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ANTICANCER BIOLOGICAL PROFILE OF SOME HETEROCYLIC MOIETIES-THIADIAZOLE, BENZIMIDAZOLE, QUINAZOLINE, AND PYRIMIDINE

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ABSTRACT

Several five and six-membered aromatic systems with three heteroatoms such as S, O, and N have been intensively researched due to their intriguing pharmacological properties. Heterocyclic compounds are chemicals that allow life to exist. Aside from that, all heteroatoms in the ring interact better with amino acids, and these interactions aid in reducing transactivation, and enhancing lipophilicity, solubility, and absorption, all of which can be exploited to improve therapeutic action. Heterocyclic nucleus 1,3,4-thiadiazole, benzimidazole, quinazoline, and pyrimidine derivatives have shown considerable biological actions such as anticancer, antimicrobial, anti-inflammatory, antidepressant, antioxidant, antifungal, antimicrobial, Carbonic anhydrase inhibitors, anticonvulsant, antibacterial activity, etc. All ring system members play a significant role in the development of novel drugs. In this review, we have highlighted the FDA approved drugs of heterocyclic compound which will pave the way for development of new entities. The current analysis focuses on synthetic derivatives of thiadiazole, benzimidazole, quinazoline, and pyrimidine that have significant anticancer biological effects on several cancer cell lines.

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Introduction

Cancer is a disease characterized by genetic or epigenetic alterations in somatic cells that result in uncontrolled cell growth and spread to other regions of the body. They are one type of neoplasm. The uncontrolled proliferation of cells in a group known as neoplasm or tumor, forms a lump or mass and might be scattered diffusely [1, 2]. Over the last two decades, we have made tremendous progress in our understanding of cancer at the molecular level. This insight has revealed a plethora of interesting new targets for the creation of effective medicines, some of which are already in clinical use [3]. Resistance to existing medications is rapidly becoming a serious global issue. One of the most important topics of research today is the development of novel chemicals to combat resistance [4]. Because of their activity in a variety of diseases, heterocyclic compounds are regarded as one of the most important types of organic chemicals employed in a variety of biological domains. The heterocyclic ring is found in many biological compounds, including DNA and RNA, chlorophyll, hemoglobin, vitamins, and many others [5]. Heterocyclic compounds are cyclic compounds that contain oxygen, nitrogen, and sulfur in the ring surrounding the carbon atom. In this review, we discussed the role of various heterocyclic rings as anti-cancer drugs, such as thiadiazole, benzimidazole, quinazoline, and pyrimidine. Thiadiazole is a heterocyclic molecule with a five-membered aromatic ring with two nitrogen and one sulfur atom. Thiadiazole is a versatile moiety with diverse biological functions [6]. The thiadiazole moiety performs tasks such as the "two-electron donor system" and "hydrogen binding domain." It also functions as a limited pharmacophore [5]. Thiadiazole and its derivatives are known as 1, 3, and 4-thiadiazole (A five-membered ring that has two nitrogen and one additional heteroatom). Thiadiazole can serve as a bio-isosteric substitute for the thiazole molecule [7]. As a result, it works similarly to third and fourth-generation cephalosporins and can thus be utilized in

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antibiotic formulations. There are four isomeric forms of thiadiazole: 1,2,3-thiadiazole, 1,2,5-thiadiazole, 1,2,4-thiadiazole, and 1,3,4-thiadiazole. Because of their diverse biological activities, 1,3,4-thiadiazole are crucial [8]. Compounds with the nucleus 1,3,4-thiadiazole, in particular, are recognized to exhibit distinct antibacterial properties [9] and anti-inflammatory activities [10]. Other intriguing functions of other substituted thiadiazole moieties have been discovered, such as analgesic activity, anti-microbial, anti-tubercular, anti-depressant, anti-oxidant, anti-convulsant, and anti-fungal. Another heterocyclic ring such as benzimidazole, a benzene-fused heterocyclic molecule, has received considerable attention in the field of modern medicinal chemistry because of its biological application [11]. Benzimidazole, the benzo derivative of imidazole, is a bicyclic aromatic chemical molecule composed of a six-membered benzene ring fused to a five-membered imidazole ring at the 4- and 5-positions [12]. Extensive biological profile and synthetic applicability in medicinal chemistry, the benzimidazole heterocyclic nucleus is known as the "Master Key." Because of the fused nitrogen nuclei, benzimidazoles are structural isosteres of nucleobases that readily engage with biomolecular targets and elicit several biological actions such as anti-cancer activity, anti-inflammatory, anti-ulcer, anti-fungal, and anti-bacterial. Quinazoline nitrogen-bearing aromatic heterocycle compound made up of fused two six-membered rings- benzene and pyrimidine which is prepared by Gabriel in 1903. The quinazoline ring can occur in four isomeric forms depending on the position of the nitrogen atoms: quinazoline, quinoxaline, cinnolines, and pthalazines [13]. Quinazoline synthesis methods are divided into five categories based on whether they are traditional or innovative, including Aza-reaction, Microwave-assisted reaction, Metal-catalyzed reaction, Ultrasound-promoted reaction, and Phase-transfer catalysis [14]. Fused ring compounds have been the focus of medicinal chemists due to their attractive biological and pharmacological applications. Though quinazolines were first recognized for their anti-malarial activity [15], later investigators have found various activities of quinazoline derivatives, such as an anti-cancer, anti-inflammation, anti-microbial, anti-viral, anti-hypertensive, etc. Pyrimidine is a heterocyclic molecule with six members and two nitrogen atoms in positions 1 and 3. Many pyrimidines have been extracted from nucleic acid hydrolyses, including the nucleotides uracil, thiamine, cytosine, etc. [16]. pyrimidine is a colorless compound with a molecular formula of $C_4H_4N_2$ and has a melting point of 22.5℃ and a boiling point of 124℃. Pyrimidines are synthesized through condensation processes between three carbon molecules and compounds having amidine structures in the presence of a catalyst such as sodium hydroxide or sodium ethoxide [17]. Pyrimidine and its derivatives are notable for their amazing biological activity due to the presence of pyrimidine bases in the DNA and RNA building blocks [18]. Many natural products and biologically active chemicals contain heterocyclic compounds containing nitrogen and/or Sulphur, including pyrimidines [19]. Pyrimidine possesses biological activities like anti-microbial, anti-inflammatory, anti-fungal, anti-viral, anti-cancer, anti-malarial, anti-tubercular, anti-HIV, etc. Based on these investigations of heterocyclic rings such as thiadiazole, benzimidazole, quinazoline and pyrimidines can provide a very good basis for the development of new hits. In **Table 1** despite the numerous marketed dugs of thiadiazole, benzimidazole, quinazoline and pyrimidine with their particular targeted therapy in cancer. The review will be beneficial in upcoming research for synthesizing and developing more promising synthetic approaches.

Anti-Cancerous Biological Activity of Heterocyclic Moieties

- *Thiadiazole*

Guan *et al.* discovered that a set of 1,3,4-thiadiazole-based hydroxamic acids were potent HDAC inhibitors. Some of them demonstrated strong growth suppression in some tumor cell lines as well as good inhibitory action in the HDAC enzyme assay. When compared to SAHA (IC50 = 0.15 lM), compound 1 (IC50 = 0.089 lM) had a stronger inhibitory effect [20].

Matysiak *et al.* investigated the antiproliferative effects of numerous N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole derivatives. In the panel substitution, alkyl, aryl, and morpholinoalkyl derivatives were utilized. The elemental, IR, 1H, 13C, and MS spectra of compounds were used to determine their structures. Four human cell lines were tested for cytotoxicity in vitro: SW707 (rectal), HCV29T (bladder), A549 (lung), and T47D (breast). Phenyl derivatives had a substantially lower effect than alkyl and morpholinoalkyl derivatives. The chemical with the strongest antiproliferative action was 2-(2,4-dichlorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole, whose ID50 was two times lower (SW707, T47D) than that of the control compound, cisplatin, which was tested in comparison [21].

Kumar *et al.* discovered a class of 5-(3-indolyl)-2-substituted-1,3,4-thiadiazole derivatives and tested their cytotoxicity against six human cancer cell lines. The most effective substance for inhibiting the proliferation of cancer cells is indolyl-1,3,4-thiadiazole, among them compound 3 which also contains 5-bromo indolyl and 4-benzyloxy-3-methoxyphenyl substituents (IC_{50} 1.5 mM, PaCa2) [22].

The 2,5-disubstituted 1,3,4-thiadiazole compounds were formed by Polkam *et al.* and tested for in vitro antimycobacterial activity against Mycobacterium smegmatis MC-155. By using the MTT colorimetric technique, these substances have also been examined for their cytotoxic activity against the cancer cell lines HT-29 and MDA-MB-231. By using spectral analysis, including 1HNMR, 13CNMR, FT-IR, mass, and HRMS, the compounds may be identified well. According to screening results, compounds 5g, 7a, and 9 showed potential cytotoxic activity against the tested cell lines and have good antitubercular activity with MIC values of 65.74 and 40.86, respectively. Among the studied series, compound 4 stands out as a powerful antimycobacterial and anticancer drug. Additionally, the above substances were examined in HEK293T human normal cells and are [23].

Luo *et al.* synthesized a variety of novel 1,3,4-thiadiazole-containing benzisoselenazolone derivatives by condensation of 2-chloroselenobenzoyl chloride and 2-amino-5-substituted-1,3,4-thiadiazole derivatives. In vitro antiproliferative activity in

SSMC-7721, MCF-7, and A-549 cells was assessed. The findings indicate that compounds 5, 6, and 7 have effective antiproliferative activity in several tumor cells [24].

From 5-substituted-1,3,4-thiadiazol-2-amine, Noolvi *et al*. created some novel 2,6-disubstituted imidazo[2,1-b][1,3,4]thiadiazole compounds. The newly synthesized compounds were tested for a single dose in vitro primary cytotoxicity by the National Cancer Institute. The two tested compounds 8 (107166/760239) were automatically scheduled for testing against the full panel of 60 human tumor cell lines at a minimum of five concentrations at 10-fold dilutions after passing the requirements for activity in this assay. 3-(2-(4-methoxyphenyl)imidazo[2,1-b] [1,3,4]thiadiazol-6-yl) aniline (compound 8) significantly reduced the growth of the Non-Small Cell Lung Cancer HOP-92 cell line and the Renal Cancer CAKI-1 cell line in vitro (GI50: 0.114 mM) (GI50: 0.743 mM) [25].

Some novel 2,6-dimethyl-N-substituted phenylmethylene-imidazo compounds were made by Terzioglu *et al.* [2,1-b] [1,3,4] From 2,6-dimethylimidazo-[2,1-b], thiadiazole-5-carbohydrazides derivatives are produced. [1,3,4] thiadiazole-5-carbohydrazide. The 3-cell line, one dose in vitro primary cytotoxicity assay used by the National Cancer Institute was used to assess the newly synthesized compounds. Cell stability or growth was determined using the Sulforhodamine B (SRB) protein assay. The best cytotoxicity was demonstrated by 2,6-Dimethyl-N-(2-hydroxyphenylmethylidene) imidazo[2,1-b] [1,3,4] thiadiazole-5-carbohydrazide (compound 9). In vitro screening of 60 human tumor cell lines by the National Cancer Institute revealed that this substance had the strongest impact on an ovarian cancer cell line (OVCAR log10 GI50 value: 5.51) [26].

Yang *et al.* developed and synthesized a variety of cinnamic acyl 1,3,4-thiadiazole amide derivatives and their biological activities were assessed as prospective tubulin polymerization and antiproliferation inhibitors. Compound 10 inhibited the growth of the MCF-7 and A549 cell lines, having the greatest in vitro activity of all the compounds, with IC50 values of 0.28 and 0.52 g/mL, respectively [27].

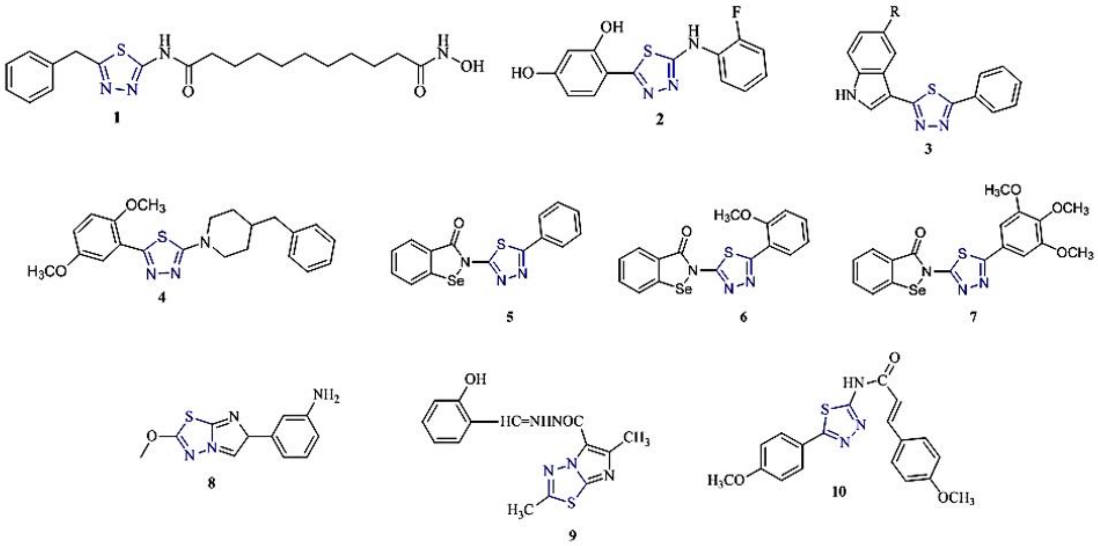


Figure 1. Derivatives of Thiadiazole

- *Benzimidazole*

Wang *et al.* synthesized and assessed the antitumor efficacy of benzimidazole derivatives. With IC50 values of 3.95 M, compound 11 demonstrated the strongest anti-proliferative action against MFC cells [28].

Designed and produced as tubulin inhibitors with strong antiproliferative action by Ren *et al.* Compound 12 efficiently overcame paclitaxel resistance in vitro by showing virtually equivalent efficacy against a paclitaxel-resistant cancer cell line with an IC50 value of 9.7 nM and the matching parental cell line (IC50 = 6.2 nM) [29].

New series of benzimidazole-connected pyrazole compounds was designed by Akhtar *et al*. concerning lung cancer cell lines, compound 13 demonstrated the strongest activity (IC50 = 2.2 M) and EGFR binding (IC50 = 0.97 M) of the group. It also caused cell cycle arrest in G2 / M phase via inducing apoptosis [30].

Huang *et al.* synthesized a benzimidazole molecule as an anticancer drug, and they tested it for cytotoxicity against the human carcinoma cell lines A-549, BFTC-905, RD, MES-SA, and HELA with an IC50 value of 2.8 M, Compound 14 is more effective against human lung (A-549) and HeLa cell lines than UK-1 [31].

Yadav *et al.* designed and evaluated benzimidazole derivatives concerning in vitro anticancer activity. Among them, compound 15, the most effective benzimidazole derivative was created. Isocitrate lyase, pantothenate synthetase, and chorismite mutase were all inhibited to varying degrees (67.56%, 53.45%, 753, and 47.56%) [32].

Marri *et al.* found in vitro anticancer efficacy of benzimdazolyl 2-amino-1,3,4-oxadiazole derivatives against HeLa, MCF7, A549, and HEK293 cell lines with IC50 values of 6.07, 0.028, 5.30, 0.09, 7.16, 0.061 and 7.56, 0.073, 7.20, 0.048, and 11.30, 0.018 M against the HeLa, MCF-7, and A549 cell lines, respectively, compounds 16a and 16b have also demonstrated good

anticancer activity. It also causes less harm to HEK-293 cells. The molecular docking results of the synthesized compounds with the EGFR protein target [33].
Woo *et al.* designed and evaluate some derivatives of benzimdazolyl curcumin imitators. Compound 17 has a potent inhibitory effect on the development of MCF-7 cancer cells in this study, with an IC50 of 1.9 M [34].
Ulviye *et al.* synthesized new benzimidazole-triazolothiadiazine compounds to operate as aromatase inhibitors with anticancer action. This compound 18, with an IC50 of 0.032 to 0.042 M compared to letrozole's IC50 of 0.024 to 0.001 M, had slightly less effective aromatase inhibitory action [35].
New series of benzimidazole compounds were synthesized and evaluated by Saglik *et al.* for the suppression of aromatase inhibitors. The 4-benzylpiperidine derivatives compound 19, with IC50 values of 0.024, 0.001 M compared to the reference medication cisplatin (IC50 = 0.021, 0.001 M), were the most effective compounds in this series for the MCF-7 cell line [36].
Ulviye *et al.* formulate and assess novel hydrazone-modified benzimidazole compounds as anticancer drugs. In this compound 20, the IC50 for MCF-7 inhibition was 0.0316 M. Due to its stronger anticancer properties and the effect of substituents on cytotoxic activity [37].

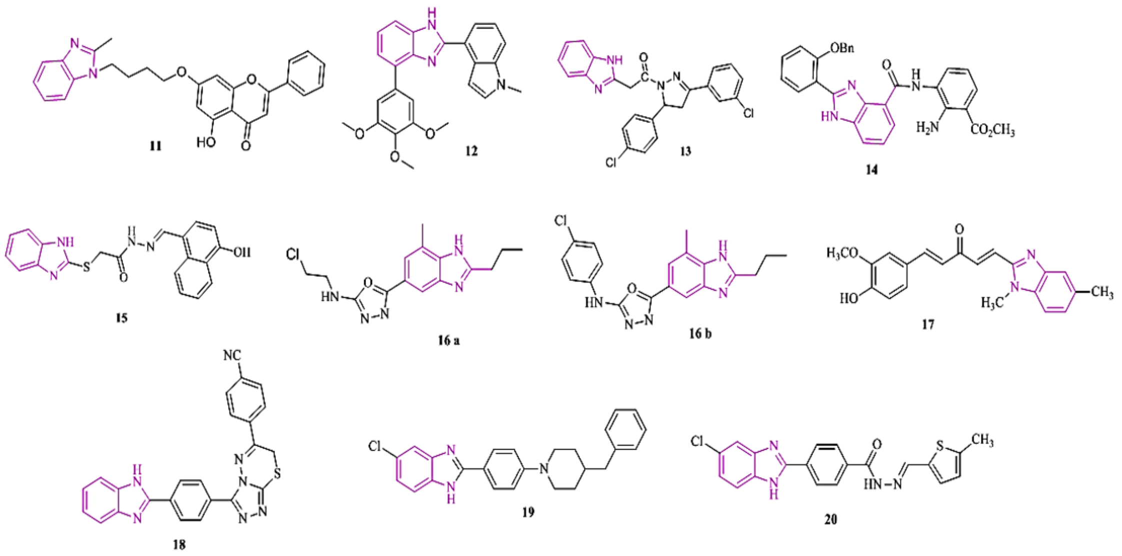


Figure 2. Derivatives of Benzimidazole

- *Quinazoline*

New quinazoline compounds were created by Abuelizz *et al.* as anticancer medications. By reacting 2- amino-5-methyl benzoic acid with butyl isothiocyanate, two new 2-thioxoquinazolin-4-one molecules were synthesized. These substances were tested in vitro against the HeLa and MDA-MB231 cancer cell lines. compound 24, 25 and 26 may be potential anticancer agents, with IC_{50} values of compounds 24 (IC_{50} = 1.85 µM), 25 (IC_{50} = 2.5 µM) and 26 (IC_{50} = 2.6 µM) the HeLa and MDA-MB231 cell line [38].
Faraj *et al*. synthesized and tested quinazoline Schiff bases 1 and 2 against the MCF7 human breast cancer cell line for anticancer activity. After 72 hours of treatment, compounds 27 and 28 displayed substantial antiproliferative activity, with IC50 values of 6.246 106 mol/L and 5.910 106 mol/L, respectively [39].
Syed *et al.* developed and analysed structurally modified aryl quinazoline-isoxazole derivatives. The MTT assay was used to investigate these compounds for anticancer uses against four human cancer cell lines MCF-7 (breast cancer). Among them, compounds 29a, 29b, 29c, 29d and 29j exhibited more potent activities, with IC_{50} values of compound 29a (IC_{50} = 1.92 ± 0.85 µM), 29b (IC_{50} = 1.47 ± 0.51 µM), 29c (IC_{50} = 0.01 ± 0.008 µM), 29d (IC_{50} = 2.08 ± 0.77 µM) 29j (IC_{50} = 0.083 ± 0.001 µM) [40].
Dhunmati *et al.* synthesized and tested the in-vitro anticancer activity of quinazoline derivatives on MCF 7 (Breast cancer) cell lines via the MTT assay at various concentration levels. In the investigations of the study, nearly 11 compounds were synthesized out of which two compounds such as 30a and 30b showed anti-cancer activity. The compound 30a has shown an inhibitory action on breast cancer cell lines in the range of 51.9% at the concentration of 62.5 (µg/ml). compounds 30b has shown an inhibitory action on breast cancer cell line in the range of 50% at the concentration of 62.5 (µg/ml) [41].
Yong *et al.* designed isoxazole-moiety-containing quinazoline derivatives for preliminary anticancer efficacy against MCF-7 cell lines utilizing the MTT technique. Among them, most compounds showed good to excellent anticancer activity, especially 31a, 31b, 31c, and 31d exhibited the more potent anticancer activity against MCF-7 cell lines. IC_{50} values of compound 31a (IC_{50} = 42.82±0.1324µM), 31b (IC_{50} = 0.11±0.0381 µM), 31c (IC_{50} = 1.99×10-4±0.0189 µM), 31d (IC_{50} = 5.74±0.00861 µM) [42].
Madhavi *et al.* created and synthesized a new class of chalcone-incorporated quinazoline derivatives. All of the chemicals created were tested for anticancer activity against four human cancer cell lines HT-29. Among them, four compounds, 32a,

32b, 32c and 32d showed more potent anticancer activity than the control drug, Combretastatin – A4, with IC_{50} values of compound 32a (IC_{50} = 0.18 µM), 32b (IC_{50} = 0.13 µM), 32c (IC_{50} = 1.56 µM), 32d (IC_{50} = 2.89 µM) [43].

Akgun *et al.* Some 6,7-disubstituted-3-2-[4-(substituted) piperazin-1-yl] derivatives were synthesized and tested. 2-oxoethyl quinazoline in vitro activity of 2,4(1H,3H)-dione derivatives against MCF-7 human cancer cell lines. The cytotoxicity screening findings show that 3-2-[4-(4-chlorobenzyl)piperazin-1-yl] 33 -2-oxoethyl quinazoline-2,4(1H,3H)-dione The maximum activity was seen against the MCF-7 cell line, with an IC50 value of 6.8 M [44].

Fröhlich *et al.* developed and synthesized five new quinazoline-artemisinin hybrids for in vitro anticancer activities against leukemia cells (CCRF-CEM and CEM/ADR5000). The antileukemia action of Hybrid 34 was similar to that of artesunic acid, with EC50 values in the low micromolar range, and it was 45 times more active against the multidrug-resistant CEM/ADR5000 cells (EC50 = 0.5 M) than the conventional medication doxorubicin [45].

Sharma *et al.,* Novel quinazolinone compounds were synthesized by reacting N-benzoyl substituted piperazine-1-carbothioamide with 2-chloromethyl quinazolinone derivatives and investigated for anticancer efficacy on MCF 7 (Breast cancer cell) using the MTT technique. Among them, compound 35 (IC_{50} = 0.16 ± 0.16 µM) was found to be the most active compared to standard methotrexate (IC_{50} = 2.20 ± 0.18 µM) and 5-fluorouracil (IC_{50} = 2.30 ± 0.49 µM) [46].

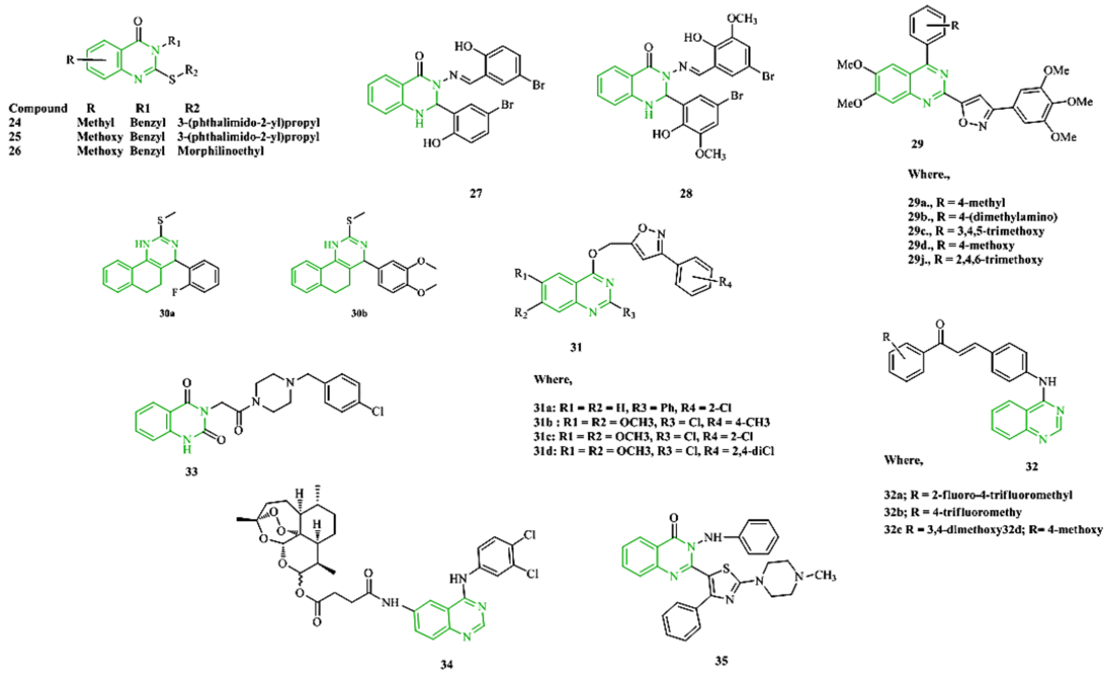


Figure 3. Derivatives of Quinazoline

- *Pyrimidine*

Emami *et al.* created and synthesized two new anticancer quinazolinone-pyrimidine and benzyl-pyrimidine hybrids. The molecule's cytotoxic properties were also tested against three malignant cell lines (HT-29, SW1116, and A549). When compared to a lung cancer cell line, almost all of the drugs showed greater antiproliferative action on colon cancer cell lines (HT-29 and SW1116). (A549). In which compounds 36 and 37 showed excellent inhibitory activities against the HT-29 cell line with an IC_{50} of 10.67±0.3 µM and 27.9±6.5 µM [47].

Masoud *et al.* synthesized 5-(2hydroxyphenylide) barbituric acid (L_1), 5-(phenyl azo) thiobarbituric acid (L_2), and 5-(phenyl azo) barbituric acid (L_3) and its complexes with Os(VIII), Ru(III), Zr(IV) and V(III) ions as anticancer agents. In which compound 5-(phenyl azo) thiobarbituric acid (L_2) 38 was good inhibitory activity against the MCF-7 cancer cell line with an IC_{50} of 22 ± 0.9 (µg/ml) [19].

Gabera *et al.* developed a new series of 1H-pyrazolo[3,4-d]pyrimidine derivatives for cancer treatment and investigated their inhibitory capabilities against the epidermal growth factor receptor (EGFR). compound 39 was further tested for its antiproliferative activities against three cancer cell lines bearing $EGFR^{WT}$ (MCF-7, HepG2, A549) with an IC_{50} of 0.50 µM, 0.01 µM, 0.62 µM, respectively, and two cancer cell lines bearing $EGFRT^{790M}$ (H1975 and HCC827) with an IC_{50} of 0.04 µM and 0.12 µM [48].

Kumar *et al.* designed and synthesized of novel series of pyrimidine bridged derivatives that were examined against breast cancer (MCF-7) and lung cancer (A549) cell lines using MTT assays. From this series, compounds 40 and 41 were found most potent in the series with IC_{50} values of 4.67 µM & 3.38 µM and 4.63 µM & 3.71 µM against MCF7 and A549 cancer cell lines, respectively [49].

Reddy *et al.* designed and synthesized biscoumarin-pyrimidine conjugates that were tested for anticancer efficacy in vitro. All of the compounds, particularly compound 42, demonstrated good selectivity profiles by exhibiting harmless behavior against healthy HEK293 cells and strong binding affinities with a drug carrier protein, HAS. Compound 42 inhibits HEK293 cells effectively, having an IC50 of 4.85 M [50].

El-Metwally *et al.* created a novel series of thieno[2,3-d] pyrimidine derivatives with IC50 values ranging from 4 to 10 M against malignant HepG2 and MCF7 cell lines. Only compound 43 increased p53 expression by 3-4 folds and decreased Topo II expression by 60% in their investigation. Furthermore, 43 demonstrated selective cytotoxicity, cell cycle arrest, and the induction of apoptosis [51].

Cherukupalli *et al.* designed and synthesized 4,6-disubstituted pyrazolo [3,4-6 d] pyrimidines as CDK2 inhibitors. SAR revealed that compounds containing thiopentane/thiophenethyl groups at C-6 and heteroatom-containing bicyclic moieties (benzofuran) at C-4 have higher CDK2 inhibitory action. Furthermore, compound 44, the most powerful molecule in this series, demonstrated antiproliferative activity against the cell lines K-562 (chronic myelogenous leukemia) and MCF-7 (breast adenocarcinoma) with IC50 values of 19.8 M and 18.9 M, respectively [52].

Diao *et al.* designed and synthesized pyrimidine-based benzothiazole derivatives as anticancer agents. Compound 46 exhibited outstanding CDK2 inhibitory activity with an IC_{50} value of 15.4 nM, which was nearly three times as potent as AZD5438 Compound 45 inhibited cell cycle progression and caused apoptosis in a concentration-dependent manner [53].

Ye *et al.* developed and produced a new anticancer 2,4-bismorpholinyl-thieno [3, 2-d] pyrimidine Compound 46 was the most effective against HCT116, PC-3, MCF-7, A549, and MDA-MB-231 cell lines, with IC50 values of 3.24 M, 14.37 M, 7.39 M, 7.10 M, and 16.85 M, respectively. This compound also inhibited the proliferation of A549 cell lines and decreased mitochondrial membrane potential. Compound 46 as the potent compound was selected for further in vitro anti-PI3Kα and anti-PI3Kβ which demonstrated 92.4% and 62.29% inhibitory activity at 1 μM [54].

M. M. Ghorab *et al.* novel pyrazolo pyrimidine compounds synthesized and investigated for anticancer efficacy in vitro against Ehrlich Ascite Carcinoma cell line 5-Benzyl-1-phenyl-1, 5-dihydropyrazolo (3, 4-d) pyrimidin-4-one shown intermediate compound 47 antitumor activity when compared to doxorubicin as a positive control, with IC50 values of 90g/ml [55].

Nadia S. El-S. *et al.* reported a new class of sulfonamide derivatives of [1,3,4]thiadiazolo[3,2-a]pyrimidines was produced and tested for anticancer activity. The synthesized compounds were examined for their anticancer actions in vitro and in vivo. Preliminary biological tests suggested that some compounds had the highest affinity to DNA, while others had modest activity. In addition, certain substances outperformed 5-fluorouracil in terms of percentage increase in the lifetime of mice implanted with Ehrlich ascites cells (positive control) [56].

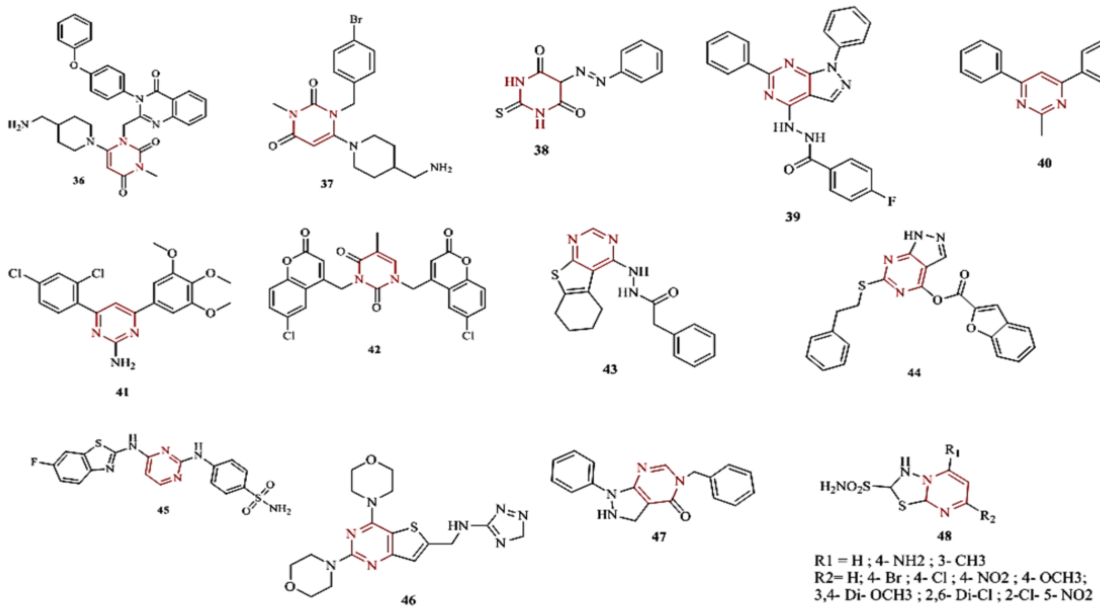
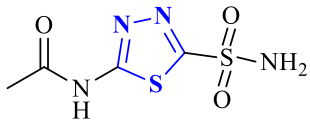
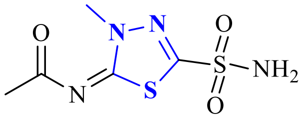
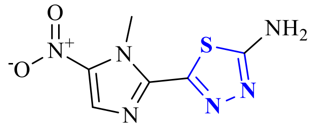
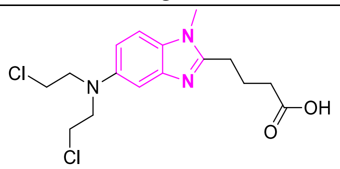
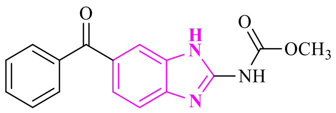
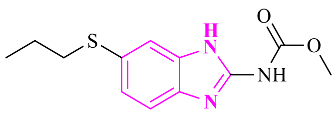
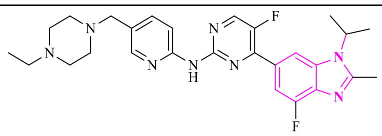
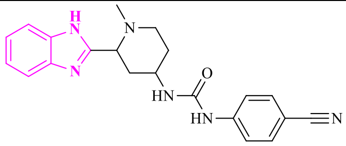
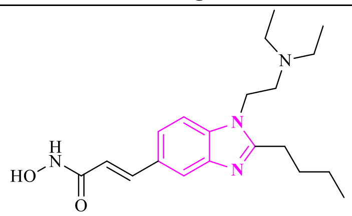
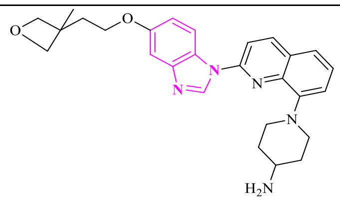
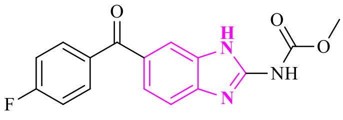
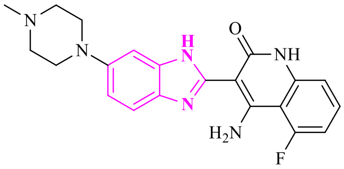
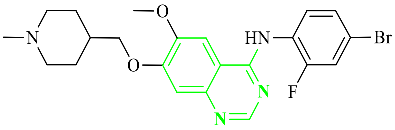
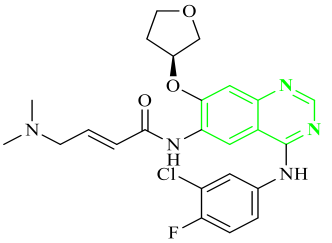
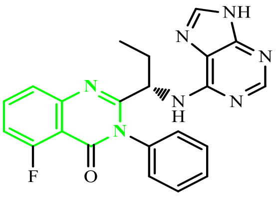
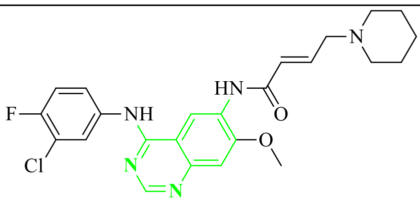
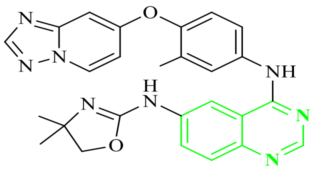
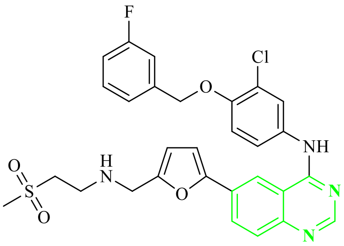


Figure 4. Derivatives of Pyrimidine

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]**
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]**

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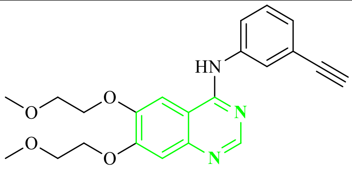
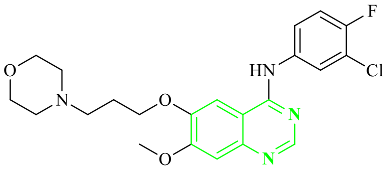
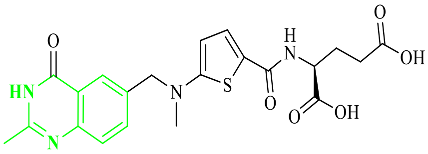
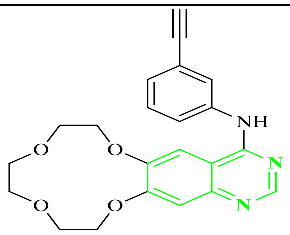
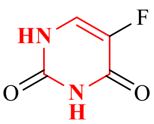
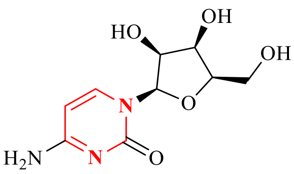
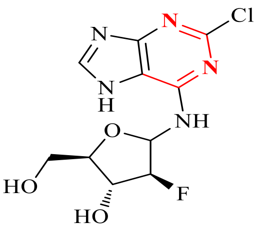
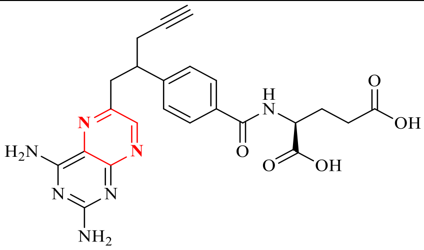
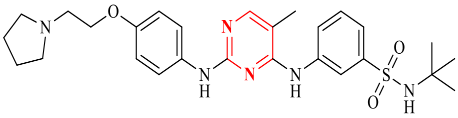
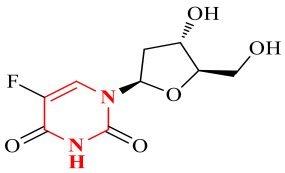
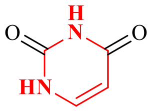
19	 **Erlotinib**	OSI PHARMS	Non-small cell lung cancer (NSCLC), pancreatic cancer	**EGFR**	**2004**	**[75]**
20	 **Gefitinib**	ASTRAZENECA	Non-small cell lung cancer (NSCLC)	**EGFR**	**2003**	**[76]**
21	 **Raltitrexed**	ASTRAZENECA	Malignant neoplasm of colon and rectum	**TS**	**1998**	**[77]**
22	 **Icotinib**	BETTA PHARMA	Non-small cell lung cancer (NSCLC)	**EGFR-TKI**	**2014 (SFDA)**	**[78]**
Pyrimidine 23	 **Fluorouracil**	BIOCHEM PHARMACEUTICA L INDUSTRIES LTD, OM BIOTEC (ONCOME D PHARMACEUTICA LS)	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]**
28	 **Floxuridine**	LGM *PHARMA*, ZHEJIANG HISUN PHARMA	Cancer of 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

In medicinal chemistry, heterocyclic compounds are one of the most important forms of organic molecules, and they are applicable to treat a variety of ailments. The primary goal of research promised in this review specifies a wide range of pharmacological activities revealed in heterocyclic compounds such as thiadiazole, quinazoline, pyrimidine, and benzimidazole. The potential applications of heterocycles as anticancer, antitubercular, anti-inflammatory, antifungal, antimicrobial, antihypertensive, anti-HIV, antiviral, antidiabetic agents, etc. A heterocycle presence in a therapeutic molecule has been found as a possible candidate for continuing drug research, and our main motive behind the work presented in this paper is to help the creation and designing of new potential medicinal agents with better activities by medicinal researchers.

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