Society of Medical Education & Research

2022, Volume 2, Issue 1, Page No: 1-16


Archive of International Journal of Cancer and Allied Science

# Biological Anticancer Activity of Heterocyclic Compounds: Thiadiazole, Benzimidazole, Quinazoline, and Pyrimidine

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## Abstract

Aromatic heterocyclic compounds with five- and six-membered rings containing heteroatoms such as sulfur (S), oxygen (O), and nitrogen (N) have been widely studied due to their promising pharmacological potential. These compounds are essential for life, and the heteroatoms in the ring structures enhance interactions with amino acids, improving properties such as lipophilicity, solubility, and absorption. These attributes play a key role in reducing transactivation, which in turn boosts the therapeutic activity of these molecules. Among these heterocyclic compounds, derivatives of 1,3,4-thiadiazole, benzimidazole, quinazoline, and pyrimidine have shown a wide range of biological effects, including anticancer, antimicrobial, anti-inflammatory, antidepressant, antioxidant, antifungal, and antibacterial activities, as well as inhibiting carbonic anhydrase and exhibiting anticonvulsant properties. These compounds are crucial in the discovery of new drugs. This review highlights FDA-approved heterocyclic compounds and their contributions to the development of new therapeutic agents. The review specifically examines synthetic derivatives of thiadiazole, benzimidazole, quinazoline, and pyrimidine, emphasizing their remarkable anticancer effects on multiple cancer cell lines.

**Keywords:** Anticancer activity, Thiadiaozle, Quinazoline, Benzimidazole, Pyrimidine

## Introduction

Cancer is a condition caused by genetic or epigenetic modifications in somatic cells, leading to abnormal cell growth and the potential spread of these cells to other parts of the body, classified as a form of neoplasm. The excessive and uncontrolled division of cells forms a mass or lump, known as a tumor or neoplasm, which can also spread throughout the body [1, 2]. Significant advancements have been made over the past two decades in our molecular understanding of cancer, uncovering numerous novel targets for the development of effective therapies, many of which are already in use in clinical settings [3]. However, resistance to current treatments has emerged as a growing global concern, making the development of new therapeutic agents to overcome this resistance one of the foremost areas of research [4]. Heterocyclic compounds are recognized as critical organic molecules in the biological sciences due to their activity in a variety of diseases. These compounds, which feature a heterocyclic ring containing oxygen, nitrogen, or sulfur atoms surrounding a carbon atom, are integral to many biological molecules, including DNA, RNA, chlorophyll, hemoglobin, and vitamins [5]. This review highlights the use of heterocyclic rings such as thiadiazole, benzimidazole, quinazoline, and pyrimidine in the development of anti-cancer drugs. Thiadiazole, a heterocyclic compound with a five-membered ring consisting of two nitrogen atoms and one sulfur atom, is recognized for its wide range of biological activities [6]. The thiadiazole structure is involved in functions such as the “two-electron donor system” and “hydrogen bonding

Access this article online

**Website:** https://smerpub.com/ **E-ISSN: 3108-4834**

**Received:** 27 October 2021; **Revised:** 21 January 2022; **Accepted:** 23 January 2022

**How to cite this article:** Sidat PS, Jaber TMK, Vekaria SR, Mogal AM, Patel AM, Noolvi M. Biological Anticancer Activity of Heterocyclic Compounds: Thiadiazole, Benzimidazole, Quinazoline, and Pyrimidine. Arch Int J Cancer Allied Sci. 2022;2(1):1-16. https://doi.org/10.51847/AX9mZwZEDA

domain" and also acts as a limited pharmacophore [5]. 1,3,4-thiadiazole and its derivatives are characterized by a five-membered ring structure containing two nitrogen atoms and one additional heteroatom. This heterocyclic compound can function as a bio-isosteric replacement for thiazole, demonstrating properties similar to third- and fourth-generation cephalosporins, which makes it useful in antibiotic formulations [7]. Thiadiazole exists in four distinct isomeric forms: 1,2,3-thiadiazole, 1,2,5-thiadiazole, 1,2,4-thiadiazole, and 1,3,4-thiadiazole. Among these, 1,3,4-thiadiazole is particularly important due to its broad biological activity [8]. Specifically, compounds containing the 1,3,4-thiadiazole structure are recognized for their antibacterial [9] and anti-inflammatory [10] properties, highlighting their therapeutic potential. Various derivatives of thiadiazole exhibit a range of noteworthy biological properties, such as analgesic, antimicrobial, anti-tubercular, anti-depressant, antioxidant, anti-convulsant, and anti-fungal activities. In addition, benzimidazole, a heterocyclic compound that combines a benzene ring with an imidazole ring, has attracted significant interest in medicinal chemistry for its diverse biological applications [11]. This bicyclic aromatic structure consists of a six-membered benzene ring fused with a five-membered imidazole ring at the 4- and 5-positions [12]. Benzimidazole's broad therapeutic potential has earned it the title of the "Master Key" in medicinal chemistry due to its extensive biological activity. The nitrogen atoms within its structure make benzimidazole an isosteric analog of nucleobases, which allows it to interact effectively with biomolecular targets, producing a variety of biological responses such as anticancer, anti-inflammatory, anti-ulcer, antifungal, and antibacterial effects. Quinazoline, another significant heterocyclic compound, consists of two fused six-membered rings, benzene, and pyrimidine, and was first synthesized by Gabriel in 1903. Quinazoline exists in several isomeric forms, including quinazoline, quinoxaline, cinnolines, and phtalazines, depending on the positioning of nitrogen atoms [13]. Synthesis methods for quinazoline derivatives are categorized into traditional and modern approaches, such as Aza-reaction, microwave-assisted reactions, metal-catalyzed reactions, ultrasound-promoted reactions, and phase-transfer catalysis [14]. Fused ring structures have garnered significant attention in the field of medicinal chemistry due to their impressive pharmacological and biological properties. Initially, quinazoline compounds were identified for their potential in treating malaria [15], but subsequent research has revealed their broader therapeutic effects, such as anti-cancer, anti-inflammatory, anti-microbial, anti-viral, and anti-hypertensive properties. Pyrimidine, another key heterocyclic compound, consists of a six-membered ring with two nitrogen atoms located at positions 1 and 3. Pyrimidine derivatives, including nucleotides like uracil, thiamine, and cytosine, are often derived from nucleic acid breakdown products [16]. This compound, with the chemical formula C4H4N2, is a colorless substance that melts at 22.5 ℃ and boils at 124 ℃. Synthesis of pyrimidine typically involves the condensation of carbon-based molecules with amidine derivatives, facilitated by catalysts like sodium hydroxide or sodium ethoxide [17]. Given its critical role in forming the backbone of DNA and RNA [18], pyrimidine and its derivatives exhibit a wide range of pharmacological activities. Many biologically active compounds, including natural substances, feature nitrogen- or sulfur-containing heterocyclic rings, such as pyrimidines [19]. Pyrimidine is known for its various biological effects, including anti-microbial, anti-inflammatory, anti-fungal, anti-viral, anti-cancer, anti-malarial, anti-tubercular, and anti-HIV activities. The exploration of these heterocyclic rings, including thiadiazole, benzimidazole, quinazoline, and pyrimidine, lays a strong foundation for discovering novel therapeutic agents. **Table 1** highlights several marketed drugs derived from these structures, which specifically target cancer therapies. This review aims to contribute valuable insights for future research in the synthesis and development of more effective and innovative drugs.

## Results and Discussion

### *Anti-cancer properties of heterocyclic compounds*

#### *Thiadiazole*

In a study by Guan *et al.* [20], several hydroxamic acids derived from 1,3,4-thiadiazole were tested for their ability to inhibit histone deacetylases (HDACs), showing promising results. One particular compound, referred to as compound 1, exhibited an IC50 value of 0.089 μM, demonstrating a stronger inhibitory effect than the commonly used HDAC inhibitor, SAHA, which had an IC50 value of 0.15 μM. These findings highlight the potential of thiadiazole-based compounds in cancer therapy [20].

Matysiak *et al.* [21] explored the antiproliferative effects of various N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole derivatives, including derivatives with alkyl, aryl, and morpholinoalkyl substituents. The compounds were characterized using elemental analysis, infrared spectroscopy, NMR, and mass spectrometry. They were tested against several human cancer cell lines: SW707 (rectal), HCV29T (bladder), A549 (lung), and T47D (breast). Alkyl and morpholinoalkyl derivatives were found to be significantly more effective than phenyl-substituted ones. The compound 2-(2,4-dichlorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole was identified as the most potent, with its ID50 being twice as low as cisplatin in SW707 and T47D cell lines [21].

In another study, Kumar *et al.* [22] synthesized a series of 5-(3-indolyl)-2-substituted-1,3,4-thiadiazole derivatives and tested their cytotoxic effects on six human cancer cell lines. Among these, the indolyl-1,3,4-thiadiazole compound, especially compound 3 (which contains 5-bromo indolyl and 4-benzyloxy-3-methoxyphenyl groups), exhibited the strongest anticancer activity, with an IC50 of 1.5 μM against PaCa2 cells, showing its potential as a therapeutic agent [22].

Polkam *et al.* [23] synthesized a range of 2,5-disubstituted 1,3,4-thiadiazole derivatives and evaluated their antimycobacterial efficacy against *Mycobacterium* smegmatis MC-155. The compounds were also tested for their cytotoxic properties against HT-29 and MDA-MB-231 cancer cell lines, using the MTT assay. The structures of these compounds were confirmed by multiple spectroscopic methods, including 1H NMR, 13C NMR, FT-IR, mass spectrometry, and HRMS. Notably, compounds 5g, 7a, and 9 demonstrated significant cytotoxicity and effective antitubercular activity, with MIC values of 65.74 and 40.86, respectively. Among the tested compounds, compound 4 showed the most potent dual activity against both cancer cells and *Mycobacterium* [23].

Luo and co-authors synthesized a new class of 1,3,4-thiadiazole-linked benzisoselenazolone derivatives by reacting 2-chloroselenobenzoyl chloride with 2-amino-5-substituted-1,3,4-thiadiazole. The compounds were evaluated for their ability to inhibit cell proliferation in SSMC-7721, MCF-7, and A-549 cell lines. The results revealed that compounds 5, 6, and 7 were particularly effective in reducing tumor cell growth in these models [24].

Noolvi *et al.* [25] developed a series of novel 2,6-disubstituted imidazo[2,1-b][1,3,4]thiadiazole derivatives from 5-substituted-1,3,4-thiadiazol-2-amine. These compounds underwent primary cytotoxicity testing at the National Cancer Institute, with two compounds (8) progressing to a broader screening against 60 human tumor cell lines at varying concentrations. The results showed that compound 8, specifically 3-(2-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl) aniline, effectively inhibited the growth of Non-Small Cell Lung Cancer (HOP-92) and Renal Cancer (CAKI-1) cell lines, with GI50 values of 0.114 μM and 0.743 μM, respectively [25].

In a separate study, Terzioglu and Gürsoy [26] synthesized 2,6-dimethyl-N-substituted phenylmethylene-imidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazide derivatives. These compounds were assessed for their cytotoxic activity against multiple human cancer cell lines through the SRB assay. The compound 2,6-Dimethyl-N-(2-hydroxyphenylmethylidene) imidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazide (compound 9) showed remarkable cytotoxicity, with its strongest effects observed in ovarian cancer (OVCAR) cell line, where it recorded a log10 GI50 value of 5.51 during screening against 60 human tumor cell lines [26].

Finally, Yang *et al*. [27] synthesized cinnamic acyl 1,3,4-thiadiazole amide derivatives and evaluated their potential as inhibitors of tubulin polymerization and antiproliferative agents. Among these derivatives, compound 10 demonstrated the most significant activity, inhibiting the growth of MCF-7 and A549 cell lines with IC50 values of 0.28 μg/mL and 0.52 μg/mL, respectively (**Figure 1**).

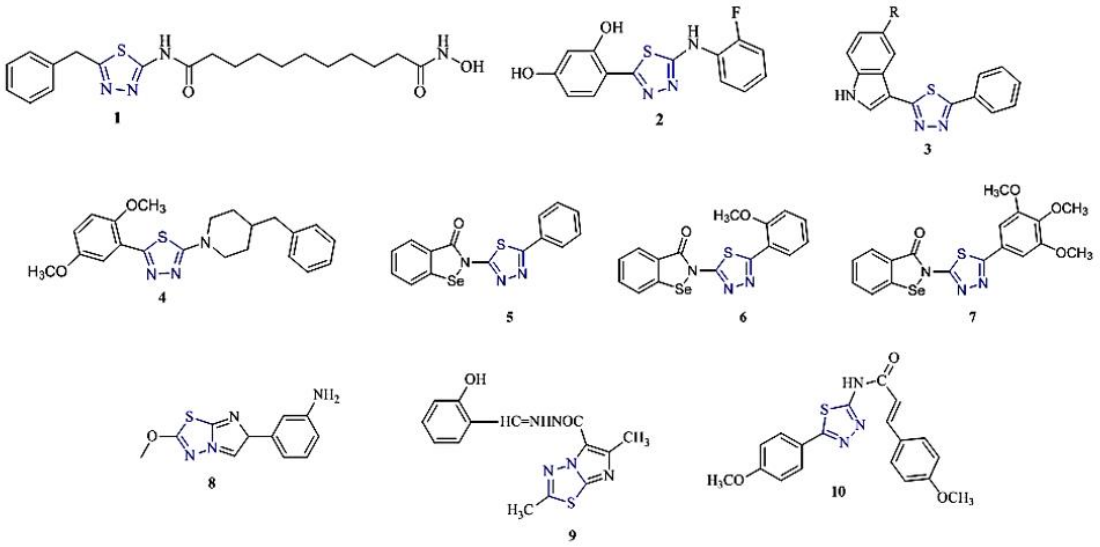


**Figure 1.** Derivatives of thiadiazole

*Benzimidazole*

Wang *et al*. [28] explored the antitumor effects of various benzimidazole derivatives. Among these, compound 11 exhibited the highest anti-proliferative potency against MFC cells, achieving an IC50 of 3.95 μM.

Ren *et al.* [29] developed a range of compounds as inhibitors of tubulin, specifically designed for their antiproliferative properties. Notably, compound 12 showed impressive results, effectively overcoming paclitaxel resistance in vitro, with an IC50 of 9.7 nM in a resistant cancer cell line, similar to its action in the parental cell line (IC50 = 6.2 nM).

Akhtar *et al.* [30] designed a series of benzimidazole-linked pyrazole derivatives aimed at targeting lung cancer cell lines. Among these, compound 13 demonstrated the most potent activity, with an IC50 of 2.2 μM against cell proliferation and an IC50 of 0.97 μM for EGFR binding. Additionally, it induced apoptosis by causing cell cycle arrest at the G2/M phase [30].

Huang *et al.* [31] synthesized a benzimidazole derivative as part of an anticancer drug development effort. Testing against various human carcinoma cell lines, such as A-549, BFTC-905, and HeLa, revealed that compound 14 was particularly effective against A-549 and HeLa cells, with an IC50 value of 2.8 μM, outperforming UK-1.

Yadav *et al.* [32] designed benzimidazole derivatives and assessed their in vitro anticancer efficacy. Compound 15 stood out as the most potent, inhibiting enzymes like isocitrate lyase, pantothenate synthetase, and chorismite mutase with inhibition percentages of 67.56%, 53.45%, and 47.56%, respectively [32].

Katikireddy *et al.* [33] tested benzimidazolyl 2-amino-1,3,4-oxadiazole derivatives on HeLa, MCF-7, A549, and HEK293 cell lines. Compounds 16a and 16b exhibited promising anticancer effects, particularly against MCF-7 and A549 cells, with IC50 values of 0.028 μM and 0.048 μM. These compounds showed low toxicity toward HEK-293 cells, and molecular docking confirmed their ability to interact with the EGFR protein target [33].

Woo *et al.* [34] designed benzimidazole-curcumin analogs, with compound 17 demonstrating strong inhibition of MCF-7 cancer cell growth. It exhibited an IC50 of 1.9 μM, highlighting its potential as an anticancer agent.

Osmaniye [35] synthesized benzimidazole-triazolothiadiazine derivatives intended as aromatase inhibitors. Compound 18 was identified with an IC50 between 0.032 and 0.042 μM, which, while less potent than letrozole (IC50 = 0.024 to 0.001 μM), still showed considerable efficacy in the aromatase inhibition assays [35].

In another study, Sağlık *et al.* [36] developed a set of benzimidazole derivatives with aromatase inhibition properties. The 4-benzylpiperidine derivatives, especially compound 19, emerged as the most effective in this series, with IC50 values of 0.024 μM and 0.001 μM, showing superior activity compared to cisplatin (IC50 = 0.021 μM) in MCF-7 cells [36].

Çevik *et al.* [37] also formulated hydrazone-modified benzimidazole compounds, evaluating their anticancer potential. Compound 20 showed significant cytotoxicity against MCF-7 cells, with an IC50 value of 0.0316 µM, further emphasizing the role of substituents in enhancing the anticancer activity of these compounds (**Figure 2**) [37].

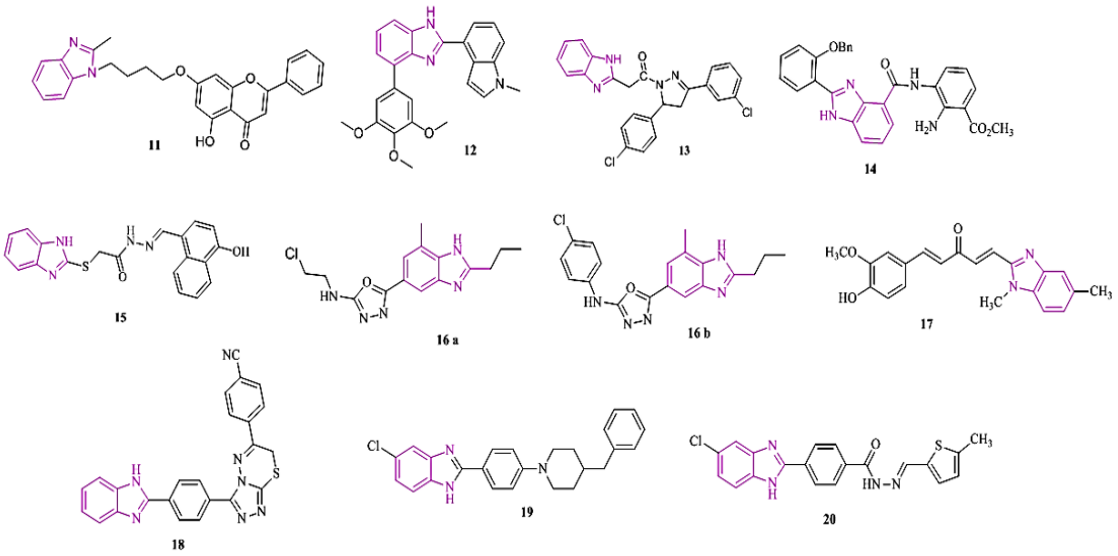



**Figure 2.** Derivatives of benzimidazole

*Quinazoline*

Abuelizz *et al.* [38] designed a new series of quinazoline derivatives as potential anticancer agents by combining 2-amino-5-methyl benzoic acid with butyl isothiocyanate. This reaction resulted in the synthesis of 2-thioxoquinazolin-4-one compounds, which were tested in vitro against HeLa and MDA-MB231 cell lines. Among these, compounds 24, 25, and 26 emerged as promising candidates with IC50 values of 1.85 µM, 2.5 µM, and 2.6 µM, respectively, for both cancer cell lines [38].

Faraj *et al.* [39] synthesized quinazoline Schiff base derivatives and assessed their anticancer potential against the MCF-7 breast cancer cell line. After 72 hours of treatment, compounds 27 and 28 showed significant antiproliferative effects with IC50 values of $6.246 \times 10^{6}$ mol/L and $5.910 \times 10^{6}$ mol/L, respectively, indicating their strong anticancer potential [39].

Syed *et al.* [40] developed modified quinazoline-isoxazole derivatives and evaluated their anticancer properties using the MTT assay against several human cancer cell lines, particularly MCF-7. The compounds 29a, 29b, 29c, 29d, and 29j exhibited notable anticancer activities with IC50 values of 1.92 ± 0.85 µM, 1.47 ± 0.51 µM, 0.01 ± 0.008 µM, 2.08 ± 0.77 µM, and 0.083 ± 0.001 µM, respectively, across the tested cell lines [40].

Wasfy *et al.* [41] explored the anticancer properties of quinazoline derivatives on MCF-7 cell lines. Out of 11 synthesized compounds, two, namely 30a and 30b, showed significant inhibition of breast cancer cell proliferation, with compound 30a inhibiting 51.9% at a concentration of 62.5 µg/mL, and compound 30b inhibiting 50% at the same concentration [41].

Yong *et al.* [42] synthesized quinazoline derivatives with isoxazole groups and tested their anticancer activities against MCF-7 cell lines. Several of these compounds exhibited strong anticancer effects, particularly 31a, 31b, 31c, and 31d, with IC50 values of 42.82 ± 0.1324 µM, 0.11 ± 0.0381 µM, $1.99 \times 10^{-4}$ ± 0.0189 µM, and 5.74 ± 0.00861 µM, respectively, indicating their promising anticancer potential [42].

Madhavi *et al.* [43] created chalcone-linked quinazoline derivatives and evaluated their anticancer properties against 4 human cancer cell lines, including HT-29. Among them, compounds 32a, 32b, 32c, and 32d showed enhanced anticancer activity compared to the control drug Combretastatin A4, with IC50 values of 0.18 µM, 0.13 µM, 1.56 µM, and 2.89 µM, respectively [43].

Akgun *et al.* [44] synthesized a series of quinazoline derivatives containing 6,7-disubstituted-3-2-[4-

(substituted) piperazin-1-yl] groups and tested them for anticancer activity. The derivative 3-2-[4-(4-chlorobenzyl)piperazin-1-yl] 33-2-oxoethyl quinazoline-2,4(1H,3H)-dione showed the highest cytotoxicity against MCF-7 cells, with an IC50 value of 6.8 µM [44]. Fröhlich *et al.* [45] synthesized quinazoline-artemisinin hybrids and tested their effectiveness against leukemia cell lines CCRF-CEM and CEM/ADR5000. Hybrid 34 demonstrated antileukemia activity comparable to artesunic acid, with EC50 values in the low micromolar range, and showed significantly higher activity against multidrug-resistant CEM/ADR5000 cells (EC50 = 0.5 µM) compared to doxorubicin [45].

Sharma and Ravani [46] synthesized quinazolinone derivatives through the reaction of N-benzoyl-substituted piperazine-1-carbothioamide with 2-chloromethyl quinazolinone and tested their anticancer activity on MCF-7 cells. Compound 35 was identified as the most potent derivative with an IC50 value of 0.16 ± 0.16 µM, significantly outperforming standard treatments such as methotrexate (IC50 = 2.20 ± 0.18 µM) and 5-fluorouracil (IC50 = 2.30 ± 0.49 µM) (**Figure 3**) [46].

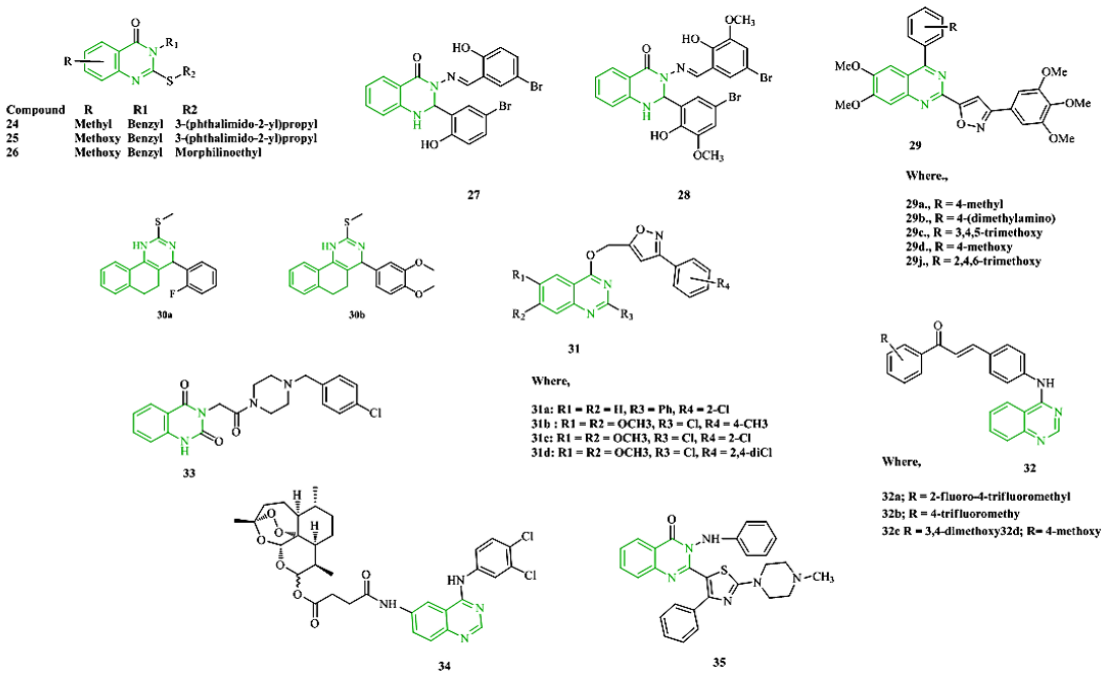



**Figure 3.** Derivatives of quinazoline

*Pyrimidine*

Emami *et al.* [47] developed innovative hybrids combining quinazolinone-pyrimidine and benzyl-pyrimidine and tested their ability to inhibit the growth of three cancer cell lines: HT-29, SW1116, and A549. The results revealed that these compounds were more effective against colon cancer cells (HT-29 and SW1116) than lung cancer cells (A549). Among the tested compounds, 36 and 37 stood out, showing significant inhibition of HT-29 cells with IC50 values of 10.67 ± 0.3 µM and 27.9 ± 6.5 µM, respectively [47].

Masoud *et al.* [19] synthesized barbituric acid derivatives, such as 5-(2-hydroxyphenylide) barbituric acid (L1), 5-(phenyl azo) thiobarbituric acid (L2), and 5-(phenyl azo) barbituric acid (L3), alongside their complexes with ions like Os(VIII), Ru(III), Zr(IV), and V(III). The compound 5-(phenyl azo) thiobarbituric acid (L2, compound 38) showed potent inhibitory effects against MCF-7 breast cancer cells, with an IC50 of 22 ± 0.9 (µg/ml) [19].

Gaber *et al.* [48] synthesized a range of 1H-pyrazolo[3,4-d]pyrimidine derivatives aimed at inhibiting the epidermal growth factor receptor (EGFR). Compound 39, in particular, was evaluated for its antiproliferative effects on several cancer cell lines with EGFRWT and EGFR T790M mutations. This compound displayed significant inhibitory activity with IC50 values of 0.50 µM, 0.01 µM, 0.62 µM, 0.04 µM, and 0.12 µM against

MCF-7, HepG2, A549, H1975, and HCC827 cells, respectively [48].

Kumar *et al.* [49] designed and synthesized pyrimidine-bridged derivatives, which were tested for their anticancer properties against MCF-7 (breast cancer) and A549 (lung cancer) cells. Among these, compounds 40 and 41 exhibited the highest potency, showing IC50 values of 4.67 μM and 3.38 μM for MCF-7 cells and 4.63 μM and 3.71 μM for A549 cells, respectively [49].

Reddy *et al.*'s [50] work focused on biscoumarin-pyrimidine conjugates, evaluating their anticancer activity in vitro. Among the compounds tested, compound 42 showed good selectivity, as it displayed no significant cytotoxicity against normal HEK293 cells while binding effectively to the drug carrier protein HAS. It inhibited HEK293 cells with an IC50 value of 4.85 μM [50].

El-Metwally *et al.* [51] synthesized a series of thieno[2,3-d]pyrimidine derivatives and tested them against HepG2 and MCF-7 cell lines. Notably, compound 43 demonstrated notable effects, including a 3-4 fold increase in p53 expression and a 60% reduction in Topo II expression. It also exhibited selective cytotoxicity, induced cell cycle arrest, and triggered apoptosis [51].

Cherukupalli et al.'s research [52] involved the design of 4,6-disubstituted pyrazolo[3,4-d]pyrimidines as potential CDK2 inhibitors. The SAR study identified that compounds containing thiopentane/thiophenethyl groups at C-6 and bicyclic heteroatom-containing moieties (like benzofuran) at C-4 were the most effective. Among them, compound 44 was the most potent, exhibiting IC50 values of 19.8 μM and 18.9 μM against K-562 (chronic myelogenous leukemia) and MCF-7 (breast adenocarcinoma) cells, respectively [52].

Diao *et al.* [53] synthesized pyrimidine-based benzothiazole derivatives for anticancer evaluation. Compound 46 was particularly effective, showing strong CDK2 inhibition with an IC50 of 15.4 nM, nearly three times more potent than AZD5438. Additionally, compound 45 induced apoptosis and disrupted cell cycle progression in a concentration-dependent manner.

Ye *et al.* [54] developed a novel anticancer agent, 2,4-bismorpholinyl-thieno[3,2-d]pyrimidine (compound 46), which exhibited strong antiproliferative activity against multiple cancer cell lines, including HCT116, PC-3, MCF-7, A549, and MDA-MB-231, with IC50 values of 3.24 μM, 14.37 μM, 7.39 μM, 7.10 μM, and 16.85 μM, respectively. Furthermore, compound 46 inhibited A549 cell proliferation and diminished mitochondrial membrane potential, while also displaying notable activity against PI3Kα and PI3Kβ (92.4% and 62.29%, respectively) at 1 μM [54].

Ghorab *et al.* [55] synthesized a series of pyrazolo-pyrimidine compounds and evaluated their anticancer efficacy against the Ehrlich Ascite Carcinoma cell line. Compound 47 exhibited intermediate activity, with an IC50 value of 90 μg/ml, when compared to the standard drug doxorubicin [55].

El-Sayed *et al.* [56] developed a novel class of sulfonamide derivatives derived from [1,3,4]thiadiazolo[3,2-a]pyrimidines, which were tested for their anticancer activity both in vitro and in vivo. Some compounds exhibited strong DNA affinity, while others showed moderate activity. Certain compounds outperformed 5-fluorouracil in extending the lifespan of mice implanted with Ehrlich ascites carcinoma cells (**Figure 4**).

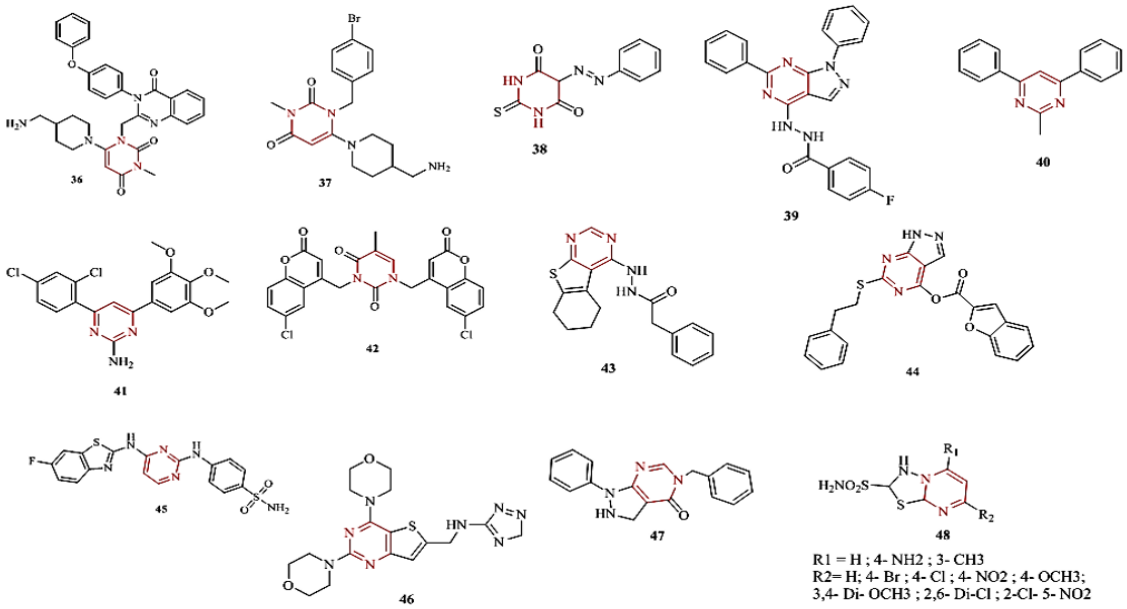
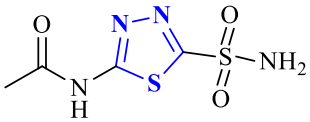
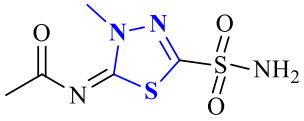
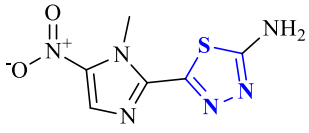
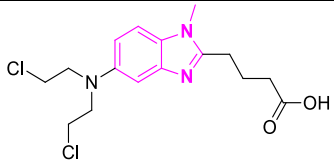
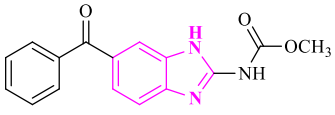
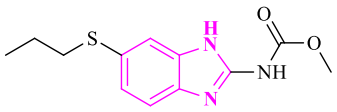
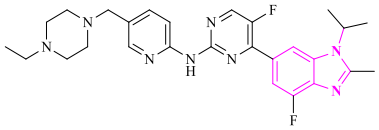
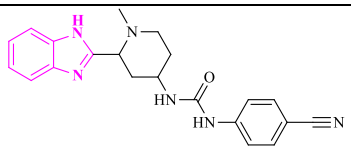
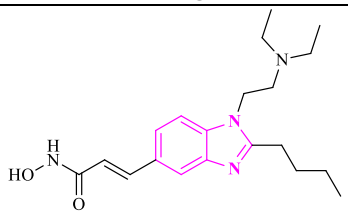
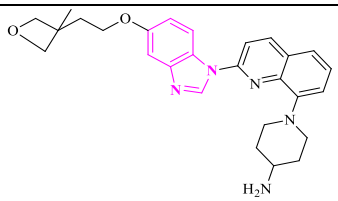
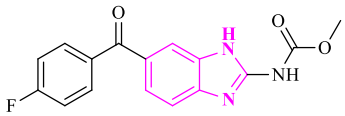
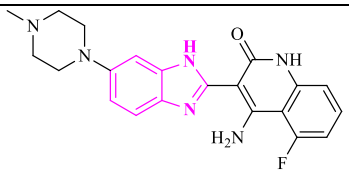
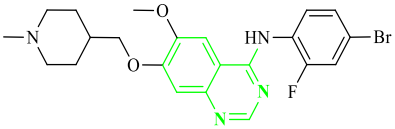



**Figure 4.** Derivatives of pyrimidine

**Table 1.** FDA-approved drugs of thiadiazole, benzimidazole, quinazoline, and pyrimidine

| Sr. No. | Marketed drug structure with Name | Manufacture company name | Cancer types | Target molecule | FDA approval year | Ref. |
|---|---|---|---|---|---|---|
| Thiadiazole 1 |  Acetazolamide | **EMCURE PHARMA** | Renal cell carcinomas | **Carbonic anhydrous inhibitor** | **2005** | **[57]** |
| **2** |  Methazolamine | **REMEDYREPACK INC.** | - | - | - | **[58]** |
| **3** |  Megazol | AKUMENTIS HEALTHCARE LTD | - | - | - | **[59]** |
| Benzimidazole 4 |  **Bendamustine** | TEVA PHARMACEUTICAL INDUSTRIES LTD. GERMAN PRODUCT | Chronic lymphocytic leukemia (Cancer of WBC) | **β- cell** | **2015** | **[60]** |
| **5** |  **Mebendazole** | MEDIX LABORATORIES | Thyroid cancer | **Tubulin protein** | **2016** | **[61]** |

| | | | | | | |
|---|---|---|---|---|---|---|
| 6 |  **Albendazole** | CIPLA FROM INDIA. ENALTEC LABS INDIA. BEIJING INFOARK CO LTD FROM CHINA. KA MALLE PHARMACEUTICALS FROM INDIA | Head and neck squamous cell cancer. | **CDK4/6** | **1996** | **[62]** |
| 7 |  **Abemaciclib** | ELI LILLY AND COMPANY | Breast cancer | **HER2** | **2015** | **[63]** |
| 8 |  **Glasdegib** | PFIZER ONCOLOGY | Acute myeloid leukemia | **hedgehog receptor inhibitor** | **2018** | **[64]** |
| 9 |  **Pracinostat** | MEI PHARMA, INC. | Tumors | **Histon deacetylase inhibitor** | **2013** | **[65]** |
| 10 |  **Crenolanib** | AROG PHARMACEUTICALS, | Acute myeloid Leukemia, Gastrointestinal Stromal Tumor | **Type 1 kinase inhibitor** | **2017** | **[66]** |
| 11 |  **Flubendazole** | JANSSEN PHARMACEUTICA N.V. | Breast cancer, prostate cancer, colorectal cancer, lung cancer. | **P53** | **1952** | **[67]** |
| 12 |  **Dovotinib** | ALLERITY THERAPEUTICS | Renal cell carcinoma, Multiple myeloma | **TKI-258** | **2021** | **[68]** |
| **Quinazoline 13** |  **Vandetanib** | ASTRAZENECA | Medullary thyroid cancer (MTC) | **EGFR, VEGFR** | **2011** | **[69]** |

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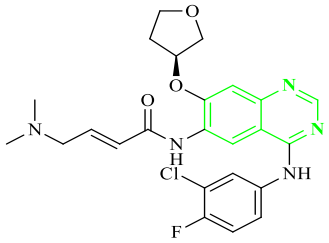
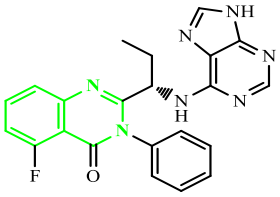
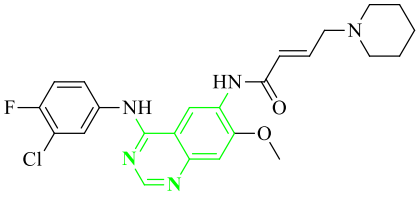
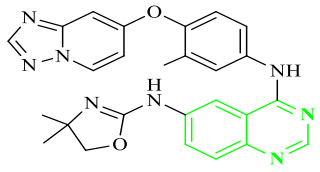
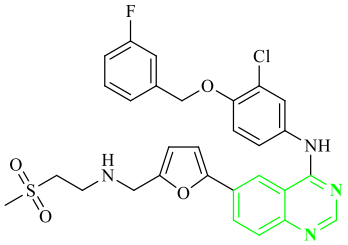
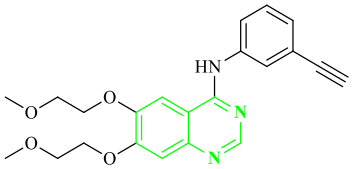
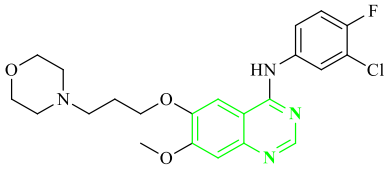
| **14** |  **Afatinib** | BOEHRINGER INGELHEIM | Non-small cell lung cancer (NSCLC) | **EGFR** | **2013** | **[70]** |
| **15** |  **Idelalisib** | GILEAD | Blood cancers | **PI3K** | **2014** | **[71]** |
| **16** |  **Dacomitinib** | PFIZER | Non-small cell lung cancer (NSCLC) with EGFR mutation | **EGFR, ERBB** | **2018** | **[72]** |
| **17** |  **Tucatinib** | SEATTLE GENETICS | Advanced unresectable or metastatic HER-2 positive breast cancer | **EGFR, HER2** | **2020** | **[73]** |
| **18** |  **Lapatinib** | NOVARTIS AND GSK | Advanced or metastatic breast cancer | **EGFR, ERBB** | **2007** | **[74]** |
| **19** |  **Erlotinib** | OSI PHARMS | Non-small cell lung cancer (NSCLC), pancreatic cancer | **EGFR** | **2004** | **[75]** |
| **20** |  **Gefitinib** | ASTRAZENECA | Non-small cell lung cancer (NSCLC) | **EGFR** | **2003** | **[76]** |

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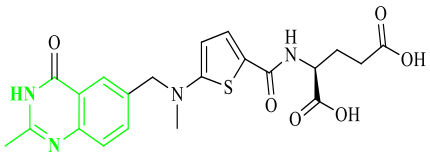
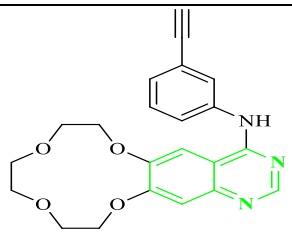
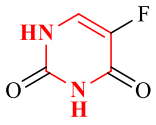
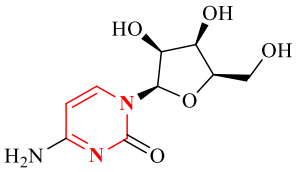
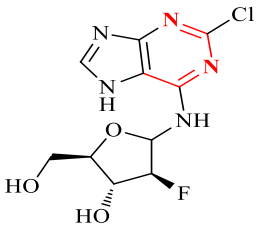
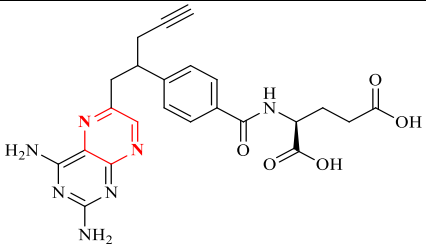
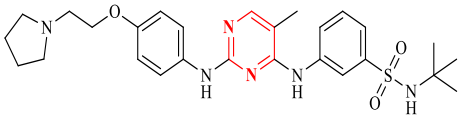
| 21 |  Raltitrexed | ASTRAZENECA | Malignant neoplasm of colon and rectum | TS | 1998 | [77] |
| 22 |  Icotinib | BETTA PHARMA | Non-small cell lung cancer (NSCLC) | EGFR-TKI | 2014 (SFDA) | [78] |
| Pyrimidine 23 |  Fluorouracil | BIOCHEM PHARMACEUTICAL INDUSTRIES LTD, OM BIOTEC (ONCOMED PHARMACEUTICALS) | Colorectal Cancer, Esophageal Cancer, Pancreatic Cancer, Breast Cancer, Cervical Cancer | HDAC | 1962 | [79] |
| 24 |  Cytarabine | EUTICALS FROM ITALY, SHANDONG OCTAGON CHEMICALS LIMITED FROM CHINA, ZHEJIANG HISUN PHARMA FROM CHINA. | Acute myeloid leukemia, Acute lymphocytic leukemia (ALL), non-Hodgkin's lymphoma primary central nervous system (CNS) lymphoma | *Ara-C* | 1969 | [80] |
| 25 |  Clofarabine | ABON PHARMS LLC, ACCORD HLTHCARE, MYLAN LABS LTD, GLAND PHARMA LTD, AMNEAL. | Acute lymphoblastic leukemia | T47D | 2004 | [80] |
| 26 |  Pralatrexate | ALLOS THERAPEUTICS LTD | Treatment of relapsed or refractory peripheral T-cell lymphoma (TCL) | *dihydrofolate reductase (DHFR)* | 2009 | [81] |
| 27 |  Fedratinib | IMPACT BIOMEDICINES | Myelofibrosis | *BRD4 and* JAK2 | 2019 | [82] |

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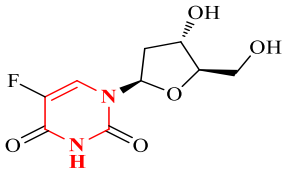
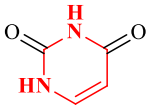
| **28** |  **Floxuridine** | LGM *PHARMA,* ZHEJIANG HISUN PHARMA | Cancer of the gastrointestinal (GI) tract (cancer of the stomach or intestines) that has spread to the liver. | - | **1970** | **[83]** |
| **29** |  **Orotic acid** | SHREYA PHARMACHEM PRIVATE LIMITED | Powerful tumor promoter, particularly in the liver. | **Hep G2** | **2015** | **[16]** |

## Conclusion

Heterocyclic compounds represent a crucial category of organic molecules in medicinal chemistry, widely utilized for treating a variety of diseases. The research outlined in this review highlights the diverse pharmacological properties exhibited by heterocyclic structures, including thiadiazole, quinazoline, pyrimidine, and benzimidazole. These compounds have shown promise as agents for treating conditions such as cancer, tuberculosis, inflammation, fungal and microbial infections, hypertension, HIV, viral diseases, and diabetes. The presence of a heterocycle in a therapeutic molecule has been identified as a significant factor in advancing drug development. This paper's primary aim is to contribute to the design and development of new, more effective medicinal agents by researchers in the field.

**Acknowledgments:** The authors express their gratitude to the Principal of Shree Dhanvantary Pharmacy College for their invaluable guidance.

**Conflict of Interest:** None

**Financial Support:** None

**Ethics Statement:** None

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