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Imidazole Analogues as Potent Anticancer in Recent Pharmaceutical Research

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ABSTRACT: Heterocyclic rings containing nitrogen are frequently found as structural elements in pharmaceuticals that are sold. Imidazole/fused imidazole rings are among these heterocycles and can be found in a variety of bioactive substances. Imidazole- and fused imidazole-containing compounds are reported to exhibit a broad range of biological activities. These structures interact with a variety of biomolecules due to their unique properties, which include high polarity and the capacity to engage in hydrogen bonding and coordination chemistry. The studies on imidazole/fused imidazole derivatives as anticancer drugs that have been published in the peer-reviewed literature between 2018 and 2020 are compiled in this review. Microtubules, tyrosine and serine-threonine kinases, histone deacetylases, the p53-Murine Double Minute 2 (MDM2) protein, poly (ADP-ribose) polymerase (PARP), G-quadraplexes, and other targets have all been demonstrated to be modulated by such molecules.
.Important aspects of structure-activity connections are also discussed, along with imidazole-containing drugs that exhibit anticancer action through unclear or unknown mechanisms. This review aims to stimulate the design and synthesis of new anticancer compounds while offering a summary of recent developments in imidazole-based anticancer medication discovery and development.

KEYWORDS: imidazole, benzimidazole, purine, anticancer, antimicrotubule, kinase inhibitor

I. INTRODUCTION

According to the 2020 World Cancer Report, slightly over 18 million new cases of cancer and nearly 10 million cancer-related deaths occurred across the globe in 2018 [1]. Cancer is also the first or second leading cause of premature death in people of ages 30–69 in most countries worldwide. It is characterized by uncontrolled cell growth which may spread to other parts of the body (known as metastasis) and invade other tissues. Although prevention efforts are critical to limit cancer incidence, the treatment of cancer often involves pharmacologic intervention. Cytotoxic chemotherapeutic agents continue to play an important role in cancer pharmacotherapy, but discovery efforts have increasingly turned to targeted therapies (drugs interfering with processes unique to the proliferation and spread of cancer cells) and immunotherapy (boosting the immune system or changing how the immune system works) as effective and less toxic forms of pharmacotherapy for cancer [2,3]. While numerous anticancer drugs are available, many forms remain difficult to cure, resulting in the mortality rates mentioned above. The toxicity, rapid development of resistance, and limited efficacy associated with currently available anticancer agents highlight the urgency to discover new compounds that can overcome the limitations of existing drugs [4].

An analysis of U.S. FDA approved drugs revealed that 59% of these small-molecule agents include nitrogen-containing heterocycles [5]. Imidazole is among the top ten and fused imidazoles (benzimidazole and imidazopyrimidine (purine)) are among the top 25 most frequently appearing nitrogen heterocycles in such small molecule drugs [5]. These ring systems are key components of structural scaffolds occurring in modern medicinal chemistry, thus forming critical building blocks for new drug design. Compounds containing an imidazole ring display a wide range of pharmacological activities including anticancer [6], antibacterial [7], antiviral [8], antiepileptic [9], antitubercular [10], and antifungal activities [11]. A range of anticancer drugs, such as dacarbazine (**1**), bendamustine hydrochloride (**2**), fludarabine phosphate (**3**), nilotinib (**4**), and ponatinib (**5**), contain imidazole and fused imidazole as structural components (see Figure 1). Many biological targets have been investigated and identified for imidazole and fused imidazole derivatives through which they are thought to exhibit their anticancer activities.

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These proposed targets include tubulin/microtubules, a range of kinases, histone deacetylases and other proteins that regulate gene expression, and additional targets as detailed in this review article.

The planar five-member ring system imidazole (1,3-diaza-2,4-cyclopentadiene) has three carbon and two nitrogen atoms in positions one and three. Imidazole itself is the most basic member of the imidazole family; its chemical formula is C3H4N2. The compound's systemic name is 1, 3 diazole; one of the annular N atoms in it bears a H atom and can be recognized as a type N pyrole. Water and other polar solvents can dissolve it. Because the hydrogen atom can be found on either of the two nitrogen atoms, it can exist in two equivalent tautomeric forms. A computed dipole of 3.61D indicates that imidazole is a strongly polar molecule that is completely soluble in water.

The molecule is categorized as aromatic because it has a sextet of π-electrons, which are made up of one electron from each of the four remaining ring atoms and two from the protonated nitrogen atom.Because imidazole is amphoteric, it can act as a base as well as an acid. Imidazole has a pKa of 14.5, which makes it slightly more acidic than alcohols but less acidic than carboxylic acids, phenols, and other imides. On N-1 is where the acidic proton is found.

Since the conjugate acid's pKa (shown above as pKBH + to distinguish between the two) is roughly 7, imidazole is roughly sixty times more basic than pyridine as a base. N-3 is the fundamental location.Numerous significant biological compounds contain imidazole. The most common is histidine, an amino acid with an imidazole side chain. Histidine is an essential component of many proteins and enzymes and is essential to hemoglobin's structure and binding properties. Histamine, another widely occurring biological molecule, can be produced by decarboxylating histidine. Imidazole has several uses, including the purification of proteins with His tags using immobilized metal affinity chromatography (IMAC). Imidazole is now a crucial component in numerous therapeutic products. Numerous fungicides, antifungal, antiprotozoal, and antihypertensive drugs contain synthetic imidazoles. Theophylline, a chemical included in coffee beans and tea leaves that activates the central nervous system, includes imidazole.

In addition to being used in medicine, imidazole has a variety of industrial uses. It is widely employed as a corrosion inhibitor on some transition metals, including copper. It is crucial to stop copper corrosion, particularly in aqueous environments where corrosion reduces copper's conductivity. Imidazole derivatives are present in a wide range of substances that are significant to industry and technology. As a fire retardant, imidazole is fused to a benzene ring and connected to benzene in the thermostablepolybenzimidazole (PBI). Additionally, imidazole is included in a number of chemicals used in electronics and photography. This review primarily highlights the imidazole moiety's pharmacological significance.It was discovered that compared to gastrointestinal parasites, imidazole is less responsive to extraintestinal parasites, specifically intravascular and intestinal resident parasites. In similar settings, the activity against developing phases is better than that against arrested or adult stages. The inhibition of hatching and larval development occurs at sub-effective concentrations when compared to adult in vivo. Compared to those used for controlling cestodes and trematodes, less are needed to achieve efficacy against nematodes. It takes more than one treatment or a greater dosage of medication to control trematodes or cestodes.

The member of class (2-alkyl benzimidazole) has been found to remove various species of nematodes and trematodes from different hosts. 4, 5, 6, 7-tetra chloro-2-trifluoromethyl benzimidazole show high activity against the nematodes Ancylostomacaninum, Haemonchuscontrtus, ascarissuum and trimatodes Fasciola hepaticaseveral 2-5 disubstitutedbenzimidazole, with proven potentials to kill various species of intestinal nematodes have also been found to posses activity against cestodiasis of man and animal. Mebendazole at the dose of 100 mg/kg cure patient suffering with T. Solium and T. Saginata.

II. LUNG CANCER

Lung cancer (both small cell and non-small cell) is the second most common cancer in both men and women in the United States (not counting skin cancer). In men, prostate cancer is more common, while breast cancer is more common in women.The American Cancer Society's estimates for lung cancer in the US for 2024 are:

- About 234,580 new cases of lung cancer (116,310 in men and 118,270 in women)
- About 125,070 deaths from lung cancer (65,790 in men and 59,280 in women)

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Lung cancer mainly occurs in older people. Most people diagnosed with lung cancer are 65 or older; a very small number of people diagnosed are younger than 45. The average age of people when diagnosed is about 70.Lung cancer is by far the leading cause of cancer death in the US, accounting for about 1 in 5 of all cancer deaths. Each year, more people die of lung cancer than of colon, breast, and prostate cancers combined.On a positive note, the number of new lung cancer cases continues to decrease, partly because more people are quitting smoking (or not starting). The number of deaths from lung cancer continues to drop as well, due to fewer people smoking and advances in early detection and treatment.Overall, the chance that a man will develop lung cancer in his lifetime is about 1 in 16; for a woman, the risk is about 1 in 17. These numbers include both people who smoke and those who don't smoke. For people who smoke, the risk is much higher, while for those who don't, the risk is lower.

- Black men are about 12% more likely to develop lung cancer than White men. The rate is about 16% lower in Black women than in White women.
- Black and White women have lower rates than men, but the gap is closing. The lung cancer rate has been dropping among men over the past few decades, but only for about the past decade in women.
- Despite their overall risk of lung cancer being higher, Black men are **less** likely to develop SCLC than White men.

Statistics on survival in people with lung cancer vary depending on the type of lung cancer, the stage (extent) of the cancer when it is diagnosed, and other factors. For survival statistics, see Lung Cancer Survival Rates.Early medical attention is crucial to preventing major health consequences. The course of treatment is determined by the patient's medical history and the disease's stage. Small cell carcinoma (SCLC) and non-small cell carcinoma (NSCLC) are the two most prevalent forms of lung cancer. While SCLC is less prevalent yet frequently grows swiftly, NSCLC is more common and grows slowly. Lung cancer is a major cause of death worldwide and a major public health problem. Lung cancer continues to be the most common cause of cancer-related death, accounting for 1.8 million deaths (18%) in 2020, according to the International Agency for Research on Cancer's (IARC) GLOBOCAN 2020 estimates of cancer incidence and mortality.

III. BREAST CANCER

Breast cancer is the most common cancer in women in the United States, except for skin cancers. It accounts for about 30% (or 1 in 3) of all new female cancers each year.The American Cancer Society's estimates for breast cancer in the United States for 2024 are:

- About 310,720 new cases of invasive breast cancer will be diagnosed in women.
- About 56,500 new cases of ductal carcinoma in situ (DCIS) will be diagnosed.
- About 42,250 women will die from breast cancer.

Breast cancer mainly occurs in middle-aged and older women. The median age at the time of breast cancer diagnosis is 62. This means half of the women who developed breast cancer are 62 years of age or younger when they are diagnosed. A very small number of women diagnosed with breast cancer are younger than 45.

Breast cancer is the second leading cause of cancer death in women. (Only lung cancer kills more women each year.) The chance that a woman will die from breast cancer is about 1 in 40 (about 2.5%).

Breast cancer death rates have been decreasing steadily since 1989, for an overall decline of 42% through 2021. The decrease in death rates is believed to be the result of finding breast cancer earlier through screening and increased awareness, as well as better treatments. However, the decline has slowed slightly in recent years.

Some variations in breast cancer can be seen in racial and ethnic groups. For example:

- The median age at diagnosis is slightly younger for Black women (60 years old) compared to White women (64 years old).
- Black women have the highest death rate from breast cancer. This is thought to be partially because Black women have have a higher risk of triple-negative breast cancer - more than any other racial or ethnic group.
- At every age, Black women are more likely to die from breast cancer than any other race or ethnic group.
- White, Asian, and Pacific Islander women are more likely to be diagnosed with localized breast cancer than Black, Hispanic, American Indian, and Alaska Native women.
- Asian and Pacific Islander women have the lowest death rate from breast cancer.

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The illness known as breast cancer is caused by aberrant breast cells that proliferate and develop into tumors. Tumors have the potential to spread throughout the body and become lethal if ignored. The milk ducts and/or the breast's milk-producing lobules are where breast cancer cells first proliferate. The first kind, known as "in situ," can be identified early on and is not life-threatening. It is possible for cancer cells to invade neighboring breast tissue. Tumors produced by this result in thickening or lumps. Metastasis is the process by which invasive tumors move to neighboring lymph nodes or other organs. Metastasis can be lethal and perhaps fatal.

IV. CERVICAL CANCER

The American Cancer Society's estimates for cervical cancer in the United States for 2024 are:

- About 13,820 new cases of invasive cervical cancer will be diagnosed.
- About 4,360 women will die from cervical cancer.

Cervical pre-cancers are diagnosed far more often than invasive cervical cancer.

Cervical cancer is most frequently diagnosed in women between the ages of 35 and 44, with the average age being 50. It rarely develops in women younger than 20.

Many older women don't realize that they are still at risk of developing cervical cancer as they age. More than 20% of cervical cancers are found in women over 65. However, these cancers rarely occur in women who have been getting regular tests to screen for cervical cancer before they were 65. See Can Cervical Cancer Be Prevented? and Cervical Cancer Screening Tests to learn more about tests used to screen for cervical cancer.

Cervical cancer incidence rates decreased by more than half from the mid-1970s to the mid-2000s, largely because of the increased use of screening, but they have stabilized over the past decade. However, in women ages 30-44, rates have increased 1.7% each year from 2012 to 2019.In contrast, rates declined 11% each year for women ages 20-24, probably reflecting the first signs of cancer prevention from HPV vaccination.

Cervical cancer was once one of the most common causes of cancer death for American women. The cervical cancer death rate has dropped by more than half since the mid-1970s because of prevention and screening, although rates have stabilized in recent years. The death rate in Black women and Native American women is about 65% higher than in White women.

Cervical cancer is the fourth most frequent malignancy in women worldwide; in 2022, there will be over 660 000 new cases. Approximately 94% of the 350 000 cervical cancer-related fatalities that year happened in low- and middle-income nations. South-East Asia, Central America, and sub-Saharan Africa (SSA) have the greatest incidence and fatality rates of cervical cancer. The disparities in access to immunization, screening, and treatment facilities, risk factors like HIV prevalence, and social and economic determinants including sex, gender bias, and poverty are all linked to regional variations in the incidence of cervical cancer. Compared to the general population, women living with HIV are six times more likely to acquire cervical cancer, and an estimated 5% of all incidences of cervical cancer are related to HIV. 20% of children whose mothers die from cancer do so as a result of cervical cancer, which disproportionately affects younger women.

Imidazoles as Tubulin Polymerization Inhibitors

Microtubules are the cylindrical components of the cytoskeleton (composed of α- and β-tubulin heterodimers) which are critical players in various cellular functions including the maintenance of cell shape, cell signaling, vesicular transport, and cell division. Because they are the primary component of the mitotic spindle, microtubules play an important role in the proliferation of cancer cells, thus making microtubules one of the most attractive targets for anticancer drugs (reviewed in reference [30]). Microtubule targeting agents can disrupt the formation of mitotic spindles at the metaphase/anaphase transition, altering tubulin assembly kinetics and causing cell-cycle arrest and apoptotic cell death. Although tubulin targeting compounds, such as taxanes [31], vinca alkaloids [32], and some newer agents, such as ixabepilone [33], are used for the treatment of cancer, multidrug resistance and poor bioavailability associated with these drugs pose challenges, as well as provide motivation, for researchers to identify new microtubule-targeted agents with high efficacy, an acceptable side effect profile, and good bioavailability.

1-Substituted-2-aryl imidazoles were synthesized by Li et al. as potential tubulin-targeted anticancer agents [34]. The target compounds were tested on MDA-MB-468, MDA-MB-231, T47D, HCT-15, HT29, and HeLa cancer cell lines along with a normal human umbilical vein endothelial

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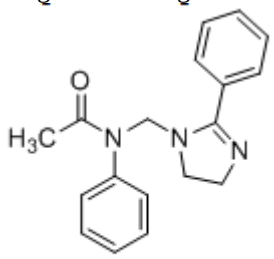
cell line (HUVEC). Many of the compounds possessing an aromatic ring on the imidazole nitrogen atom displayed potent antiproliferative activities with IC_{50} values in the 80–1000 nM range. Among these, compound **6** (see Figure 2 for structures of compounds **6**–**19**) showed the highest potency, with IC_{50} values from 80–200 nM against HCT-15, HT29, HeLa, and MDA-MB-468 cells, while compound **7** exhibited good potency against HeLa and HCT-15 cells (IC_{50} values of 100 and 200 nM, respectively). In terms of the SAR, the placement of an aliphatic group on the imidazole nitrogen and the replacement of imidazole with an amide or ester group led to a loss of activity. Compound **6** was a better inhibitor of porcine brain tubulin polymerization (IC_{50} = 0.4 μM) than either colchicine (IC_{50} = 7.5 μM) or combretastatin A-4 (IC_{50} = 1.1 μM). At its IC_{50} concentration, compound **6** caused arrest of MDA-MB-468 cells in the G_2/M phase of the cell cycle. In an MDA-MB-468 breast cancer xenograft model performed in nude mice, i.p. administration of compound **6** (60 mg/kg every other day for 21 days) suppressed tumor growth by 77% compared to control, without causing obvious weight loss in the animals.

Wang et al. designed novel anticancer compounds based on the clinical drug candidate VERU-111 (**8**) where structural modification of the 3,4,5-trimethoxyphenyl group in this compound led to improved anticancer activity [35]. The authors presented an elegant synthetic approach where 3-methoxybenzo[4,5]-dioxene (a ring system found in the most potent compound) was synthesized using a second-generation Grubbs catalyst via ring closing metathesis. The antiproliferative effects of these compounds were evaluated on A375, M14, and RPMI7951 human melanoma cell lines. Compound **9** (containing a 3-methoxybenzo[4,5]-dioxene ring system) was the most active, with IC_{50} values of 1.1 nM, 1.2 nM and 3.3 nM on A375, M14, and RPMI7951 cell lines, respectively. When the trimethoxyphenyl group present in compound **8** was replaced with 4-methoxybenzo[d][1,3]dioxole, 5-methoxy-2,3-dihydrobenzo[b][1,4]dioxene, or 6-methoxy-3,4-dihydro-2H-benzo[b][1,4]dioxepine, the activity was greatest with the dioxole ring-containing compound and decreased with increasing ring size. Incubation of compound **9** with bovine brain tubulin at a concentration of 10 μM resulted in nearly complete inhibition of tubulin assembly. The X-ray crystal structure of compound **9** bound to the tubulin/stathmin-like domain of RB-3/tubulin tyrosine ligase complex confirmed that **9** binds to the colchicine site on β-tubulin. When given at a dose of 30 mg/kg every other day for 15 days by i.p. injection, compound **9** inhibited tumor growth by 73.9% in an A375 murine melanoma xenograft model without significant weight loss.



1a

Additional work regarding **8** (also known as ABI-231) conducted by Wang et al. reported structure-activity relationship (SAR) studies around the 3-indole moiety of this molecule [36]. Target compounds were screened against the A375, WM164, and M14 human melanoma cell lines. Among these compounds, **10**–**12** displayed the greatest potency, with IC_{50} values ranging from 1.6–8.0 nM against the cancer cell lines tested. In terms of the SAR for 3-indolyl compounds, derivatives bearing bulky groups at the other positions on the indole ring system displayed reduced activity, while substitution with a methyl group at the 4-position of indole (compound **10**) resulted in a marked increase in antiproliferative activity. When the point of attachment to the indole ring system was changed, compounds where trimethoxybenzoyl imidazole was placed at the 4-, 5-, or 6-position of indole displayed superior antiproliferative activity compared to the compound harboring this substitution at the C7 position of indole. Compounds **10**–**12** were tested against the NCI 60 cell line panel and displayed low nanomolar IC_{50} values against most of these cell lines. At a concentration of 10 μM, compounds **10** and **11** completely inhibited the polymerization of purified bovine brain tubulin in vitro. Further, X-ray crystallographic studies verified that the lead compound **8**, as well as compounds **10** and **11**, bind at the colchicine site on tubulin. Intraperitoneal injection of compound **11** (30 mg/kg/day on alternate days for 20 days) resulted in 90.6% tumor growth inhibition in an A375 melanoma xenograft model in nude mice. In a lung metastasis model conducted in C57BL mice, animals treated with 30 mg/kg compound **11** for two weeks (five days per week)

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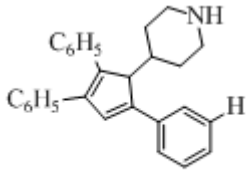
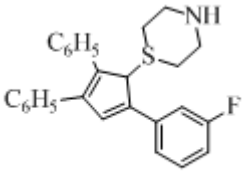
by intraperitoneal injection showed an 80.9% decrease in metastasis. Moreover, in a taxane-resistant PC-3 (PC-3/TxR) mouse model, administration of compound **11** (30 mg/kg) resulted in an 83.8% reduction in tumor growth and 62.8% decrease in the average tumor weight compared to controls.

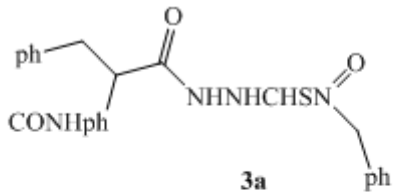


2a



2b

Bai et al. reported on 5-(3,4,5-trimethoxybenzoyl)-4-methyl-2-(p-tolyl) imidazole (BZML, **13**), a compound with potent activity against colorectal cancer cell lines that inhibits tubulin polymerization and causes DNA damage [37]. Compound **13** displayed potent IC_{50} values of 27.42, 23.12, and 33.14 nM against SW480, HCT116, and Caco-2 cells, respectively, while the Caco-2 cell line was insensitive to both paclitaxel and doxorubicin (IC_{50} values > 1800 nM). When tested at a concentration of 60 nM, compound **13** disrupted microtubules in these cell lines as assessed by immunofluorescence microscopy and increased the number of γ-H2AX foci in the cell lines mentioned above, indicating the induction of DNA damage. Moreover, this compound decreased P-glycoprotein (P-gp) expression and enhanced the activity of both doxorubicin and paclitaxel in the Caco-2 cell line at a concentration of 60 nM.



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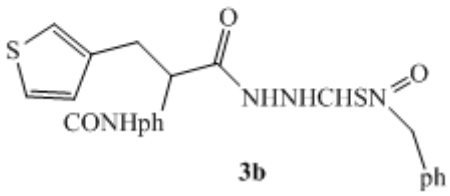

3b

A series of new imidazopyridine-triazole conjugates were reported as potential tubulin polymerization inhibitors and were screened against A549, DU-145, HCT116, and MDA-MB 231 cancer cell lines [38]. Compounds **14** and **15** displayed IC_{50} values of 0.51 and 0.63 µM against the A549 cell line, respectively, and exhibited the greatest potency against the four cancer cell lines overall. At a concentration of 3 µM, compounds **14** and **15** inhibited tubulin polymerization in a fluorescence-based assay by 59% and 56%, respectively, while the standard compound nocodazole displayed 55% inhibition. At 1 µM concentrations, compounds **14** and **15** also caused a dramatic increase in the percentage of A549 cells in the G_2/M phase. Molecules bearing an unsubstituted phenyl ring at the C2 position of the imidazopyridine system generally displayed the greatest potency.

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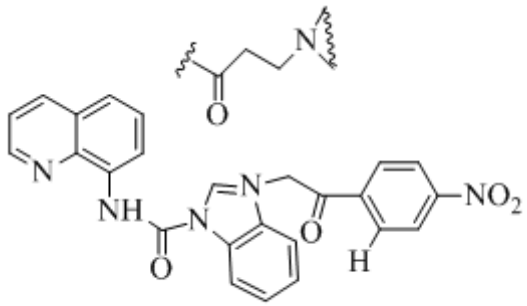
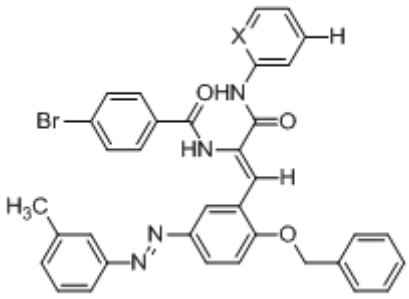


4a

Narasimha Rao et al. synthesized a library of imidazothiadiazole-oxindole conjugates and evaluated their antimicrotubule activity, as well as their antiproliferative activity, against HeLa, MCF-7, and MIAPaCa-2 cancer cell lines and HEK-293 human embryonic kidney cells [39]. Compounds **16**–**19** displayed the greatest activity overall, exhibiting submicromolar or low micromolar GI_{50} values against all three cell lines. When compound **18** was screened against the NCI 60 cancer cell line panel, GI_{50} values below 5.0 µM were observed against most of these cell lines, with the exception of leukemia and colon cancer cells. Compounds **16**, **17**, and **18** were inhibitors of bovine brain tubulin polymerization, displaying IC_{50} values of 5.6, 2.8, and 4.6 µM, respectively. Accumulation of HeLa cells in the G_2/M phase was observed upon incubation with 5 µM concentrations of compounds **16**–**18**, while these compounds activated caspase-3 in HeLa cells at 2 µM concentrations. While the SAR was complex, inclusion of a nitro group either on the oxindole system or on the phenyl ring generally decreased the anticancer activity.



5a

Baig et al. synthesized imidazothiazole-benzimidazole derivatives as potential tubulin polymerization inhibitors and tested their cytotoxicity against HeLa, A549, MCF-7, and DU-145 cancer cell lines [40]. Compound **20** (see Figure 3 for structures of compounds **20**–**32**) exhibited an IC_{50} value of 1.09 µM against the A549 cancer cell line. Analogs bearing a 4-methoxy substitution on the phenyl ring at C6 of the imidazothiazole ring system generally displayed high activity against the A549 cell line, although the substitutions on the benzimidazole ring system at C5 also influenced activity. Compound **20** inhibited porcine tubulin polymerization in a fluorescence-based assay with an IC_{50} value of 1.68 µM, while the IC_{50} value for the standard compound nocodazole was 1.99 µM in this assay. At a concentration of 2 µM, compound **20** caused the accumulation of A549 cells in the G_2/M phase of the cell cycle.

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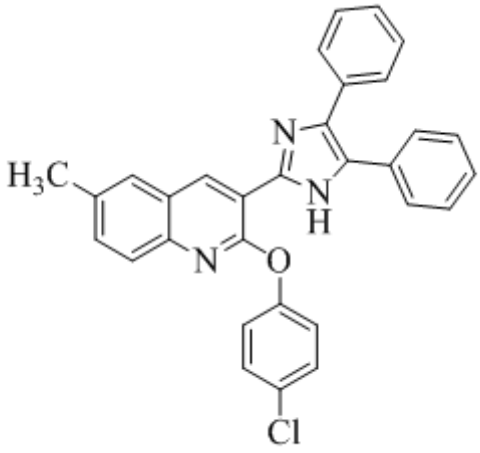

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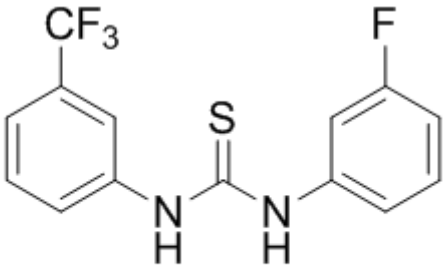

7a

V. CONCLUSION

Cancer is one of the leading causes of mortality worldwide, placing a huge burden on the healthcare system and exacting a staggering human toll. Despite the many drugs available for treatment of various types of cancer, the side effects, resistance profiles, and variable efficacy of these drugs provides the motivation to discover new anticancer compounds. As illustrated in this review article, considerable attention has been devoted to the synthesis and anticancer evaluation of imidazole and fused imidazole derivatives in recent years. This review summarizes the in vitro and in vivo efficacy studies performed with these derivatives, mechanistic studies conducted on these candidates, and the SAR of the series presented. The work recapped here demonstrates that these imidazole-containing derivatives display anticancer activity through a wide range of mechanisms. While it is impossible to predict with certainty the candidates and approaches described in this review that will have the greatest impact on the treatment of cancer, the following future outlook identifies molecules and strategies that appear to be particularly promising to the authors. Although extensive work on antimicrotubule agents as anticancer compounds has been performed in the past, antitubulin candidates related to compound **8** show outstanding efficacy in murine cancer models [35,36], suggesting that compounds with this scaffold may have a future in cancer therapy. At the time of the writing of this review, a phase 3 trial is being planned to evaluate compound **8** for treating metastatic, castration-resistant prostate cancer (ClinicalTrials.gov Identifier: NCT04844749). Kinases are popular drug targets, but there have been selectivity issues due to their structural and sequence similarity. Considering the covalent binding of Nek2 inhibitors **85** and **87** to their putative target

REFERENCES

[1]. Arora, Rashmi, A. Kaur, and N. S. Gill. "Analgesic and anti-inflammatory activity of some newly synthesized novel pyrazole derivatives of benzimidazole." Curr. Res. Chem 4 (2012): 76-87.

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[2]. Azzam, Rasha A., Heba A. Elboshi, and Galal H. Elgemeie. "Synthesis, physicochemical properties and molecular docking of new benzothiazole derivatives as antimicrobial agents targeting DHPS enzyme." Antibiotics 11, no. 12 (2022): 1799.
[3]. Rostamizadeh, Shahnaz, and SA GhHousaini. "Microwave-assisted preparation of 2-substituted benzothiazoles." Phosphorus, Sulfur, and Silicon and the Related Elements 180, no. 5-6 (2005): 1321-1326.
[4]. Patil, Sachin S., and Vivek D. Bobade. "Simple and efficient one-pot synthesis of 2-substituted benzoxazole and benzothiazole." Synthetic communications 40, no. 2 (2009): 206-212.
[5]. Rostamizadeh, Shahnaz, and SA GhHousaini. "Microwave-assisted preparation of 2-substituted benzothiazoles." Phosphorus, Sulfur, and Silicon and the Related Elements 180, no. 5-6 (2005): 1321-1326.
[6]. Patil, Sachin S., and Vivek D. Bobade. "Simple and efficient one-pot synthesis of 2-substituted benzoxazole and benzothiazole." Synthetic communications 40, no. 2 (2009): 206-212.
[7]. Al-Qalaf, Fawzia, Ramadan Ahmed Mekheimer, and Kamal UsefSadek. "Cerium (IV) ammonium nitrate (CAN) catalyzed one-pot synthesis of 2-arylbenzothiazoles." Molecules 13, no. 11 (2008): 2908-2914.
[8]. Guo, Hong Yun, Ji Chao Li, and You Le Shang. "A simple and efficient synthesis of 2-substituted benzothiazolescatalyzed by H2O2/HCl." Chinese Chemical Letters 20, no. 12 (2009): 1408-1410.
[9]. Azarifar, Davood, BehroozMaleki, and MehrnazSetayeshnazar. "A simple, microwave-assisted, and solvent-free synthesis of 2-arylbenzothiazoles by acetic acid–promoted condensation of aldehydes with 2-aminothiophenol in air." Phosphorus, Sulfur, and Silicon 184, no. 8 (2009): 2097-2102.
[10]. Pratap, Umesh R., Jyotirling R. Mali, Dhanaji V. Jawale, and Ramrao A. Mane. "Bakers' yeast catalyzed synthesis of benzothiazoles in an organic medium." Tetrahedron letters 50, no. 12 (2009): 1352-1354.
[11]. Reddy, P., Y. Lin, and H. Chang. "Synthesis of novel benzothiazole compounds with an extended conjugated system." Arkivoc 16 (2007): 113-122.
[12]. ALJAMALI, DR NAGHAM MAHMOOD, HAYDER GHANIM CHFAT, and DR SAHER MAHMOOD JAWD. "Benzothiazol Derivatives (Synthesis, Investigation, Bio-Studying)." International Journal of Pharmaceutical Research 11, no. 1 (2019).
[13]. Boger, Dale L. "A convenient preparation of 2-substituted benzothiazoles." The Journal of Organic Chemistry 43, no. 11 (1978): 2296-2297.
[14]. Tale, R. H. "Novel synthesis of 2-arylbenzothiazoles mediated by ceric ammonium nitrate (CAN)." Organic letters 4, no. 10 (2002): 1641-1642.
[15]. Evindar, Ghotas, and Robert A. Batey. "Parallel synthesis of a library of benzoxazoles and benzothiazoles using ligand-accelerated copper-catalyzedcyclizations of ortho-halobenzanilides." The Journal of Organic Chemistry 71, no. 5 (2006): 1802-1808.
[16]. Rey, Valentina, Silvia M. Soria-Castro, Juan E. Argüello, and Alicia B. Peñéñory. "Photochemical cyclization of thioformanilides by chloranil: An approach to 2-substituted benzothiazoles." Tetrahedron Letters 50, no. 33 (2009): 4720-4723.
[17]. Mu, Xue-Jun, Jian-Ping Zou, Run-Sheng Zeng, and Jun-Chen Wu. "Mn (III)-Promoted cyclization of substituted thioformanilides under microwave irradiation: a new reagent for 2-substituted benzothiazoles." Tetrahedron letters 46, no. 25 (2005): 4345-4347.
[18]. Feng, Enguang, He Huang, Yu Zhou, Deju Ye, Hualiang Jiang, and Hong Liu. "Metal-free synthesis of 2-substituted (N, O, C) benzothiazoles via an intramolecular C− S bond formation." Journal of Combinatorial Chemistry 12, no. 4 (2010): 422-429.