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Review Article

Imidazopyridine scaffold as an effective tubulin polymerization inhibitor

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ABSTRACT

Tubulin and the tubulin cycle, which have many vital cellular functions in living cells, are privileged targets for the development of anticancer drug candidates. In the processing of cellular processes, especially cell division, alpha and beta tubulin polymerize to form microtubules and continue the cycle by depolymerizing again. Disruption of the polymerization-depolymerization dynamics of microtubules by various agents causes mitotic cell arrest and subsequent cell death via apoptosis. This review summarizes the tubulin cycle, cancer, and target regions. Tubulin has three main target binding sites: taxane, vinca, and colchicine. In particular, the colchicine binding site, which is the current target for disrupting the tubulin cycle, is inhibited by various synthetic compounds, and the common properties of these compounds are emphasized. The results show that highly effective cytotoxic agents can be developed by modifying the imidazopyridine scaffold, which remains open to exploration. The remarkable antitubulin and cytotoxic effects of recently developed compounds with an imidazopyridine ring are interesting. A detailed report of anti-tubulin agents with imidazopyridine structures, among the tubulin polymerization inhibitors developed to date, and an evaluation of the structure–activity relationship is presented here. In addition, the new molecular topology established in this review based on the structure-activity relationships of imidazopyridine will inspire research groups to develop new imidazopyridine-based anti-tubulin agents with clinical anticancer potential in the near future.

Keywords: Anti-tubulin, Cytotoxicity, Imidazopyridine, Structure-Activity Relationship

INTRODUCTION

Cancer, which threatens humanity globally and ranks second among deaths with known causes, has been reported to have reached approximately 10 million deaths (or 1 in every 6 deaths) per year since 2020, according to WHO data, and even cancer-related deaths are increasing every year (Sung et al. 2021). Cancer, a heterogeneous and multifactorial disease, occurs with the uncontrolled growth and proliferation of cells with a series of molecular or genomic alterations in the cells (Brown et al. 2023). Under normal circumstances, after a cell completes its task, it receives a message that it has died and is replaced by a new, healthy cell (Galluzzi et al. 2007). However, cancer cells can continue to live and proliferate by exploiting the microenvironment around them to their advantage and begin to prevent the survival of other healthy cells (Aponte & Caicedo, 2017).

Chemotherapeutic agents continue to be an important key point in the treatment of cancer at the cellular level (Tilsed, Fisher, Nowak, Lake, & Lesterhuis, 2022). In general, classical chemotherapeutics can be classified as alkylating agents that cause DNA damage (Chu & Rubin, 2018), antimetabolites that inhibit DNA or RNA synthesis (Devita, Lawrence, & Rosenberg, 2008), topoisomerase inhibitors that disrupt DNA topology (Tewey, Rowe, Yang, Halligan, & Liu, 1984), and tubulin inhibitors that disrupt cellular functions (Schiff, Fant, & Horwitz, 1979). However, countless studies have been conducted on the agents that cause DNA-induced cellular death, which also cause serious side effects in healthy cells, and efforts are still being made to develop agents with low side effects (Swift & Golsteyn, 2014). Therefore, the development of targeted and minimally adverse chemotherapeutic agents is of vital importance in modern cancer treatment. Based on these findings, in this review, we focused on the treatment of cancer at the cellular level, specifically tubulin-targeted inhibitors.

Tubulin and microtubular cycle

Tubulin is a vital component of the eukaryotic cytoskeleton and microtubules in living cells. Alpha and beta tubulin, the main structures of tubulin proteins, polymerize and build microtubules that are involved in many cellular functions (Moore & Sarah, 2020). A single microtubule with a diameter of 25 nm is formed by the lateral combination of 13 end-to-end protofilaments, and when it reaches a specific concentration,

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the heterodimerization and subsequent polymerization process begins (Kaur, Kaur, Gill, Soni, & Bariwal, 2014). In addition, microtubules exhibit dynamic stability, constantly transitioning between periods of growth and shrinkage. The polymerization process of α and β-tubulins in microtubules, which hydrolyse GTP to GDP, undergoes depolymerization with GDP, causing the cycle to repeat (Figure 1) (Sontag, Staley, & Ericson, 2005; Akhmanova & Steinmetz, 2008). In addition to its important role in many cellular processes, such as protection of the cellular structure, intracellular transport, and signal transduction, it plays an important role in cell division. Disruption of this cycle makes microtubules an important target in anticancer drug research (Howard & Hyman, 2003).

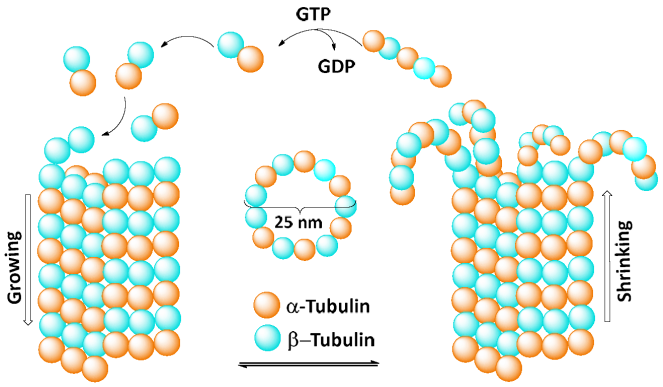

Figure 1. Cycle of microtubule; polymerization and depolymerization

Disruption of the polymerization-depolymerization dynamics of microtubules by various agents causes mitotic cell arrest and subsequent apoptosis (Jordan & Wilson, 2004). These agents target three binding sites in tubulin: taxane, vinca, and colchicine (Nogales, Whittaker, Milligan, & Downing, 1999; Ravelli et al., 2004). Among these agents, agents targeting the taxane binding site inhibit depolymerization, while agents targeting the vinca or colchicine binding site inhibit polymerization (Dumontet & Jordan, 2010). Although taxane and vinca alkaloids are highly effective, they have a complex structure that is difficult to synthesize, generally have poor bioavailability, and resistance to such ligands in cancer cells has focused research on the colchicine binding site (Li et al., 2015).

Colchicine binding site for inhibition of microtubule polymerization

The colchicine binding site consisted of a deep hydrophobic pocket located at the dimerized internal interface between α-tubulin and β-tubulin (Figure 2) (Gou, Li, Guo, & Zhen, 2019). The hydrophobic nature of the colchicine binding site has enabled the development of new tubulin inhibitors with colchicine-like hydrophobic properties.

The structure of colchicine (**1**) is less complex in terms of synthesis, allowing colchicine and its derived ligands to advance to clinical trials for the discovery of antitumor agents (Jordan, 2002). However, although the narrow therapeutic window of colchicine towards this target has enabled the development of some colchicine prodrugs, the short half-life of colchicine-based prodrugs and serious side effects, such as cardiotoxicity, have caused them to be withdrawn from clinical use (Lu, Chen, Xiao, Li, & Miller, 2012; Field, Kanakkanthara, & Miller, 2014; Lippert, 2007).

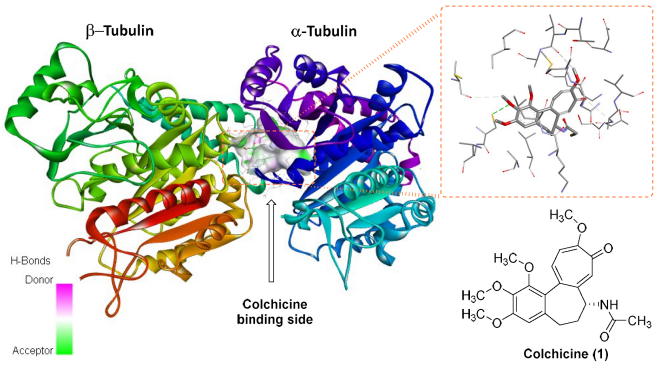

Figure 2. Colchicine binding site and colchicine structure located between α-tubulin and β-tubulin (Pdb code:1SA0)

Natural compounds targeting the colchicine binding site include steganacin (**2**), podophyllotoxin (**3**), and combretastatin (**CA-1** and **CA-4**), which are important antitumor compounds bearing bi-aryl groups like colchicine (Figure 3). Among these, the simple chemical structure and strong anti-tubulin cytotoxic effects of combretastatin derivatives are particularly interesting. However, the poor aqueous solubility, low bioavailability, and short biological life of combretastatin derivatives have led to studies on the development of new and more stable anti-tubulin ligands (Ohsumi et al., 1998).

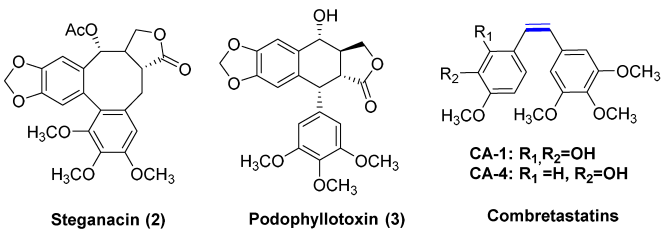

Figure 3. Natural compounds with antitubulin effects that target the binding site of colchicine

The simplicity of its structure and important pharmacological properties makes combretastatin a leading compound in the development of new anti-tubulin inhibitors. In structure-activity studies of combretastatin derivatives, it was determined that the bi-aryl group connected by an ethylenic bridge with a cis configuration provides optimum tubulin inhibition and cytotoxicity (Nam, 2003). This perspective has, over time, allowed the

development of heterocyclic structures such as imidazole (**4**), isoxazole (**5**), oxadiazole (**6**), triazole (**7,8**), and imidazopyridine (**9**) to lock the ethylenic cis configuration between the two aryl rings and to develop additional groups that can interact in the colchicine binding site (Figure 4) (Shan, Zhang, Liu, Wang, & Dong, 2011; Stroylov et al., 2020; Thammathong et al., 2023; Zhang et al., 2007).

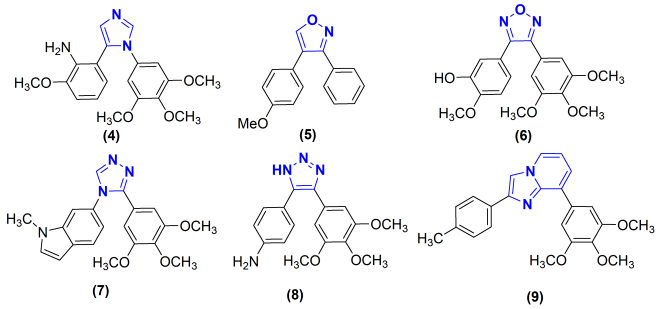

Figure 4. Tubulin polymerization inhibitors with a heterocyclic core bridge

The antitubulin effects of heterocyclic structures other than imidazopyridine on tubulin polymerization has been the subject of many reviews. The remarkable antitubulin and cytotoxic effects of recently developed compounds with an imidazopyridine ring are interesting. Therefore, this review focused on compounds with imidazopyridine rings that target the colchicine binding site for tubulin inhibition. The data to be presented will shed light on various research groups investigating the development of promising imidazopyridine-based anti-tubulin agents.

The privileged structure of imidazo[1,2-a]pyridines

The N-containing heterocyclic imidazopyridine structure, formed by the fusion of imidazole and pyridine rings, has attracted great attention in the field of medicinal chemistry due to its unique pharmacological properties. It is known that the imidazopyridine ring has major antiprotozoal, antibacterial, antifungal, antiviral, anti-inflammatory, hypnoselective, antipyretic, anxioselective, antiapoptotic, and anticancer activities. In fact, it has the main structure of imidazopyridine, which is in many clinical uses. For example, zolpidem (**10**) in the treatment of insomnia, alpidem (**11**), necopidem (**12**), and saripidem (**13**) as anxiolytics, zolimidine (**14**) in the treatment of peptic ulcers, rifaximin (**15**) in the treatment of traveller's diarrhoea, olprinone (**16**) as cardiotonic, miroprofen (**17**) as an analgesic, GSK812396 (**18**) in HIV detection, ND-09759 (**19**), and Q203 (**20**) in antituberculosis treatment have the imidazopyridine pharmacophore structure used in clinical and preclinical trials (Figure 5) (Khatun, Singh, Bader, & Sofi, 2022).

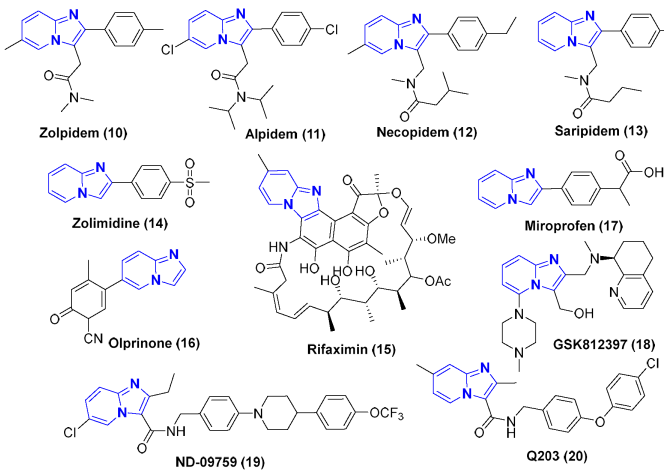

Figure 5. Structures of imidazopyridine derivatives and their candidate compounds

Recent studies have shown that compounds with an imidazopyridine structure can be used as anticancer agents because of their selective effects on various cancer pathways. These imidazopyridine-containing compounds, such as compounds **21** (Kim, Jeong, Lee, Hong, & Hong, 2011) and **22** (Kendall et al., 2007) as angiogenesis and PI3K inhibitors, compounds **23** (Kamal et al., 2010) and **24** (Martínez-Urbina et al., 2010) as CDK inhibitors, compound **25** as a promising agent for glioblastoma (Güçlü et al., 2018), and compound **26** (Xi et al., 2017) as a Nek2 inhibitor, have been reported to act as apoptosis-inducing agents (Figure 6).

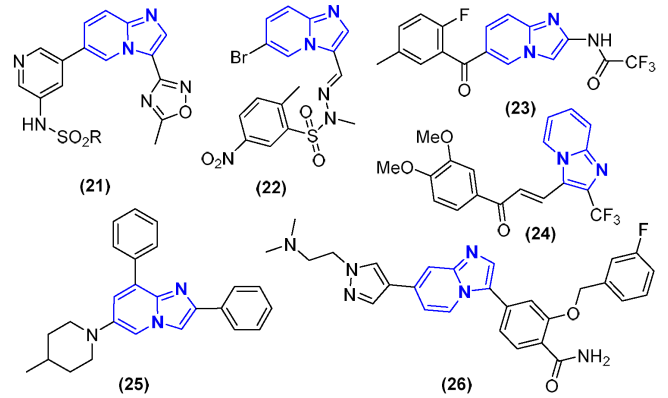

Figure 6. Imidazopyridine derivatives exert antiproliferative effects through various pathways

Efforts to develop different synthetic strategies for this privileged structure of imidazo[1,2-a]pyridines have been investigated, and various approaches have been adopted for this purpose. These can be classified into some subcategories, such as condensation, multicomponent, oxidative coupling, tandem reaction, and hydroamination reaction, and Figure 7 provides a

summary of the synthesis of imidazopyridine (Bagdi, Santra, Monir, & Hajra, 2015).

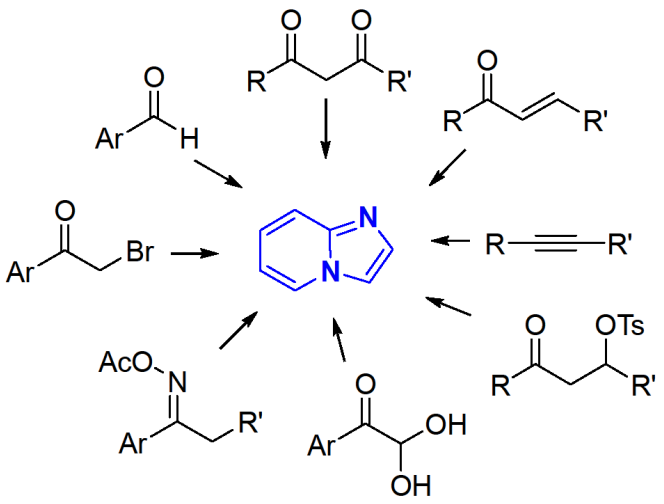

Figure 7. Synthesis of imidazo[1,2-a]pyridines from basic chemicals.

The unique pharmacological properties of imidazopyridine and their facile synthesis using easily accessible starting reagents intensify research on this ring. In this review, studies on the anticancer potential of imidazopyridine structure through tubulin polymerization inhibition, particularly in recent years, are summarized.

Scaffolds of imidazopyridine as tubulin polymerization inhibitors

In 2007, isoquinoline-linked imidazopyridine derivatives were synthesized using a three-component method, and their cytotoxic effects were examined using the A549 cancer cell line. These derivatives (especially compound **27**) exerted antitumor effects of up to 65% on A549 cancer cells at a concentration of 12.5 µM (Meng et al., 2007). Later, a new type of isoquinoline-fused imidazopyridine derivative was developed in 2011, with the idea that this compound could exert antitumor effects by inhibiting tubulin polymerization. It has been reported that compound **28**, developed as a microtubule-targeting agent, causes conformational changes in tubulin in cancer cells by targeting the colchicine binding site and can inhibit it by binding to tubulin at a concentration of 10.6 µM in a cell-free environment (Zhang et al., 2011). Subsequently, in 2016, a structurally simpler group was developed again based on the imidazopyridine structure, and it was found that compound **29** had higher cytotoxic activity in HeLa cancer cells and higher tubulin polymerization inhibition (IC_{50}: 3.41 µM) than colchicine (IC_{50}: 3.79 µM) (An et al., 2016) (Figure 8).

In another study in 2013, oxindole-linked imidazopyridine derivatives were designed and synthesized to investigate their

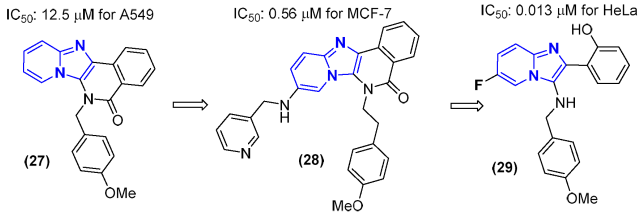

Figure 8. Development of tubulin polymerization inhibitors based on isoquinoline-fused imidazopyridine

cytotoxic effects on breast cancer cell lines. Among the synthesized series, compound **30** was observed to have a potential anticancer effect at an IC_{50}: 0.6 µM concentration and it arrested MCF-7 cells in the G2/M phase. Additionally, compound **30** inhibited tubulin polymerization comparable to that of colchicine, and SAR and molecular docking studies also showed that compound **30** targets the colchicine binding site (Kamal et al., 2013) (Figure 9).

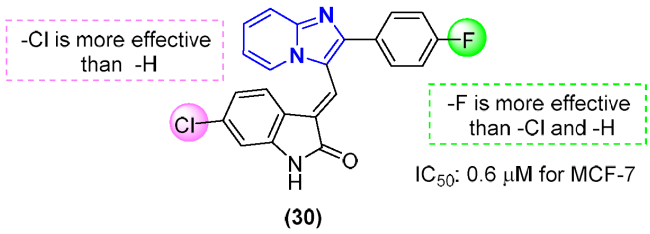

Figure 9. Oxindole-linked imidazopyridine derivatives for tubulin polymerization inhibition

In 2014, imidazopyridine-benzimidazole hybrid compounds were designed and synthesized for tubulin polymerization. The synthesized compounds were found to be effective in large-scale cancer cell line studies, especially in leukaemia, lung, colon, central nervous system, melanoma, ovarian, renal, prostate, and breast cancer cells. Among the molecules, compound **31** was found to have the highest antiproliferative effect with IC_{50}: 0.43-7.73 µM concentration in the tested cell lines. Additionally, compound **31**, which inhibits tubulin polymerization at IC_{50}: 1.75 µM concentration, was found to arrest MCF-7 cells in the G2/M phase, inducing apoptosis. It has been reported that **31**, which targets the colchicine binding site in molecular docking studies, can also inhibit the PI3K/Akt pathway (Kamal et al., 2014) (Figure 10).

In another study in 2014, 2-aryl-3-arylamino-imidazopyridine derivatives were designed as tubulin polymerization inhibitors based on the CA-4 structure, and their effects on ex vivo tubulin polymerization were examined. Among the compounds understood to disrupt tubulin microtubule dynamics, compound **32** inhibited tubulin polymerization with IC_{50}: 12 µM concentration (IC_{50} for CA-4: 9 µM). It was determined that its cytotoxic effect on kidney cancer (HEK 293T) caused 50% cell death at 10 µM

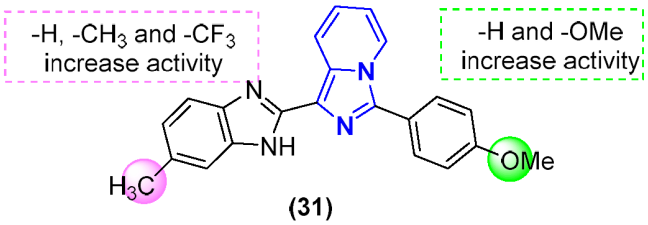

Figure 10. Benzimidazole-linked imidazopyridine derivatives for tubulin inhibition

concentration and had a lower cytotoxic effect on healthy Vero cells. In cell cycle analysis, compound **32**, which arrested HEK-93T cells in the G2/M phase, triggered apoptotic cell death and targeted the colchicine binding site via molecular docking studies (Figure 11) (Sanghai et al., 2014).

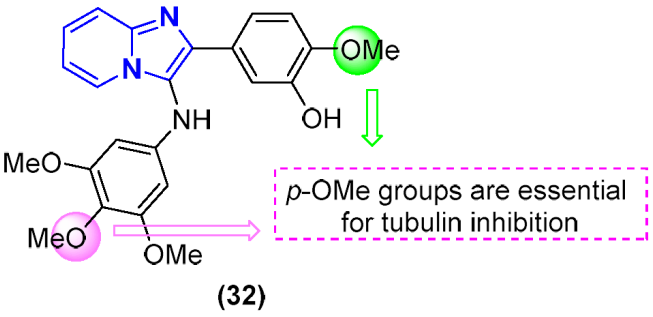

Figure 11. CA-4-inspired imidazopyridine derivatives inhibit tubulin growth

In a study conducted in 2015, a series of imidazopyridine-benzimidazole hybrid compounds were designed and synthesized, based on nocodazole with a benzimidazole structure, which is a colchicine binding site-targeted tubulin polymerization inhibitor. In the results of the cytotoxic effect of the synthesized compounds on the A-549 (lung), Hela (cervical), DU-145 (prostate), and B-16 (melanoma) cancer cell lines, compound **33** targeted the A549 cancer cell line with an IC_{50}: 1.48 µM concentration. In the cell cycle analysis of the A549 cell line, compound **33** arrested the cells in the G2/M phase. Compound **33**, which was found to trigger apoptotic cell death in advanced cell culture applications, inhibited tubulin polymerization at a concentration of 2.06 µM. In molecular modelling studies, it has been emphasized that compound **33**, which exhibits high binding affinity to the colchicine binding site, may be a potential anticancer agent (Kamal et al., 2015) (Figure 12).

A series of imidazopyridine-propenone conjugates for tubulin polymerization inhibition were designed and synthesized in 2017. The cytotoxic effects of the synthesized compounds on prostate (DU-145), lung (A549), cervical (Hela), and breast (MCF-7) cancer cell lines were examined, and compound **34** was found to have a significant cytotoxic effect on the A549 cancer cell line (IC_{50}: 0.86 µM). Flow cytometry analysis showed

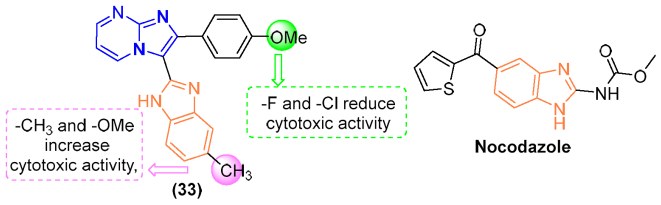

Figure 12. Nocodazol-inspired imidazopyridine/pyrimidine derivatives inhibit tubulin growth

that compound **34** arrested cancer cells in the G2/M phase by inhibiting tubulin polymerization (IC_{50}: 1.82 µM). Additionally, compound **34** was found to induce apoptosis in Hoechst staining and Annexin V-FITC assays and was also found to target the colchicine binding site via molecular dynamics studies. Therefore, it has been reported that the developed imidazopyridine derivatives may be new anticancer agents that inhibit microtubules (Sayeed, Nayak, Shareef, Chouhan, & Kamal, 2017) (Figure 13).

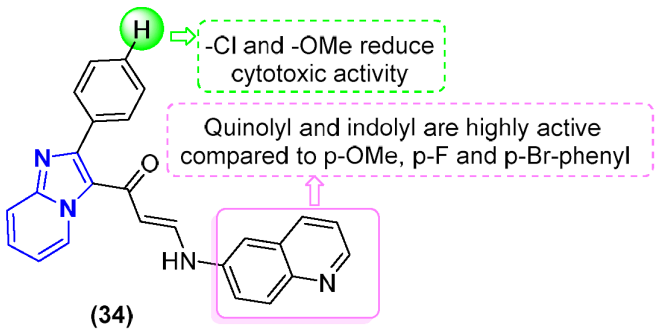

Figure 13. imidazopyridine-propenone conjugates for tubulin inhibition

In 2017, carbonitrile-substituted imidazopyridine derivatives targeting the colchicine binding site were designed based on the CA-4 structure. First, cytotoxic activity studies were conducted by synthesizing derivatives with 2,3,4-trimethoxyphenyl groups, and compound **35** was determined to be the most potent compound in terms of structure–activity relationship. Based on the structure–activity relationship results, a series of indolyl-containing imidazopyridine derivatives were synthesized using the biosterism approach. The cytotoxic effects of the compounds on five different cancer cell lines (HT-29, H460, A549, MKN-45, and SMMC-7721) were examined. The most potent compound **36** exhibited remarkable cytotoxic effects with IC_{50} values of 0.01 µM, 0.04 µM, 0.54 µM, 2.4 µM, and 5.6 µM, respectively. Immunofluorescence studies showed that the compound competitively targets the colchicine-binding site, and the compound was found to indeed target the colchicine-binding site in *in silico* studies (Liu et al., 2017) (Figure 14).

In another study, a series of triazole-linked imidazopyridine derivatives were designed and synthesized in 2018. The cytotoxic effects of the compounds on prostate (DU-145), lung

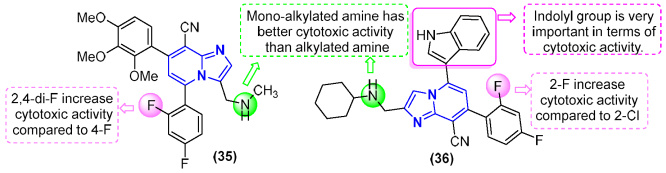

Figure 14. Carbonitrile-substituted imidazopyridine derivatives for tubulin polymerization inhibition

(A549), HCT-116 (Colon), and breast (MCF-7) cancer cell lines were examined, and compound **37** was found to have an IC_{50}: 0.51 µM value in the A549 cancer cell line. In flow cytometry analysis, it was emphasized that it causes cell death through apoptosis by arresting cells in the G2/M phase. Additionally, in immunocytochemistry studies, compound **37** was found to inhibit the polymerization of microtubules with a nocodazole-like effect (Sayeed, Vishnuvardhan, Nagarajan, Kantevari, & Kamal, 2018) (Figure 15).

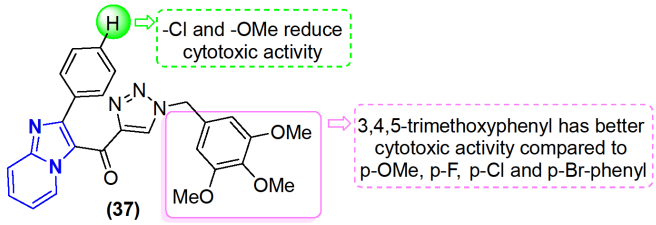

Figure 15. Imidazopyridine-linked triazoles as tubulin inhibitors

In 2018, new compounds with curcumin-inspired imidazopyridine structures were reported to be potential anticancer agents as tubulin polymerization inhibitors. Their antiproliferative effects on cancer cell lines were tested using the MTT assay. Compounds are effective against cervical cancer (HeLa), gastric cancer (HGC-27), lung cancer (NCI-H460), prostate cancer (DU-145 and PC-3), and breast cancer (4T1) compared with normal human prostate (RWPE-1) cells. The results showed that compound 38 was the highest antiproliferative agent in PC-3, HGC-27, and HeLa (IC_{50}: 2.11 ± 0.27 µM, 2.21 ± 0.25 µM, 2.53 ± 0.01 µM respectively). Additionally, compound **38** was found to be effective in the G2/M phase in PC3 cells and inhibited tubulin polymerization with IC_{50}: 8.44 µM. Additionally, molecular docking results confirmed that compound **38** targets the colchicine binding site (Ramya et al., 2018) (Figure 16).

In a study conducted in 2021, oxadiazole-linked imidazopyridine derivatives were designed as tubulin polymerization inhibitors, and their antiproliferative activities were examined in lung cancer (A549) and prostate cancer (PC-3, DU-145) cell lines. Among the compounds, compound **39** showed very high cytotoxicity with an IC_{50} value of 2.8 µM in the A549 cell line and arrested A549 cancer cells in the G2/M phase. Additionally, compound **39** was observed to inhibit tubulin polymerization (IC_{50} 3.45 µM). Molecular modelling studies have determined

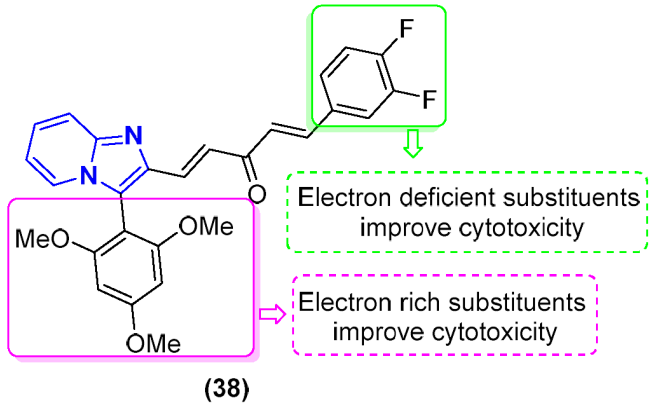

Figure 16. Curcumin-inspired imidazopyridine derivatives inhibit tubulin growth

that the compound has a high binding affinity in the α/β-tubulin active site (Sigalapalli et al., 2021) (Figure 17).

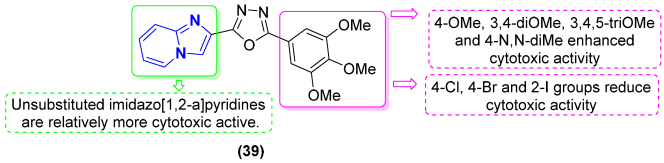

Figure 17. Oxadiazole-linked imidazopyridine derivatives for tubulin inhibition

In a study conducted in 2022, by performing structure-based virtual screening for microtubule-targeted ligands, it was determined that 1000 ligand molecules matched according to colchicine binding site-targeted pharmacophore groups. 2746 of these compounds were eliminated by the docking method, 99 were determined to be antitubulin targeted, and 13 were able to exceed toxicological risks. The cytotoxic effects of 13 related compounds (MCF-7, MDA-231 and A549) on cancer cells were examined, and compound **40** was determined to have very high cytotoxicity ($IC_{50} \leq 20$ µM). Interestingly, among these compounds, only the imidazopyridine-containing compound was determined to be the highest tubulin polymerization inhibitor (IC_{50}: 6.1 uM). It was determined that compound 40, which was determined to arrest MCF-7 cells in the G2/M phase in cell cycle analysis, actually targets the colchicine binding site in molecular docking and dynamic studies. The synthesizability of the target compounds was also investigated. Based on the SAR analysis results of compound **40**, a new tubulin polymerization inhibitor compound **41** containing pyrimidine was synthesized and found to be a tubulin polymerization inhibitor from the molecular dynamics results (Elseginy, Oliveira, Shoemark, & Sessions, 2022) (Figure 18).

In a study conducted in 2023, novel N-imidazopyridine-noscapine derivative anti-tubulin agents with high affinity for the colchicine binding site were designed using *in silico* meth-

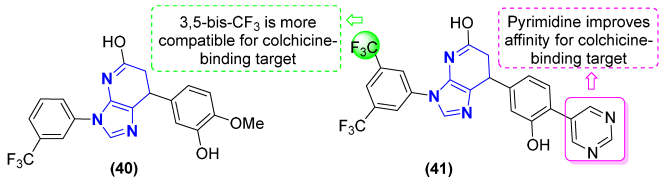

Figure 18. Imidazopyridine scaffolds were prepared via virtual screening and docking for tubulin inhibition

ods. Among the designed and synthesized compounds, compound **42** was found to have very high antiproliferative activity in MCF-7 and MDA-MD-231 breast cancer cell lines (IC_{50} value is 5.26 µM against MCF-7 and 7.78 µM against MDA-MB-231) and had no cytotoxic effect on healthy cells (IC_{50}: 1510.4 µM for HEK cell line). It was determined that compound **42** arrested the MDA-MD-231 breast cancer cell line in the G2/M phase and dramatically reduced the solid tumour without damaging any organs in the *in vivo* model (Pragyandipta et al., 2023) (Figure 19).

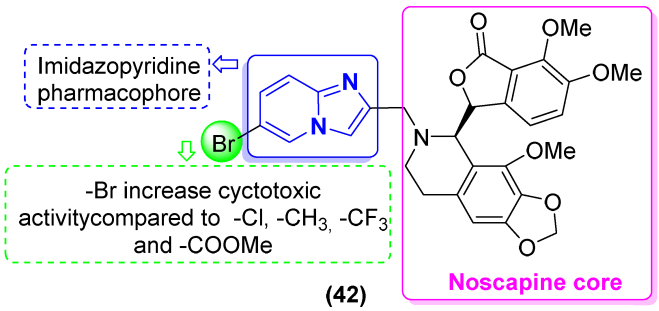

Figure 19. Imidazopyridine-noscapinoids for tubulin inhibition

CONCLUSION

Microtubules are a promising target for developing potent anticancer drug candidates. Inhibition of the tubulin cycle, which is involved in many cellular processes, enables the development of safe drug candidates with lower toxicological risks. Targeting the colchicine-binding site in tubulin targets and even developing simpler chemical structures than colchicine and combretastatin for this target could create potential anticancer drug candidates. Based on the crystal structure of tubulin, it is now easier to design selective synthetic compounds for tubulin inhibition. Highly effective antiproliferative agents have been developed with various cyclic and heterocyclic molecular modifications, such as substituted phenyl, indole, quinoline, and benzimidazole, which have been developed for the colchicine binding site. However, due to the unique pharmacophore feature of the imidazopyridine structure for the colchicine binding site, there is no doubt that even more effective tubulin polymerization inhibitors can be achieved with various molecular modifications of this compound.

Based on the imidazopyridine structure we present here, various tubulin polymerization inhibitors developed to date have been investigated in detail in terms of structure–activity relationship and summarized under four main headings. Imidazopyridine ring; 1st: The unsubstituted form of positions 5, 6, 7, and 8 is an effective pharmacophore group; 2nd: the 2-position should be phenyl or phenyl with electron-donating groups; 3rd: The 3-position must contain a sp^2 hybridized atom or a directly bonded cyclic or heterocyclic group; 4th: It can be said that heteroaryl groups, especially heterobicyclic groups, are more effective (Figure 20).

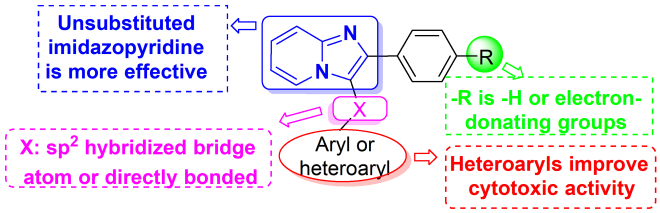

Figure 20. Structure–activity relationship of the imidazopyridine scaffold as a tubulin inhibitor

Together with all these suggestions, this article provides insights for the innovative design of new imidazopyridine-based antitubulin agents with increased efficacy, specificity, safety, and openness to discovery. Moreover, the imidazopyridine structure is a promising pharmacophore for tubulin polymerization and may serve as a potential lead for the synthesis of clinically important candidates in the near future.

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