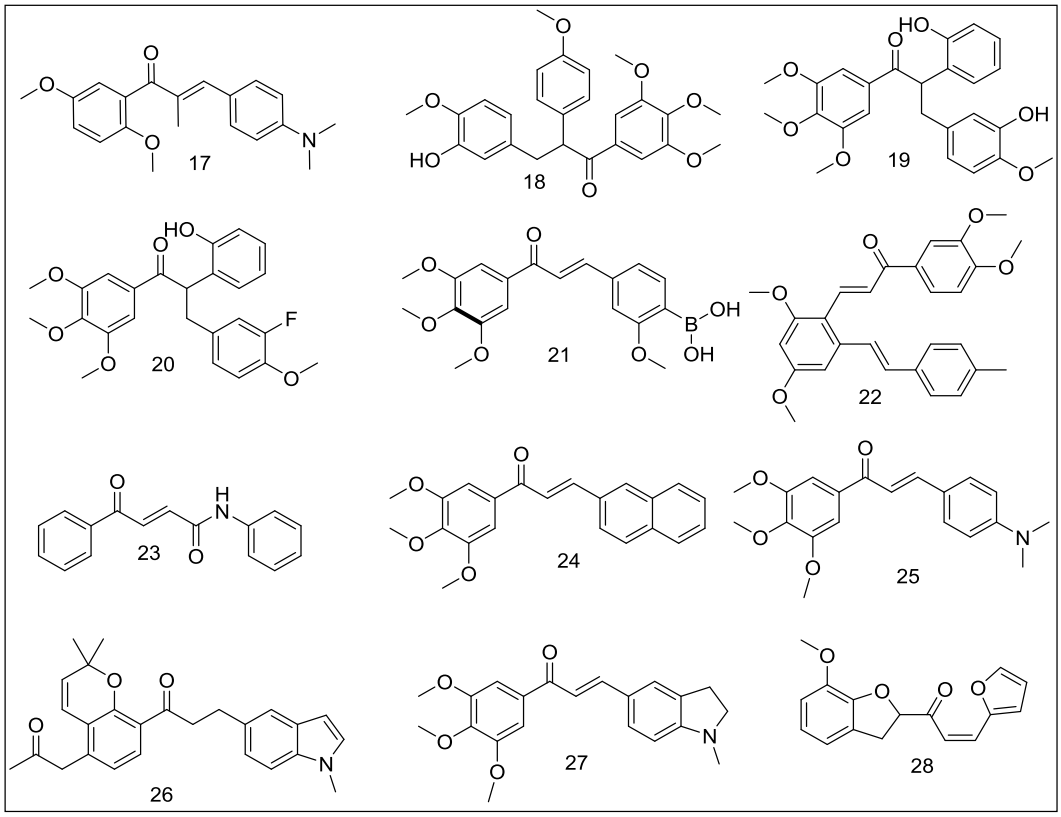

Ducki and group synthesized a series of combretastatinlike chalcone and screened their antiproliferative activity. Compounds bind with β-tubulin leads to microtubule polymerization which results in an accumulation of cells in the G2/M phase as determined by colchicine binding. Compounds **19, 20** showed the most potent activity (Ducki et al., 2009). Kong and group designed and synthesized boronic acid analogues of chalconeswith effort to compare biological activities with combretastatin A-4, a potent inhibitor of tubulin polymerization. They utilized the trimethoxy, boronic group and found **21**as the best molecule in this series (Kong et al., 2010). Raun and group synthesized resveratrol derivatives**22** possessing chalcone moiety were synthesized and characterized, and their biological activities were also evaluated as tubulin polymerization inhibitors. Compound **23** exhibited as most potent inhibitor in vitro(Ruan et al., 2011). Vitorovi and group synthesized (E)-4-aryl- 4-oxo-2-butenoic2-butenoic acid amides derivatives and reported antiproliferative activity against human tumor cell lines. These compounds showed anti-proliferative activity with IC_{50} value in <20µM (Vitorović-Todorović et al., 2013). Salum and group designed and synthesized 3,4,5-trimethoxy chalcone derivatives and evaluated for inhibition of tubulin assembly and cytotoxicity against various human cancer cell lines. The trimethoxy group tubulin interaction with binding sites showed antiproliferative, and antimitotic effects.The compound **24**and**25**were found to be most potent(Salum et al., 2013). Wang and group synthesized a novel series of pyranochalcone derivatives containing indole moiety and reported inhibition of tubulin polymerization. Compound **26** showed most potent inhibitory activity against cancer cell line(G. Wang et al., 2014). Yan and group synthesized and evaluated a novel chalcone**27** which showed good anti-proliferative activity (Yan et al., 2016). Coskun and group synthesized a series of1-(7-ethoxy-1-benzofuran-2-yl) substituted chalcone**28** derivatives which showed good antiproliferativeactivity (Coskun, Erkisa, Ulukaya, Coskun, & Ari, 2017).

1.5.4 Combrastatins

Combretastatin**29** are a class of natural stilbenoid phenol, which present in the bark of Combretumcaffrum (family-Combretaceae), commonly known as South African bush willow (R. Cao et al., 2012). Extract of this tree was used by Zulus as herbal remedies and as paint for spears.

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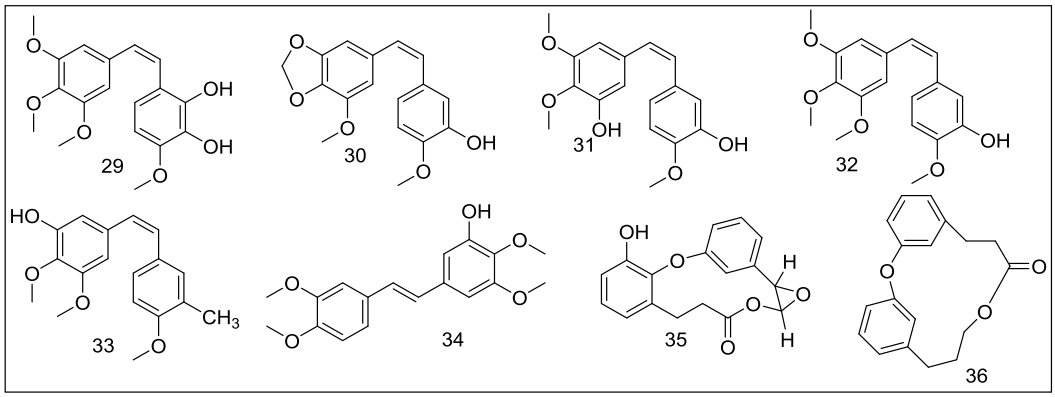
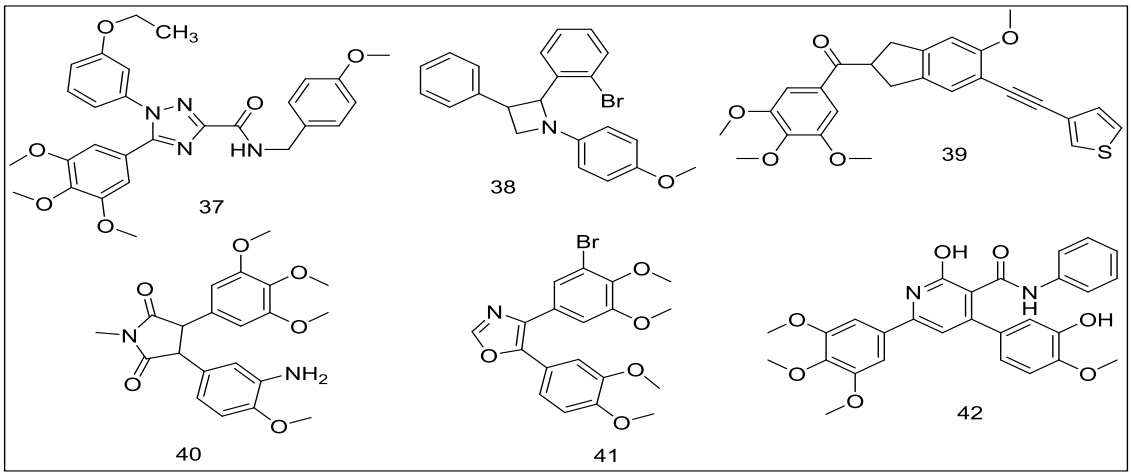
From the C. caffrum a series of active constituents likestilbenes, phenanthrenens, and bibenzyles were isolated. Out of these active compound,stilbenes are reported to be cytotoxic and active against various cancer cell lines (Kingston, 2009).



Combretastatin are grouped mainly in two series: A-series and D-series. The A series includes compounds which have difference in substitution, functional group, chain extension are combretastatin A-1 (**29**), A-2(**30**), A-3(**31**), A-4(**32**), A-5(**33**), A-6(**34**) while D-series includes compounds which are 17 membered macrocyclic lactones are D-1(**35**), and D-2(**36**) (Seddigi et al., 2017).

Recently, Mustafa and group synthesized a hybrid form of combretastatin**37**in which they introduced 1, 2, 4-triazoles in their structure. This helped to restrict the cis confirmation of the product and trimethoxy help to get interaction at colchicine binding site. These combines are active in HEPG2 and HC-60 cell lines with the IC_{50} in micromolar range (Mustafa et al., 2017). Elmeligie and group also restrict the cis confirmation by introducing azitidine in their structure. They synthesized and evaluated azididine-2-one derivatives **38** and tested their antiproliferative activity over HS371T and CC480co which showed activity in micromolar range (Elmeligie, Taher, Khalil, & El-said, 2017). Fan and group replace B ring of combretastatin with the Benzo[b]furans ring **39** and restrict the cis form with aketo group. The Benzo[b]furans have also good antiproliferative activity with the IC_{50} value in micromolar range (Fan, Luo, & Ma, 2017).Zang and group used hydatoin in compound **40** to restrict the cis confirmation of biaryls. Generally, hydantoin is used in anti-convulsant drugs but recent studies showed that this also hasantiproliferative property. This addition showed good activity against HeLa, A2780, HCT-116, MDA-MB-231 cell lines with IC_{50} in micromolar range (M. Zhang et al., 2017).



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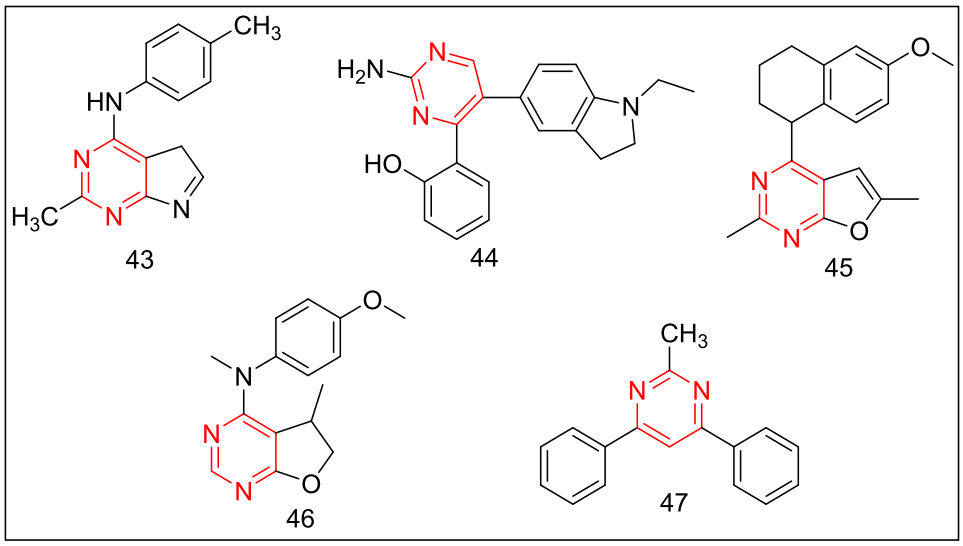
Recently another group, Stefanskiet al introduced heterocyclic ring in compound **41** which restrict the cis conformation of the ring. The biaryl system contains methoxy group which helped to bind the molecule with the binding site. They checked their antiproliferative potential over MCF-7, MDA-MD-231, A549, and SK0V3 in which it showed good inhibition activity in micromolar range (Stefański et al., 2018). Another group introduced pyridine ring to restrict the cis conformation. Shringareet al synthesized pyridine bridged biaryls**42** which showed good antiproliferative activity againstMCF-7 cancercell line with IC_{50} value in micromolar range (Shringare et al., 2018).

2.6 Pyrimidine ring in anticancer compounds

The pyrimidine is a part of many FDA approved drugs an also used as a scaffold in many reported anticancer agents (Prachayasittikul et al., 2017). Many research groups utilized pyrimidine in their structure to target the cancer cells. Gangjee and group synthesized two series of pyrimidine fused compounds with 6-CH_3cyclopenta[d]pyrimidine and pyrrolo[2,3-d]pyrimidine scaffolds**43**. These compounds were found to be potent with good antiproliferative activity at nanomolar concentration and target the colchicine binding site of tubulin (Gangjee et al., 2010). Xie and group synthesized of a series of 2,4,5-substituted pyrimidine derivatives**44**, which found to be potent over cancer cell line in nanomolar concentration and authors found their interactions with tubulin at colchicine binding site (Xie et al., 2011).



Zhang and group synthesized a series of 4-substituted 2,6-dimethylfuro[2,3-d]pyrimidines**45** which act as dual inhibitors of the microtubules and tyrosine kinases with conformational restrict structure. These compounds exhibited microtubules de-polymerization activity with EC_{50} values in nanomolar range. These compounds may act single and via multiple way help to target cancer cells (X. Zhang et al., 2015). Devambatla and group utilized the previously reported structure and synthesized N-aryl-5-methylfuro[2,3- d]pyrimidin-4-amines **46** form of 4-amino-5-methylfuro[2,3-d]pyrimidine showed antiproliferative activity in nanomolar concentration (Devambatla et al., 2016). Kumar and group utilized pyrimidine in their structure by introducing this ring as a linker between two biphenyl ring**47** to maintain its cisform showed good activity micromolar concentration which is better than the standard inhibitor colchicine (B. Kumar et al., 2018).

2.7 Piperazine ring in anticancer compounds

The Piperazine is the part of many anticancer agents. It is used in many reported structure in which it helped to get additional interaction with amino acids, used as a chain extender, increased the bioavailability and solubility of agents. Theimatinib**48** which is an FDA approved drug used a methyl piperazine in its structure. By using this solubility and oral bioavailability of drug increased and it is used as anticancer for the treatment of Leukemia (Capdeville, Buchdunger, Zimmermann, & Matter, 2002). Another group Chopra et al.tested some

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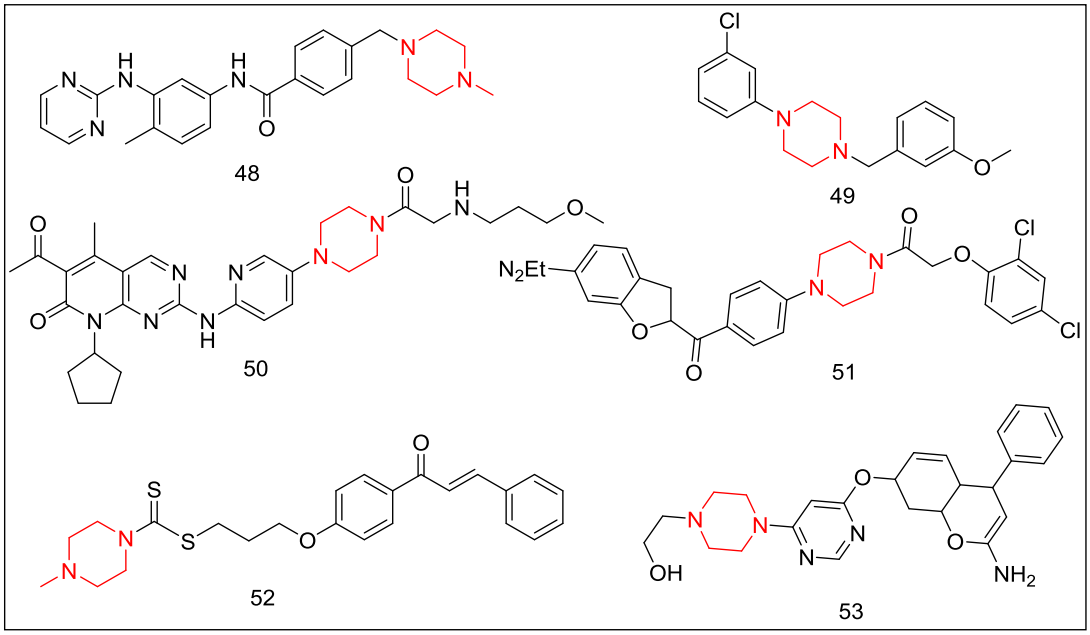
synthesized piperazine derivative over some cancer cell lines. The tested compounds **49**containpiperazine in their structure which showed good antiproliferative activity within nanomolar range (Chopra, Anderson, & Giardina, 2014). Wang and group synthesized a series of palbociclib analogue**50**which contains a piperazine in their structure. They modification with piperazine helped to get good activity in nanomolar range (P. Wang, Huang, Wang, & Gu, 2016). On the other hand, Mao and group synthesized a hybrid series of benzofuran and piperazinein which**51** was found to be potent against cancer cell lines. The other halogen-substituted piperazine found to be most active with IC_{50} value was in nanomolar range(Mao et al., 2016).Fu and group introduced dithiocarbamate–chalcone**52** derivative which contain piperazine in their structure. The piperazine help to get additional binding and showed good antiproliferative activity in nanomolar range (Fu et al., 2016).



Parveen and group also utilized piperazine in their structure. They synthesized piperazine and chromon mixed new structure**53** which were found to be active and showed good antiproliferative activity within the micromolar concentration (Parveen, Ahmed, Idrees, Khan, & Hassan, 2017).

CONCLUSION

Microtubules and their associated proteins have emerged as viable targets within the drug discovery program, mainly in the treatment of cancer. Special lead molecules are recognized that bind to one of the four binding sites of tubulin thereby inhibiting the polymerization or depolymerization, amongst them CA-4 is a lead molecule, tat binds to the colchicine binding site and exerts antiproliferative activity by the inhibition of tubulin proteins polymerization. Simplicity of structure and ease of synthesis with potent activity make this molecule, one of the most researched lead molecules in anti-cancer drug development. Vast research endeavors were undertaken to broaden new derivatives of CA-4 to cope with the demanding situations inside the improvement of anticancer drugs. Moreover, cis-orientation of the double bond was identified to be most crucial for activity along with a trimethoxy aromatic ring. To nullify the possible isomerization of the cis orientation to an inactive trans orientation, different approaches have been developed.The replacement of the cis-bond with a heterocyclic moiety is of significant potential as it results in the desired conformational restriction as well as addition of new pharmacological properties because of incorporation of heteroatoms.

AbbreviationsMCF-7: epithelial cell line isolated from the breast tissue of a patient and can be used in breast cancer research; CA-4:Combretastatin A-4 phosphate is is a microtubule destabilising drug; MDA-MD-231:is an epithelial cell line isolated from the breast tissue of an adenocarcionma patient

and can be used in cancer and immuno-oncology research.

Ethics approval and consent to participate Not applicable

Consent for publication Not applicable.

Availability of data and materials Not applicable

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REFERENCES

[1]. Abraham, J., & Staffurth, J. (2016). Hormonal therapy for cancer. Medicine, 44(1), 30-33.

[2]. Alushin, G. M., Lander, G. C., Kellogg, E. H., Zhang, R., Baker, D., & Nogales, E. (2014). High-resolution microtubule structures reveal the structural transitions in αβ-tubulin upon GTP hydrolysis. Cell, 157(5), 1117-1129.

[3]. Amalraj, A., Pius, A., Gopi, S., & Gopi, S. (2017). Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives–A review. Journal of traditional and complementary medicine, 7(2), 205-233.

[4]. Baselga, J. (2001). The EGFR as a target for anticancer therapy—focus on cetuximab. European Journal of Cancer, 37, 16-22.

[5]. Bhat, K. M., & Setaluri, V. (2007). Microtubule-associated proteins as targets in cancer chemotherapy. Clinical Cancer Research, 13(10), 2849-2854.

[6]. Boumendjel, A., Boccard, J., Carrupt, P.-A., Nicolle, E., Blanc, M., Geze, A., . . . Dumontet, C. (2008). Antimitotic and antiproliferative activities of chalcones: forward structure–activity relationship. Journal of medicinal chemistry, 51(7), 2307-2310.

[7]. Cao, R., Liu, M., Yin, M., Liu, Q., Wang, Y., & Huang, N. (2012). Discovery of novel tubulin inhibitors via structure-based hierarchical virtual screening. Journal of chemical information and modeling, 52(10), 2730-2740.

[8]. Cao, W., Gu, Y., Meineck, M., & Xu, H. (2014). The combination of chemotherapy and radiotherapy towards more efficient drug delivery. Chemistry–An Asian Journal, 9(1), 48-57.

[9]. Capdeville, R., Buchdunger, E., Zimmermann, J., & Matter, A. (2002). Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug. Nature reviews Drug discovery, 1(7), 493.

[10]. Chakraborti, S., Das, L., Kapoor, N., Das, A., Dwivedi, V., Poddar, A., . . . Panda, D. (2011). Curcumin recognizes a unique binding site of tubulin. Journal of medicinal chemistry, 54(18), 6183-6196.

[11]. Chen, H. H., & Kuo, M. T. (2017). Improving radiotherapy in cancer treatment: Promises and challenges. Oncotarget, 8(37), 62742.

[12]. Chen, Q., Hou, Y., Hou, G.-G., Sun, J.-F., Li, N., Cong, W., . . . Wang, C.-H. (2016). Design, synthesis, anticancer activity and cytotoxicity of novel 4-piperidone/cyclohexanone derivatives. Research on Chemical Intermediates, 42(12), 8119-8130.

[13]. Chopra, A., Anderson, A., & Giardina, C. (2014). Novel piperazine-based compounds inhibit microtubule dynamics and sensitize colon cancer cells to tumor necrosis factor-induced apoptosis. Journal of Biological Chemistry, 289(5), 2978-2991.

[14]. Coffey, J. C., Wang, J., Smith, M., Bouchier-Hayes, D., Cotter, T., & Redmond, H. (2003). Excisional surgery for cancer cure: therapy at a cost. The lancet oncology, 4(12), 760-768.

[15]. Coskun, D., Erkisa, M., Ulukaya, E., Coskun, M. F., & Ari, F. (2017). Novel 1-(7-ethoxy-1-benzofuran-2-yl) substituted chalcone derivatives: Synthesis,

characterization and anticancer activity. European journal of medicinal chemistry, 136, 212-222.

[16]. Dasgeb, B., Kornreich, D., McGuinn, K., Okon, L., Brownell, I., & Sackett, D. (2018). Colchicine: an ancient drug with novel applications. British Journal of Dermatology, 178(2), 350-356.

[17]. Devambatla, R. K. V., Namjoshi, O. A., Choudhary, S., Hamel, E., Shaffer, C. V., Rohena, C. C., . . . Gangjee, A. (2016). Design, synthesis, and preclinical evaluation of 4-substituted-5-methyl-furo [2, 3-d] pyrimidines as microtubule targeting agents that are effective against multidrug resistant cancer cells. Journal of medicinal chemistry, 59(12), 5752-5765.

[18]. Dickens, E., & Ahmed, S. (2018). Principles of cancer treatment by chemotherapy. Surgery-Oxford International Edition, 36(3), 134-138.

[19]. Dubey, K. K., Kumar, P., Labrou, N. E., & Shukla, P. (2017). Biotherapeutic potential and mechanisms of action of colchicine. Critical reviews in biotechnology, 37(8), 1038-1047.

[20]. Ducki, S., Mackenzie, G., Greedy, B., Armitage, S., Chabert, J. F. D., Bennett, E., . . . Lawrence, N. J. (2009). Combretastatin-like chalcones as inhibitors of microtubule polymerisation. Part 2: Structure-based discovery of alpha-aryl chalcones. Bioorganic & medicinal chemistry, 17(22), 7711-7722.

[21]. Elmeligie, S., Taher, A. T., Khalil, N. A., & El-said, A. H. (2017). Synthesis and cytotoxic activity of certain trisubstituted azetidin-2-one derivatives as a cis-restricted combretastatin A-4 analogues. Archives of pharmacal research, 40(1), 13-24.

[22]. Emens, L. A., Ascierto, P. A., Darcy, P. K., Demaria, S., Eggermont, A. M., Redmond, W. L., . . . Marincola, F. M. (2017). Cancer immunotherapy: opportunities and challenges in the rapidly evolving clinical landscape. European Journal of Cancer, 81, 116-129.

[23]. Fan, Y., Luo, Y., & Ma, C. (2017). Synthesis and cytotoxic evaluation of combretastatin A-4 analogues of benzo [b] furans. Monatshefte für Chemie-Chemical Monthly, 148(10), 1823-1832.

[24]. Ferrara, N. (2005). VEGF as a therapeutic target in cancer. Oncology, 69(Suppl. 3), 11-16.

[25]. Fu, D.-J., Zhang, S.-Y., Liu, Y.-C., Zhang, L., Liu, J.-J., Song, J., . . . Liu, H.-M. (2016). Design, synthesis and antiproliferative activity studies of novel dithiocarbamate–chalcone derivates. Bioorganic & medicinal chemistry letters, 26(16), 3918-3922.

[26]. Gangjee, A., Zhao, Y., Lin, L., Raghavan, S., Roberts, E. G., Risinger, A. L., . . . Mooberry, S. L. (2010). Synthesis and discovery of water-soluble microtubule targeting agents that bind to the colchicine site on tubulin and circumvent Pgp mediated resistance. Journal of medicinal chemistry, 53(22), 8116-8128.

[27]. Gerova, M., Aleksandrova, E., Ivanova, Y., Stanisheva, D., Momekov, G. T., & Petrov, O. (2017). Synthesis and cytotoxic activity of new heterocyclic analogues of resveratrol, containing benzoxazolone ring. BULGARIAN CHEMICAL COMMUNICATIONS, 49, 71-75.

[28]. Hadfield, J. A., Ducki, S., Hirst, N., & McGown, A. T. (2003). Tubulin and microtubules as targets for anticancer drugs. Progress in cell cycle research, 5, 309-325.

[29]. Hsieh, H.-P., Liou, J.-P., Lin, Y.-T., Mahindroo, N., Chang, J.-Y., Yang, Y.-N., . . . Chen, T.-W. (2003). Structure–activity and crystallographic analysis of benzophenone derivatives—the potential anticancer agents. Bioorganic & medicinal chemistry letters, 13(1), 101-105.

[30]. Jagathnath Krishna, K., & Sebastian, P. (2017). Cancer Incidence and Mortality: District Cancer Registry, Trivandrum, South India. Asian Pacific Journal of Cancer Prevention, 18(6), 1485-1491.

[31]. Jordan, M. (2002). Mechanism of action of antitumor drugs that interact with microtubules and tubulin. Current Medicinal Chemistry-Anti-Cancer Agents, 2(1), 1-17.

[32]. Jordan, M. A., & Wilson, L. (2004). Microtubules as a target for anticancer drugs. Nature Reviews Cancer, 4(4), 253.

[33]. Kanthou, C., & Tozer, G. M. (2009). Microtubule depolymerizing vascular disrupting agents: novel therapeutic agents for oncology and other pathologies. International journal of experimental pathology, 90(3), 284-294.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1481-1497 www.ijprajournal.com ISSN: 2456-4494

[34]. Kaur, R., Kaur, G., Gill, R. K., Soni, R., & Bariwal, J. (2014). Recent developments in tubulin polymerization inhibitors: an overview. European journal of medicinal chemistry, 87, 89-124.
[35]. Kerr, D. J., Hamel, E., Jung, M. K., & Flynn, B. L. (2007). The concise synthesis of chalcone, indanone and indenone analogues of combretastatin A4. Bioorganic & medicinal chemistry, 15(9), 3290-3298.
[36]. Kingston, D. G. (2009). Tubulin-interactive natural products as anticancer agents. Journal of natural products, 72(3), 507-515.
[37]. Kong, Y., Wang, K., Edler, M. C., Hamel, E., Mooberry, S. L., Paige, M. A., & Brown, M. L. (2010). A boronic acid chalcone analog of combretastatin A-4 as a potent anti-proliferation agent. Bioorganic & medicinal chemistry, 18(2), 971-977.
[38]. Koo, M. M., Hamilton, W., Walter, F. M., Rubin, G. P., & Lyratzopoulos, G. (2018). Symptom Signatures and Diagnostic Timeliness in Cancer Patients: A Review of Current Evidence. Neoplasia, 20(2), 165-174.
[39]. Kumar, A., Sharma, P. R., & Mondhe, D. M. (2017). Potential anticancer role of colchicine-based derivatives: an overview. Anti-cancer drugs, 28(3), 250-262.
[40]. Kumar, B., Sharma, P., Gupta, V. P., Khullar, M., Singh, S., Dogra, N., & Kumar, V. (2018). Synthesis and biological evaluation of pyrimidine bridged combretastatin derivatives as potential anticancer agents and mechanistic studies. Bioorganic chemistry, 78, 130-140.
[41]. Kumar, G. B., Nayak, V. L., Sayeed, I. B., Reddy, V. S., Shaik, A. B., Mahesh, R., . . . Kamal, A. (2016). Design, synthesis of phenstatin/isocombretastatin-oxindole conjugates as antimitotic agents. Bioorganic & medicinal chemistry, 24(8), 1729-1740.
[42]. Li, W., Sun, H., Xu, S., Zhu, Z., & Xu, J. (2017). Tubulin inhibitors targeting the colchicine binding site: a perspective of privileged structures. Future medicinal chemistry, 9(15), 1765-1794.
[43]. Ling, L., Yao, C., Du, Y., Ismail, M., He, R., Hou, Y., . . . Li, X. (2017). Assembled liposomes of dual podophyllotoxin phospholipid: preparation, characterization and in vivo anticancer activity. Nanomedicine, 12(6), 657-672.
[44]. Lord, C. J., & Ashworth, A. (2008). Targeted therapy for cancer using PARP inhibitors. Current opinion in pharmacology, 8(4), 363-369.
[45]. Lozada-García, M. C., Enríquez, R. G., Ramírez-Apán, T. O., Nieto-Camacho, A., Palacios-Espinosa, J. F., Custodio-Galván, Z., . . . Pérez-Villanueva, J. (2017). Synthesis of Curcuminoids and Evaluation of Their Cytotoxic and Antioxidant Properties. Molecules, 22(4), 633.
[46]. Ma, J., Li, J., & Tian, Y.-S. (2017). Synthesis and bioactivity evaluation of 2, 3-diaryl acrylonitrile derivatives as potential anticancer agents. Bioorganic & medicinal chemistry letters, 27(1), 81-85.
[47]. Mahoney, K. M., Rennert, P. D., & Freeman, G. J. (2015). Combination cancer immunotherapy and new immunomodulatory targets. Nature reviews Drug discovery, 14(8), 561.
[48]. Mao, Z.-W., Zheng, X., Lin, Y.-P., Hu, C.-Y., Wang, X.-L., Wan, C.-P., & Rao, G.-X. (2016). Design, synthesis and anticancer activity of novel hybrid compounds between benzofuran and N-aryl piperazine. Bioorganic & medicinal chemistry letters, 26(15), 3421-3424.
[49]. Mgbonyebi, O. P., Russo, J., & Russo, I. H. (1998). Antiproliferative effect of synthetic resveratrol on human breast epithelial cells. International journal of oncology, 12(4), 865-874.
[50]. Murty, M., Penthala, R., Polepalli, S., & Jain, N. (2016). Synthesis and biological evaluation of novel resveratrol-oxadiazole hybrid heterocycles as potential antiproliferative agents. Medicinal Chemistry Research, 25(4), 627-643.
[51]. Musgrove, E. A., Caldon, C. E., Barraclough, J., Stone, A., & Sutherland, R. L. (2011). Cyclin D as a therapeutic target in cancer. Nature Reviews Cancer, 11(8), 558.
[52]. Mustafa, M., Abdelhamid, D., Abdelhafez, E. M., Ibrahim, M. A., Gamal-Eldeen, A. M., & Aly, O. M. (2017). Synthesis, antiproliferative, anti-tubulin activity, and docking study of new 1, 2, 4-triazoles as potential combretastatin analogues. European journal of medicinal chemistry, 141, 293-305.
[53]. O'Donnell, L., & O'Bryan, M. K. (2014). Microtubules and spermatogenesis. Paper

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 1481-1497 www.ijprajournal.com ISSN: 2456-4494

presented at the Seminars in cell & developmental biology.

[54]. Parveen, I., Ahmed, N., Idrees, D., Khan, P., & Hassan, M. I. (2017). Synthesis, estrogen receptor binding affinity and molecular docking of pyrimidine-piperazine-chromene and-quinoline conjugates. Bioorganic & medicinal chemistry letters, 27(18), 4493-4499.

[55]. Pellegrini, F., & Budman, D. R. (2005). Tubulin function, action of antitubulin drugs, and new drug development. Cancer investigation, 23(3), 264-273.

[56]. Peyrot, V., Leynadier, D., Sarrazin, M., Briand, C., Rodriquez, A., Nieto, J., & Andreu, J. (1989). Interaction of tubulin and cellular microtubules with the new antitumor drug MDL 27048. A powerful and reversible microtubule inhibitor. Journal of Biological Chemistry, 264(35), 21296-21301.

[57]. Prachayasittikul, S., Pingaew, R., Worachartcheewan, A., Sinthupoom, N., Prachayasittikul, V., Ruchirawat, S., & Prachayasittikul, V. (2017). Roles of pyridine and pyrimidine derivatives as privileged scaffolds in anticancer agents. Mini reviews in medicinal chemistry, 17(10), 869-901.

[58]. Rajak, H., Kumar Dewangan, P., Patel, V., Kumar Jain, D., Singh, A., Veerasamy, R., . . . Dixit, A. (2013). Design of combretastatin A-4 analogs as tubulin targeted vascular disrupting agent with special emphasis on their cis-restricted isomers. Current pharmaceutical design, 19(10), 1923-1955.

[59]. Ravelli, R. B., Gigant, B., Curmi, P. A., Jourdain, I., Lachkar, S., Sobel, A., & Knossow, M. (2004). Insight into tubulin regulation from a complex with colchicine and a stathmin-like domain. Nature, 428(6979), 198.

[60]. Ross, W. E. (1985). DNA topoisomerases as targets for cancer therapy. Biochemical pharmacology, 34(24), 4191-4195.

[61]. Ruan, B.-F., Lu, X., Li, T.-T., Tang, J.-F., Wei, Y., Wang, X.-L., . . . Zhu, H.-L. (2012). Synthesis, biological evaluation and molecular docking studies of resveratrol derivatives possessing curcumin moiety as potent antitubulin agents. Bioorganic & medicinal chemistry, 20(2), 1113-1121.

[62]. Ruan, B.-F., Lu, X., Tang, J.-F., Wei, Y., Wang, X.-L., Zhang, Y.-B., . . . Zhu, H.-L. (2011). Synthesis, biological evaluation, and molecular docking studies of resveratrol derivatives possessing chalcone moiety as potential antitubulin agents. Bioorganic & medicinal chemistry, 19(8), 2688-2695.

[63]. Salum, L. B., Altei, W. F., Chiaradia, L. D., Cordeiro, M. N., Canevarolo, R. R., Melo, C. P., . . . Santos-Silva, M. C. (2013). Cytotoxic 3, 4, 5-trimethoxychalcones as mitotic arresters and cell migration inhibitors. European journal of medicinal chemistry, 63, 501-510.

[64]. Schneider, Y., Vincent, F., Duranton, B. t., Badolo, L., Gossé, F., Bergmann, C., . . . Raul, F. (2000). Anti-proliferative effect of resveratrol, a natural component of grapes and wine, on human colonic cancer cells. Cancer letters, 158(1), 85-91.

[65]. Seddigi, Z. S., Malik, M. S., Saraswati, A. P., Ahmed, S. A., Babalghith, A. O., Lamfon, H. A., & Kamal, A. (2017). Recent advances in combretastatin based derivatives and prodrugs as antimitotic agents. MedChemComm, 8(8), 1592-1603.

[66]. Shringare, S. N., Chavan, H. V., Bhale, P. S., Dongare, S. B., Mule, Y. B., Patil, S. B., & Bandgar, B. P. (2018). Synthesis and pharmacological evaluation of combretastatin-A4 analogs of pyrazoline and pyridine derivatives as anticancer, anti-inflammatory and antioxidant agents. Medicinal Chemistry Research, 27(4), 1226-1237.

[67]. Siegel, R. L., Miller, K. D., & Jemal, A. (2017). Cancer statistics, 2016. CA: a cancer journal for clinicians, 66(1), 7-30.

[68]. Stefański, T., Mikstacka, R., Kurczab, R., Dutkiewicz, Z., Kucińska, M., Murias, M., . . . Kaczmarek, M. (2018). Design, synthesis, and biological evaluation of novel combretastatin A-4 thio derivatives as microtubule targeting agents. European journal of medicinal chemistry, 144, 797-816.

[69]. Tripathi, K. (2013). Essentials of medical pharmacology (7 ed.): JP Medical Ltd.

[70]. Vitorović-Todorović, M. D., Erić-Nikolić, A., Kolundžija, B., Hamel, E., Ristić, S., Juranić, I. O., & Drakulić, B. J. (2013). (E)-4-Aryl-4-oxo-2-butenoic acid amides, chalcone–aroylacrylic acid chimeras: Design, antiproliferative activity and inhibition of tubulin polymerization. European journal of medicinal chemistry, 62, 40-50.

[71]. Wang, G., Li, C., He, L., Lei, K., Wang, F., Pu, Y., . . . Chen, J. (2014). Design, synthesis and biological evaluation of a series of pyrano chalcone derivatives containing indole moiety as novel anti-tubulin agents. Bioorganic & medicinal chemistry, 22(7), 2060-2079.

[72]. Wang, P., Huang, J., Wang, K., & Gu, Y. (2016). New palbociclib analogues modified at the terminal piperazine ring and their anticancer activities. European journal of medicinal chemistry, 122, 546-556.

[73]. Xie, F., Zhao, H., Li, D., Chen, H., Quan, H., Shi, X., . . . Hu, Y. (2011). Synthesis and biological evaluation of 2, 4, 5-substituted pyrimidines as a new class of tubulin polymerization inhibitors. Journal of medicinal chemistry, 54(9), 3200-3205.

[74]. Yan, J., Chen, J., Zhang, S., Hu, J., Huang, L., & Li, X. (2016). Synthesis, evaluation, and mechanism study of novel indole-chalcone derivatives exerting effective antitumor activity through microtubule destabilization in vitro and in vivo. Journal of medicinal chemistry, 59(11), 5264-5283.

[75]. Yu, X., Che, Z., & Xu, H. (2017). Recent advances in the chemistry and biology of podophyllotoxins. Chemistry-A European Journal, 23(19), 4467-4526.

[76]. Zhang, M., Liang, Y.-R., Li, H., Liu, M.-M., & Wang, Y. (2017). Design, synthesis, and biological evaluation of hydantoin bridged analogues of combretastatin A-4 as potential anticancer agents. Bioorganic & medicinal chemistry, 25(24), 6623-6634.

[77]. Zhang, X., Raghavan, S., Ihnat, M., Hamel, E., Zammiello, C., Bastian, A., . . . Gangjee, A. (2015). The design, synthesis and biological evaluation of conformationally restricted 4-substituted-2, 6-dimethylfuro [2, 3-d] pyrimidines as multi-targeted receptor tyrosine kinase and microtubule inhibitors as potential antitumor agents. Bioorganic & medicinal chemistry, 23(10), 2408-2423.

[78]. Zhang, X., Rakesh, K., Shantharam, C., Manukumar, H., Asiri, A., Marwani, H., & Qin, H.-L. (2017). Podophyllotoxin derivatives as an excellent anticancer aspirant for future chemotherapy: A key current imminent needs. Bioorganic & medicinal chemistry.