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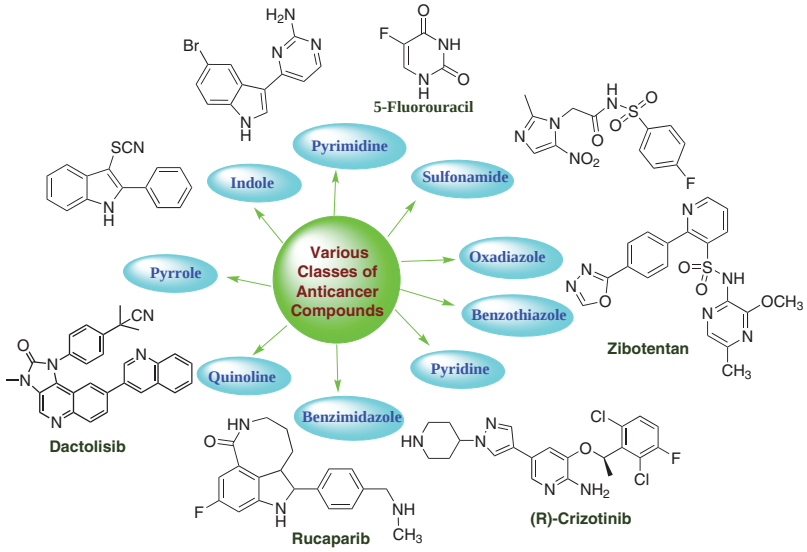
A Review of Recent Progress on the Anticancer Activity of Heterocyclic Compounds

Beena Negi*
Aarshiya Kwatra

Department of Chemistry, Gargi College, University of Delhi, Siri Fort Road, New Delhi 110049, India
beenanegi@gargi.du.ac.in



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Abstract Cancer is one of the most daunting illnesses in the world as compared to many other human diseases. This review article aims to summarize the literature that is already published based on heterocyclic anticancer compounds. Under this broad topic we try to shed a light on anticancer potentiality of oxygen-, sulfur-, and nitrogen-containing heterocyclic compounds, such as quinolines, pyrroles, pyrimidines, pyridines, indoles, also sulfonamides linked heterocycles, benzimidazoles and oxadiazoles.

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Key words N-heterocycles, benzimidazoles, indoles, sulfonamide, pyrimidines, anticancer drugs

1 Introduction

Cancer is a disorder caused by the uncontrolled proliferation of cells which affects the surrounding tissues.[1] Many anticancer medications have been developed and are available in the market but the need to produce anticancer drugs persists because the current drugs are poisonous, inefficient, less soluble, and less selective.[2] The World Health Organisation (WHO) has developed a worldwide action plan for 2013–2030 to prevent and control noncommunicable diseases with the goal of reducing premature death from cancer,[3] cardiovascular disease, diabetes, and chronic respiratory diseases by 25%.[4] This review article compiles all available literature on the cytotoxic action of various chemicals on cancer cells. Scientists, researchers, scholars, and manufacturers have worked extensively on therapeutic targets and development tactics.

1.1 Drugs in Use for Cancer Treatment

Anticancer agents are difficult to classify; previously they were grouped into six categories: (a) alkylating agents, (b) antimetabolites, (c) natural products, (d) hormones and antagonists, (e) miscellaneous. However, several of the most important agents have recently joined the miscellaneous group.

Alkylating chemicals and related compounds prevent DNA replication by forming covalent bonds with the SDNA. Antimetabolites are compounds that hinder or interfere

Table 1 Anticancer Drugs

Entry	Drug name	Type	Type of cancer treated
1	mechlorethamine, cyclophosphamide, ifosfamide, melphalan/sarcolysin, chlorambucil	alkylating agent (nitrogen mustard)	acute and chronic lymphocytic leukemia, etc.
2	altretamine, thiotepa, procarbazine (*N*-methylhydrazine, MIH), busulfan	alkylating agent (ethyleneimines and methylmelamines, methylhydrazine derivative, alkyl sulfonate nitrosoureas)	ovarian, bladder, breast cancer, etc.
3	methotrexate (formerly amethopterin)	antimetabolites (folic acid analogues)	breast, head, neck, and lung cancer
4	fluorouracil (5-fluorouracil, 5-FU), capecitabine, cytarabine (also known as cytosine arabinoside)	antimetabolites (pyrimidine analogues)	breast, colon, esophageal, stomach
5	hydroxyurea, tretinoin, arsenic trioxide, imatinib	miscellaneous agents substituted urea differentiating agents, protein tyrosine kinase	chronic myelogenous, acute promyelocytic leukemia
6	paclitaxel, docetaxel, etoposide	natural and semi-synthetic products, taxanes, epipodophyllotoxins	ovarian, breast, lung, head, and neck cancer
7	vinblastine, vinorelbine, vincristine	natural and semi-synthetic products, Vinca alkaloids	Hodgkin's disease; non-Hodgkin's lymphoma

with one or more of the metabolic processes responsible for DNA production. Cytotoxic antibiotics or those derived from microbes that inhibit mammalian cell division. Plant compounds such as taxanes, campothecins and vinca alkaloids; the bulk of them have a specific effect on microtubule function, which influences mitotic spindle formation.

The most important hormones include steroids (glucocorticoids, estrogens, and androgens) as well as drugs that limit hormone release or interfere with their effects.[5] Table 1 displays some anticancer agents with different mechanisms of action.

1.2 Recently Discovered Anticancer Drugs

Anticancer medications have many limitations including resistance by chemicals in cancer cells, numerous adverse effects, and the fact that they affect both cancer and healthy cells. The study to produce good anticancer treatments that can overcome the challenges mentioned above is ongoing and a few anticancer drugs are being licensed by the Food and Drug Administration in 2023 (Table 2).

Biographical Sketches

Dr Beena Negi is an alumna of Gargi college and presently is a lecturer at Gargi college, University of Delhi (UoD). She is a trained synthetic organic chemist. She has published numerous research papers in international journals. She has authored a book on the chemistry of heterocyclic compounds. Her academic interests are green chemistry and synthetic medicinal chemistry. She was the deputy coordinator for Open Book Examinations, UoD. She was a member of the editorial team of the annual magazine of UoD Highlights 2021, 2022, and 2023. She had been a member of committee of courses for both UG and PG at the Department of Chemistry, University of Delhi. Her lectures on green chemistry are available on her you tube channel https://www.youtube.com/watch?v=6sGDo6UW89w&t=18s.

Aarshiya Kwatra has completed her Bachelor's degree from Miranda House, University of Delhi followed by a Master's degree from M.D.U., Rohtak. She did her B.Ed. from M.D.U. Rohtak and has mentored many children for IIT-JEE and NEET. Her academic interests are Green Chemistry and Medicinal Chemistry.

Heterocyclic compounds exhibit diverse pharmacological activities.[8] Hormones, vitamins, antibiotics, and other biological compounds found in living organisms are composed of heterocyclic molecules. While heterocyclic compounds with a sulfur atom account for the bulk of FDA-approved drugs, heterocyclic compounds with a nitrogen atom are regarded to be the most common type of chemical material utilized in medicinal chemistry.[9] Many physiologically active natural products used in conventional treatment or approved prescription medications contain nitrogen-containing heterocyclic compounds. Many of their synthetic equivalents are available in the therapeutic market to treat a range of ailments. This article discusses the anticancer activity of numerous heterocyclic compounds and derivatives as well as their structures *in vitro* activity and IC_{50} values.

Table 2 Anticancer Drugs Recently Approved by the FDA

Entry	Drug name	Type of cancer treated
1	retifanlimab-dlwr[6]	metastatic or recurrent locally advanced Merkel cell carcinoma
2	enfortumab[7]	locally advanced or metastatic urothelial carcinoma
3	epcoritamab-bysp[6]	relapsed or refractory diffuse large β-cell lymphoma
4	glofitamab-gxbm[6]	relapsed or refractory diffuse large β-cell lymphoma
5	talquetamab-tgv[6]	relapsed or refractory multiple myeloma

This review focuses on the anticancer activity of heterocyclic-based compounds.

2 Various Classes of Compounds as Anticancer Agents

2.1 Quinoline Derivatives as Anticancer Agents

The bioactive heterocyclic compounds quinoline and quinolone derivatives are important classes in the pharmaceutical field because of their diverse pharmacological properties which include antibacterial, anti-inflammatory, anticancer, anti-HCV, antitubercular, antimalarial, anti-HIV, and anti-Alzheimer activities.[10] Dimers typically exhibited some unusual features when compared to the comparable monomeric compounds which is why they have generated a lot of interest recently. Derivatives of quinoline/quinolone possess good anticancer activity. The following are drugs undergoing clinical trials or are used to treat cancer: quinoline derivative dactolisib (a quinoline dimer); topotecan; vosaroxin (or voreloxin, a quinolone derivative), the first anticancer drug that was approved by the US FDA in 2009 as an orphan drug for treating acute myeloid leukemia; and quarfloxacin (Figure 1). In addition, results of phase I clinical trial for dactolisib, which is a PI3K inhibitor, displayed its good efficiency in treating a number of solid tumors. So, quinoline/quinolone compounds have the potential to be cancer-fighting substances.

Various review articles and books have made a comprehensive review of current developments of quinoline-based anticancer agents.[16]

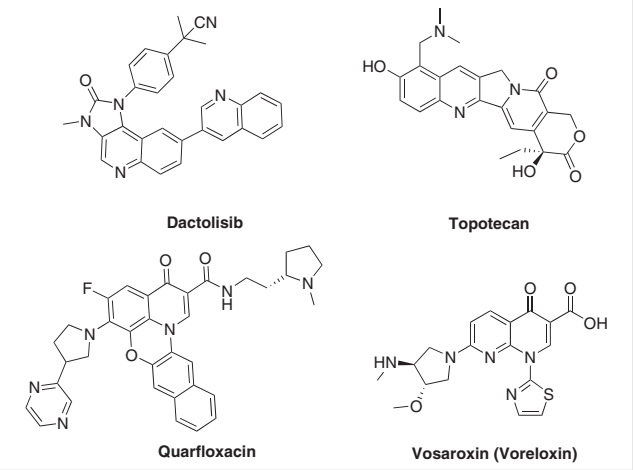


Figure 1 FDA-approved quinoline/quinolone-based drugs

Li et al. investigated the *in vitro* antitumor effects of a series of bisquinoline derivatives connected by the 4-oxy-3-fluoroaniline moiety on a panel of cancer cell lines (H460, HT-29, MKN-45, U87MG, and SMMC-7721) (see Figure 2).[11] Preliminary data indicate that all compounds tested had moderate to good cytotoxic effects (IC_{50}: 0.011–3.56 μM) on cancer cells with potencies in the single-digit μM range and high selectivity for the H460 and MKN-45 cell lines. Compound **2** was more powerful than its analogue counterpart **1**, implying that using fluoro in the R^2 position could boost activity. Compound **1b** with an IC_{50} of 0.011–0.15 μM was shown to be 2.9–10.9 times more efficient than foretinib for all selected cancer cell lines highlighting the need for additional study. Its capacity to inhibit c-Met kinase was found to be comparable to foretinib. Further research found that the 2-quinolone can substitute for the quinoline motif. Compared to foretinib, the 2-quinolone-quinoline derivative **3** was shown to be 6.1 times more active against H460, 2.4 times more active against HT-29, and 2.1 times more active against U87MG cell lines with an IC_{50} value of 0.031–0.52 μM. Compound **3** had significant potency against c-Met (IC_{50} = 1.21 nM), moderate inhibitory impact against F1t-3 (IC_{50} = 2.15 nM), and low potency against c-Kit, VEGFR-2, PDGFR-b, and EGFR (IC_{50} = 362. 8 to>100,000 nM). Based on this research, it can be stated that compound **3** largely affects c-Met and Flt-3 and it may be considered for optimization. [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazole-tethered fluoroquinolone-fluoroquinolone compounds **4** and **5**

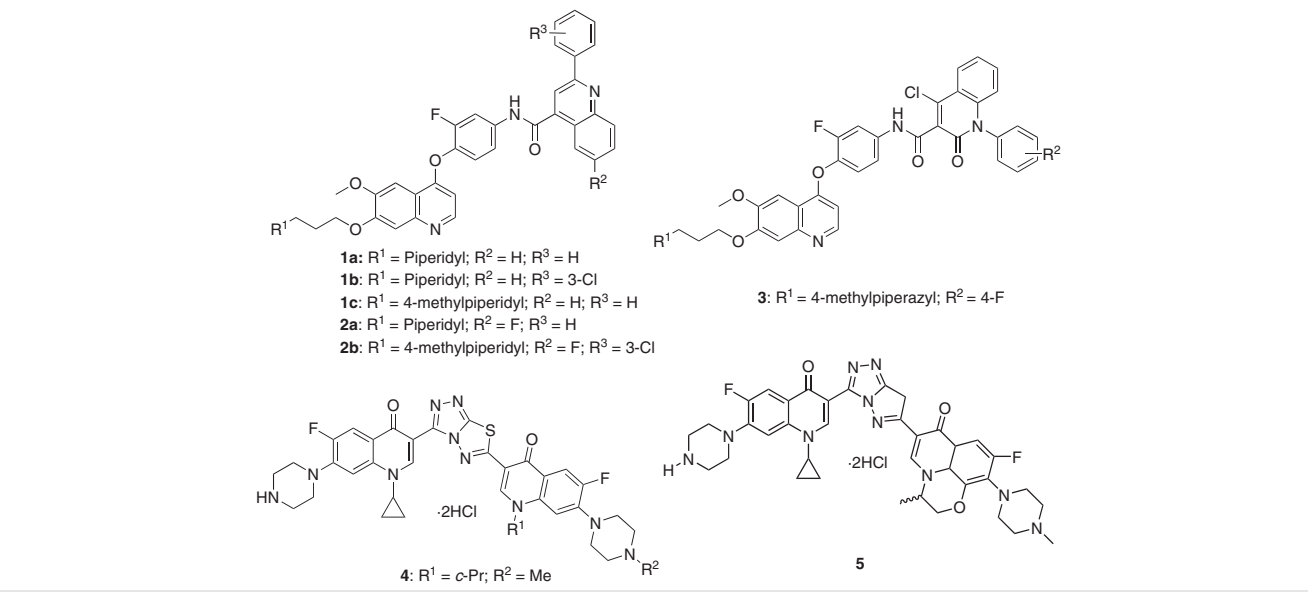


Figure 2

were tested on L1210, CHO, and HL60 cell lines. All compounds displayed cytotoxicity with IC_{50} values ranging from 0.12–26.2 μM. Compound **4** with an IC_{50} value of 0.54 μM and compound **5** with and IC_{50} value of 0.12 μM had the strongest effects on HL60 cells, proving that the cyclopropyl group of at N1 of fluoroquinolone is crucial for its high cytotoxicity.

2.1.1 Secosteroid-Quinoline Hybrids

13,17-Secoestra-1,3,5(10)-trien-17-oic acid *N*′-(quinolylmethylene)hydrazides **6** and **7** were shown to have a high selectivity index (Figure 3).[12] In luciferase reporter assays, compounds **6** and **7** displayed excellent antiestrogenic potential as compared to tamoxifen. Compound **6** and **7** displayed good activity against MCF-7 cells with an IC_{50} value of 1.7 μM for compound **6** and 1.5 μM for compound **7**. NCI/ADR-RES cells are multidrug resistant cells and compounds **6** and **7** were persistent towards these cells with IC_{50} value 1.5 μM for **6** and 3.5 μM for **7**. These were the defining characteristics of these successful drugs.

2.1.2 8-Hydroxyquinoline-Chalcone Hybrids with Dual Tubulin/EGFR Kinase Inhibition

Compounds **8** and **9** were tested for cell cycle, wnt1/β-catenin gene suppression, and apoptosis (Figure 4).[13] Western blot determined the apoptotic markers Bax, Bcl2, Casp3, Casp9, PARP1, and β-actin. The compounds **8** and **9** are promising antiproliferative candidates that inhibit EGFR kinase and polymerize tubulin. Compounds **8** and **9** exhibited good activity with an IC_{50} value of 0.097 ± 0.006 μM and 0.334 ± 0.002 μM, respectively against EGFR kinase inhibition and 5.3 ± 0.33 μM and 10.84 ± 0.67 μM, respectively, against tubulin polymerization inhibition

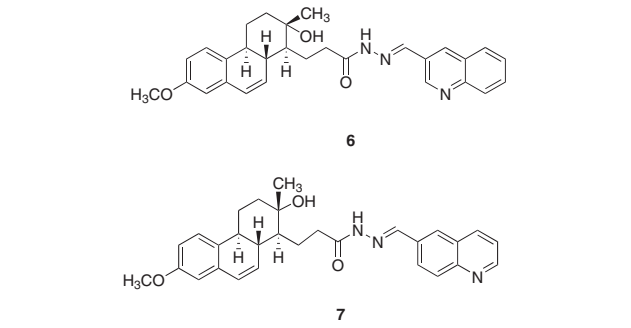


Figure 3

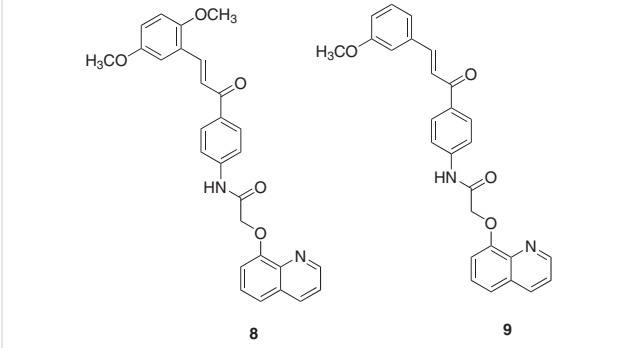


Figure 4

2.1.3 Quinoline Derivatives as Small Molecule Mutant EGFR Inhibitors Targeting Resistance in NSCLC

The selected cell lines were HCC827, H1975 (L858R/T790 M), A549 (WT EGFR), A-549, and BEAS-2B.[14] Many quinoline compounds displayed great cytotoxicity. Among all compounds, **10** (Figure 5) was found to possess high activity with IC_{50} values of 0.010 μM, 0.21 μM, 0.99 μM, and 2.99 μM as compared to osimertinib with IC_{50} values of 0.0042 μM, 0.04 μM, 0.92 μM, and 2.67 μM.

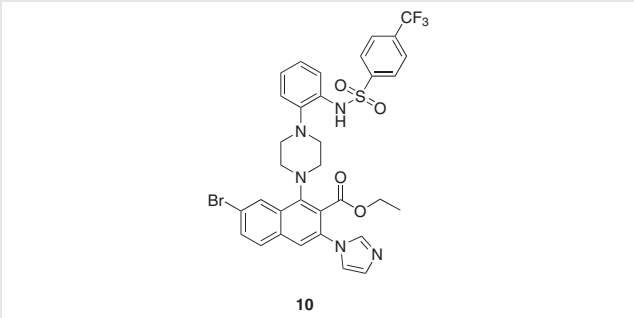


Figure 5

2.1.4 Tetra-, Penta-, and Hexacyclic Phenothiazines Modified with a Quinoline Moiety

Compound **11**, a 3-(dimethylamino)propyl-substituted diquinothiazine, showed high activity with an IC_{50} value of 0.3 μM against A549 cell line (see Figure 6).[15] Compound **12**, a 2-(diethylamino)ethyl-substituted diquinothiazine, displayed good cytotoxic activity against the SNB-19 cell line. Compound **13**, possessing a 2-[(2-chloroethyl)ureido]ethyl substituent, has excellent activity with an IC_{50} value of 87 nM against the SK-MEL-5 melanoma cell line. Leukemia (CCRF-CEM and MOLT4), colon (HCT-116), CNS (SNB-75 and SF-295), prostate (PC-3), non-small cell lung (NCI-H460 and HOP-92), ovary (IGROV-1, OVCAR-4, and OVCAR-5), and breast (MDA-MB-460) were the selected cancer cell lines. Less actions (IC_{50} = 0.25–1.0 μM) were seen for these cancer lines. 2-(Diethylamino)ethyl-substituted **14** (IC_{50} = 0.19 μM) and 3-(dimethylamino)propyl-substituted **15** (IC_{50} = 0.29 μM) displayed good activity against the ovarian cancer cell line IGROV-1.

2.1.5 3,5-Disubstituted Quinolines

3,5-Disubstituted quinolines with substitution at the 3,5-positions are powerful inhibitors of c-Jun N-terminal kinases (JNKs) that produce anticancer action.[16] JNK1, JNK2, and JNK3 are three different genes that produce JNKs. The prospective therapeutic target for neurodegenerative illnesses, such as Parkinson's disease, Alzheimer's disease, and other CNS disorders, is JNK3 inhibition because it has been demonstrated to trigger neuronal death. A growing number of medicines for anticancer activities are now focusing on JNK3.[16] Jiang et al. (2007) reported synthesis of a novel family of powerful c-Jun N-terminal kinase (JNK) inhibitors with p38 selectivity.[17] 3,5-Disubstituted quinolines were produced from 4-(2,7-phenanthrolin-9-yl)phenol. The inverse sulfonamide *tert*-butyl analogue **16** (Figure 7) in the X-ray crystal structure of JNK3 indicated an unanticipated binding mode for this novel scaffold with the protein and had a strong inhibitory effect against JNK3 (0.15 μM IC_{50}) but not against p38.

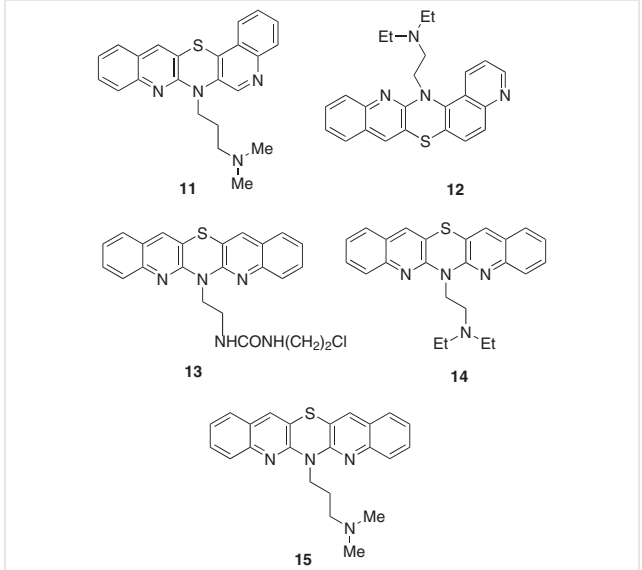


Figure 6

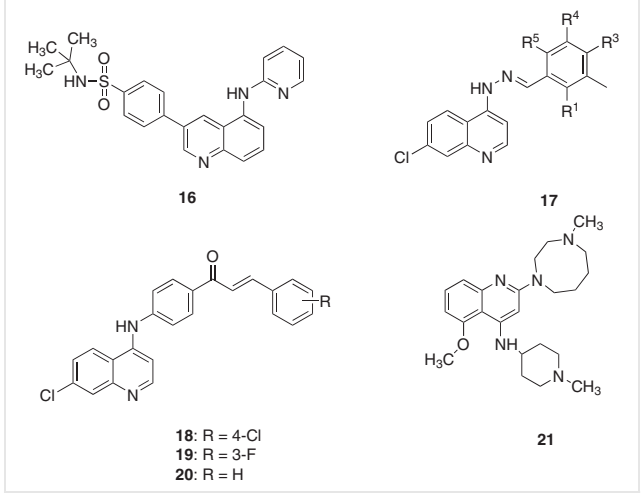


Figure 7

2.1.6 4,7-Disubstituted Quinolines

7-Chloro-4-quinolinylhydrazone derivatives **17** (Figure 7) as anticancer medications was reported by Bispo et al.[18] The synthesized compounds were tested against cancer cell lines using MTT assay. The anticancer activity results demonstrated that compounds had good cytotoxic activity against cancer cell lines, i.e., SF-295, colon; HTC-8 colon, and HL-60 leukemia, with IC_{50} values in range from 0.314 to 4.65 μg/mL.

Ferrer et al. in 2009 reported many novel [(7-chloroquinolin-4-yl)amino]-substituted chalcone derivatives that were tested for *in vitro* antiproliferative efficacy against human prostate LNCaP tumor cells (Figure 7).[19] Compounds 4-chloro-4′-[(7-chloroquinolin-4-yl)amino]chalcone (**18**) with IC_{50} value 7.93 ± 2.05 μg/mL, 4′-[(7-chloroquinolin-4-yl)amino]-3-fluorochalcone (**19**) with IC_{50} values of 7.11 ± 2.06 μg/mL, and 4′-[(7-chloroquinolin-4-yl)amino]chalcone (**20**) with IC_{50} value of 6.95 ± 1.62 μg/mL were good inhibitors of human prostate cell. Xiang et al. reported that 5-methoxy-2-(4-methyl-1,4-diazepan-1-yl)-*N*-(1-methylpiperidin-4-yl)quinolin-4-amine (**21**) inhibited EZH2 with an IC_{50} value of 1.2 μM.[20] Compound **21** reduced H3K27me3 levels across cells and shown effective inhibitory properties for the tumor cell lines HCT15 and MD-MBA-231.

2.1.7 2-Substituted 4-Amino-6-haloquinolines

Jiang et al. designed, synthesized and evaluated series of 2-substituted 4-amino-6-haloquinolines and the cancer cell lines selected were H-460, HT-29, HepG2, and SCG-7901.[21] (*E*)-N^1-[6-Chloro-2-(4-methoxystyryl)quinoline-4-yl]-N^2,N^2-dimethylethane-1,2-diamine (22) (Figure 8) has a 4-methoxystyryl group at C2 and a (dimethylamino)alkylamino substituent at C4 has been considered strongly for further structural modifications. This compound possesses good anticancer properties with IC_{50} values of 0.03 μM against H-460 cancer cell line, 0.55 μM against HepG2 cancer line, and 1.24 μM against SGC-7901 cancer cell line; these values showed that it is 2.5 to 186 more active than gefitinib.

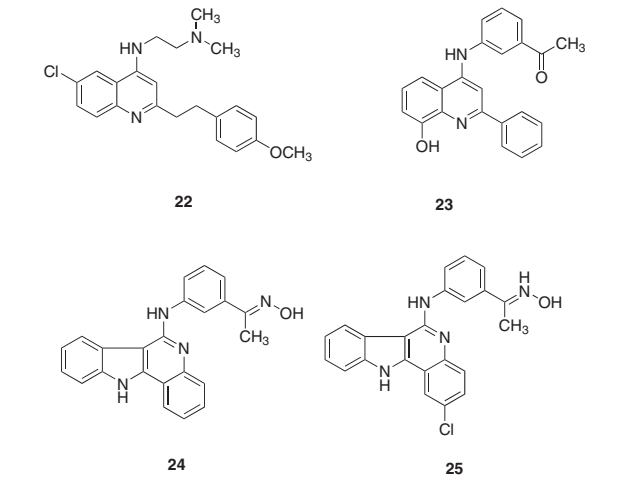


Figure 8

2.1.8 4-Anilino-8-hydroxy-2-phenylquinolines

Chen et al. in 2006 synthesized many 4-anilino-8-methoxy-2-phenylquinoline and 4-anilino-8-hydroxy-2-phenylquinoline derivatives and tested their antiproliferative ability.[22] Compound **23** (Figure 8) inhibited the development of cancer cells, such as HCT116 (colon cancer) with GI_{50} = 0.07 μM, MCF7 with GI_{50} = <0.01 μM, and MDA-MB-435 (breast cancer) with GI_{50} = 0.01 μM.

2.1.9 Indolo, Pyrrolo, Benzofuro, and 6-Anilinoindolo Quinolines

Chen et al. in 2002 prepared indolo-, pyrrolo-, and benzofuro-quinolin-2(1*H*)-ones and 6-anilinoindoloquinoline derivatives.[23] These were tested *in vitro* using three cell lines: MCF7 (breast), NCI-H460 (lung), and SF-268 (CNS). 1-[3-(11*H*-Indolo[3,2-*c*]quinolin-6-ylamino)phenyl]ethenone oxime hydrochloride (**24**) with GI_{50} = 1.70 μM and its 2-chloro derivative **25** with GI_{50} = 1.35 μM were found to be very potent (Figure 8). Both these compounds **24** and **25** with a GI_{50} value of less than 0.01 μM inhibited the growth of SNB-75, which is a CNS cancer cell.

2.2 Benzimidazoles as Anticancer Agents

Benzimidazoles are heterocyclic compounds of great importance. They possess antitumor, antiproliferative, anticancer, antimicrobial, and antioxidant activity.[24] Benzimidazole is structural analogue of purines which are part of DNA nucleotides.[25] Thiabendazole (or thiabenzazole), telmisartan, pimobendan, pantoprazole, omeprazole, etonitazene, carbendazim, benomyl, and albendazole are benzimidazole compounds which possess great pharmacological value. Veliparib, selumetinib, pracinostat, nocodazol, liarozol, glasdegib, galeterona, dovitinib, crenolanib, bendamustina, and abemaciclib are some organic derivatives of benzimidazole and these compounds are in clinical trials for determining their anticancer properties.

De, Banerjee, and co-workers reviewed benzimidazoles in 2023 with the aim to develop a comprehensive SAR (structure–activity relationship).[26] While Ebenezer and coworkers reviewed benzimidazoles in drug discovery between 2020–2022.[27]

Garuti et al. synthesized BZ-4,7-dione compounds (Figure 9). These compounds were tested against molt-3 cells. These cells were derived from human lymphoblastic leukemia.[28] Compounds **26** (IC_{50} = 1.32 μM) and **27** (IC_{50} = 2.63 μM) showed good antiproliferative activity. Compound **28**,

IC_{50} = 0.98 µM against SW620 cells, was active compared to doxorubicin (IC_{50} = 0.72 µM. Chojnacki et al. determined antiproliferative and protein-kinase inhibitory effects in anticancer treatment.[29] Compound **29** with Ki = 1.96 µM and compound **30** with Ki = 0.91 µM displayed good protein kinase 2 (CK2) inhibitory activity. Due to this these compounds can be considered for further research.

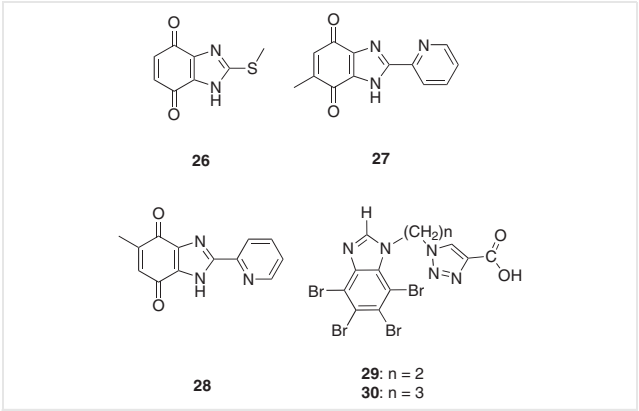


Figure 9

Abd El-Meguid et al.[30] reported that compounds **31** (IC_{50} = 0.25 ± 0.003 µM) and **32** (IC_{50} = 0.19 ± 0.004 µM) showed good activity as compared to erlotinib (IC_{50} = 1.23 ± 0.005 µM) against HER2 cell (Figure 10). Also compound **31** with an IC_{50} value of 0.157 ± 0.007 µM and compound **32** (IC_{50} = 0.109 ± 0.014 µM) displayed excellent activity against EGFR when compared to erlotinib (IC_{50} = 0.079 ± 0.001 µM).

Compound **33** (Figure 10) possess an IC_{50} of 4.30 nM against PARP1 and 1.58 nM against PARP2 enzymes substantial *in vitro* antitumor activity.[31]

Compounds **34** and **35** (Figure 10) were more active as compared to standard compound staurosporine.[32] Compound **34** possess an IC_{50} of 2.02 ± 0.13 µM against the MCF-7 cell line and compound **35** displayed an IC_{50} value of 3.30 ± 0.21 µM against the MDA-MB-231 cell line.

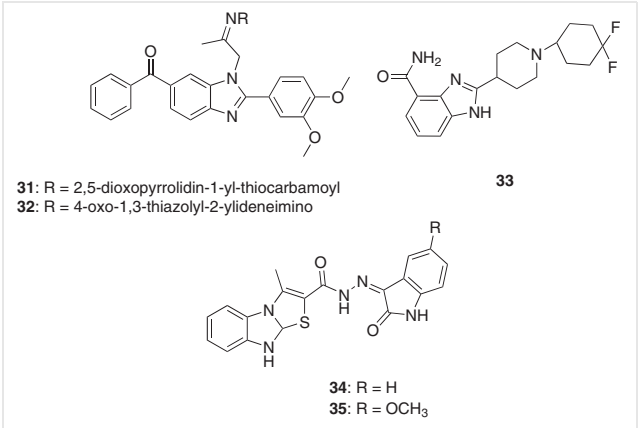


Figure 10

Compound **36** with an IC_{50} value of 0.33 µM and compound **37** with an IC_{50} value of 0.38 µM against EGFR kinase where as erlotinib caused inhibition with an IC_{50} value of 0.39 µM (Figure 11).[33]

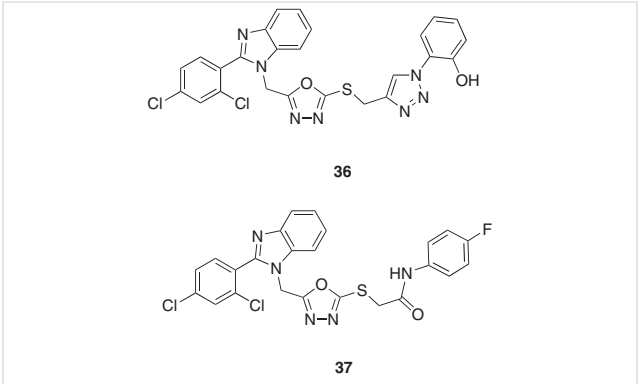


Figure 11

MBIC, dovitinib, selimetinib, and abemaciclib (Figure 12) are some benzimidazole based anticancer drugs (Figure 12). Benzimidazole derivatives are good microtubule inhibitor.[34] Methyl 2-(5-fluoro-2-hydroxyphenyl)-1*H*-benzimidazole-5-carboxylate (MBIC) with a methyl ester is substituted with a hydroxyl group at C-2 whereas a fluoro group at C5 position in the aryl ring inhibits microtubule and are very active against breast cancer cells.[35] MBIC has the following values against: breast cancer cells IC_{50} 0.73–20.4 µmol/L, cervical cancer cells IC_{50} = 0.21 µmol/L, hepatocellular carcinoma cells IC_{50} = 2.92 µmol/L, lung cancer cells IC_{50} = 1.29 µmol/L, and colorectal cancer cells IC_{50} = 2.72 µmol/L.

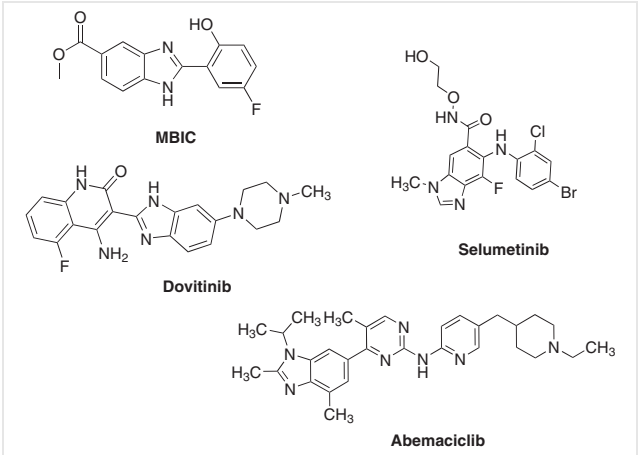


Figure 12 Benzimidazole-based anticancer drug

Compound **38** is an imidazole[1,5-*a*]pyridine-benzimidazole hybrid (see Figure 13) which possess good cytotoxic activity against 60 human cancer cell lines.[36] The GI_{50} values of compound **38** against cell free assay, leukemia cells, breast cancer cells, ovarian cancer cells, melanoma cells, lung cancer cells, colorectal cancer cells, CNS cancer cells, renal cancer cells, and prostate cancer cells are 1.71 µmol/L, 1.47–2.92 µmol/L, 2.17–3.09 µmol/L, 2.05–6.95 µmol/L, 1.39–4.61 µmol/L, 0.42–3.85 µmol/L, 3.63–7.19 µmol/L, 2.97–5.49 µmol/L, 1.67–7.73 µmol/L, and 1.88–2.85 µmol/L, respectively.

Dovitinib, ((3*E*)-4-amino-5-fluoro-3-[5-(4-methylpiperazine-1-yl)-1,3-dihydrobenzimidazol-2-ylidene]quinoline-2-one also known as CHIR-258 or TKI258) is the lactate salt of a benzimidazole–quinoline compound that function as a multitargeted growth factor receptor kinase inhibitor.[37] The IC_{50} values against FLT-3, FGFR1, VEGFR3/FLT4, c-Kit, and FGFR3 are 0.001 µmol/L, 0.008 µmol/L, 0.008 µmol/L, and 0.002 µmol/L, 0.009 µmol/L, respectively.

Selumetinib [6-[4-bromo-2-chlorophenyl)amino]-7-fluoro-3-methyl-3*H*-benzimidazole-5-carboxylic acid (2-hydroxyethoxy)amide] is a MEK inhibitor; it targets MEK1 and MEK2. It binds at MEK1/2 and disrupts the interaction of both ATP and substrate and the assessment of the ERK activation loop.[38] It has an IC_{50} for MEK1 of 0.014 µmol/L and MEK 2 of 0.53 µmol/L.

Abemaciclib is a CDK inhibitor. It has been approved by FDA to be used as adjuvant with endocrine therapy to treat breast cancers.[39] Abemaciclib has IC_{50} = 0.002 µmol/L against CDK4 and 0.01 µmol/L against CDK6. Compounds **39** and **40** are RAF kinase inhibitors (Figure 13). Compound **39** has IC_{50} = 0.002 mmol/L and **40** has IC_{50} = 0.014 mmol/L against the B-RAFV600E oncogenic protein;[40] against melanoma cells, compound **39** has 4.6 µmol/L and **40** has IC_{50} = 2.3 µmol/L.

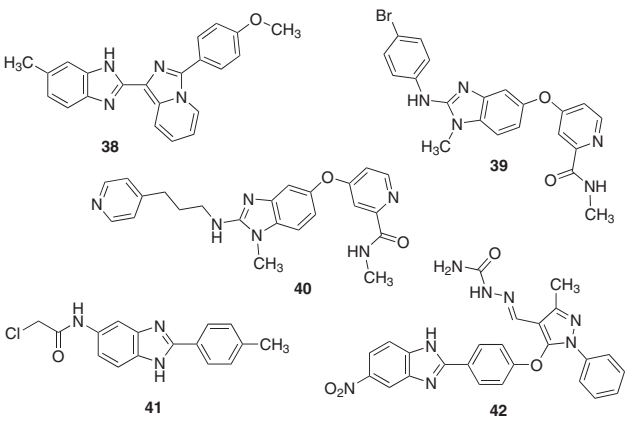


Figure 13

(2-Chloro-*N*-(2-*p*-tolyl-1*H*-benzimidazole-5-yl)acetamide (**41**; Figure 13), a 2-arylbenzimidazole, is an RTK inhibitor for EGFR, VEGFR-2, and PDGFR.[41] The IC_{50} value of **41** against liver cancer cells is 2 µmol/L.

Compound **42**, with a carbamoyl hydrazone substituent, synthesized by Galal et al. is a CHK2 inhibitor (Figure 13).[42] It inhibits cell cycle progression in ER+ MCF7 breast, HeLa cervical, and HepG2 hepatocellular cancer cell lines. The IC_{50} values of **42** for CHK2, cervical cells, and breast cancer cells are 0.041 µmol/L, 11.7 µmol/L, and 13.8 µmol/L, respectively.

Compounds **43** and **44** (Figure 14) are 1,2,3-triazolyl-linked 2-arylbenzimidazole derivatives. Compound **43** is a 4-chlorophenyl-substituted 1,2,3-triazolyl *N*-isopropylamidine whereas compound **44** is a benzyl-substituted 1,2,3-triazolyl imidazoline; both possess excellent activity.[43] Compounds **43** and **44** have IC_{50} = 0.05 µmol/L and 0.07 µmol/L, respectively, against liver cancer cells.

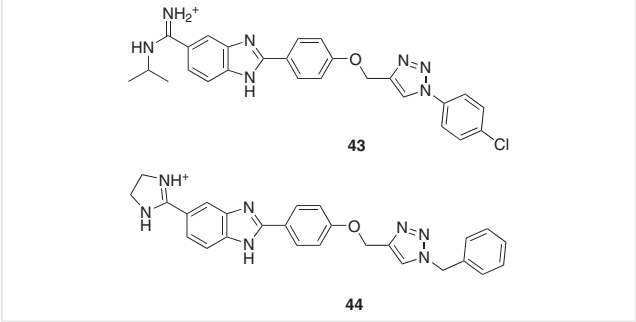


Figure 14

Rucaparib is a tricyclic benzimidazole carboxamide derivative (Figure 15). It targets PARP-1, -2, and -3 with IC_{50} = 0.8 against PARP-1, IC_{50} = 0.5 against PARP-2, and IC_{50} = 28 nmol/L against PARP-3.[44,45] It has been approved by the FDA and the European Medicine Agency for treating ovarian, fallopian tube, and peritoneal cancers as well as advanced solid tumors with evidence of germline or somatic BRCA mutation.

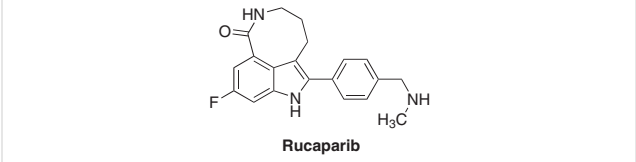


Figure 15 A benzimidazolecarboxamide derivative as an anticancer drug

2.3 Indole: A Privileged Scaffold for the Design of Anticancer Agents

Indole and its derivatives have a biologically significant role.[46] It binds to a variety of receptors and enzymes with high affinity because of its distinct structural motif. It is

also utilized as anticonvulsant, anti-inflammatory, antimicrobial, antituberculosis, anticancer, anti-HIV, antiviral, and antioxidant. Several synthetic medications that contain indole include sumatriptan, indolemycin, indomethacin, pindolol, and reserpine. Several pharmacologically significant compounds that include indole are: tryptophan, serotonin, indole-3-acetic acid, melatonin, and reserpine.

Wan, Tang, and co-workers have reviewed indole as a privileged scaffold for the design of anticancer agents.[47]

Compound **45** is a 1*H*-pyrazolo[3,4-*b*]pyridine derivative (Figure 16).[48] It possesses good activity for pim kinases inhibition with an IC_{50} value of 9 nM for pim-1, 39 nM for pim-2, and 12 nM for pim-3. Additionally, compound **45** demonstrated outstanding suppression of additional kinases, including Flt-3, c-Kit, PDGFR, and Kdr. Replacing the 1*H*-pyrazolo[3,4-*b*]pyridine core by an indole gives compound **46** (Figure 16). With an IC_{50} value of 4 nM for pim-1, 42 nM for pim-2, and 22 nM for pim-3, this substitution preserved the inhibitory activity against pim kinases but lost the ability to inhibit other kinases.

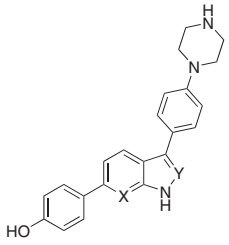


Figure 16

Compound **47** (Figure 17) displayed good inhibitory activity against pim kinases with an IC_{50} < 2 nM for pim-1, IC_{50} = 10 nM for pim-2, and IC_{50} < 2 nM for pim-3.[48]

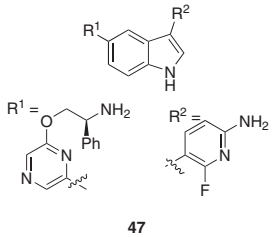


Figure 17

An indole alkaloid meridian C (**48**) was obtained from a marine source (Figure 18). Its IC_{50} value of 1.04 μM indicates that it exhibits good action against Pim-1. Lee and co-workers synthesized compound **49** with an IC_{50} value in the nanomolar range with IC_{50} values for the kinases Pim-1, Pim-2, and Pim-3 of 3 nM, 110 nM, and 7 nM, respectively.[49] They explored the SAR of 3,5-disubstituted indoles, replacing the 2-aminopyrimidine ring of **49** for a phenyl ring in order to increase its activity. By changing the substituents and locations on the phenyl ring, this was able to maintain the physicochemical properties while observing an increase in hydrophobic contacts with pim-1. As pim inhibitors, these attempts produced a number of unique indole compounds. Compound **50** displayed good activity for pim-1 and pim-3 and its IC_{50} value was found to be in nanomolar range with single digit value. With the exception of casein kinase 2 (CK2), the most active compound **50** had comparable outstanding inhibitory effects against pim-1 and pim-3 with single digit nanomolar IC_{50} values and remarkable selectivity over 14 protein kinases. It was significantly more effective than compound **51** in its excellent antiproliferative action against the MV4-11 cell line (IC_{50} = 0.8 μM). Compound **48** was adapted to increase its inhibitory action against pim-2. Compound **50** displayed three pim isoforms with single digit nanomolar IC_{50} values (Pim-1: IC_{50} = 5 nM; Pim-2: IC_{50} = 259 nM; Pim-3: IC_{50} = 10 nM).

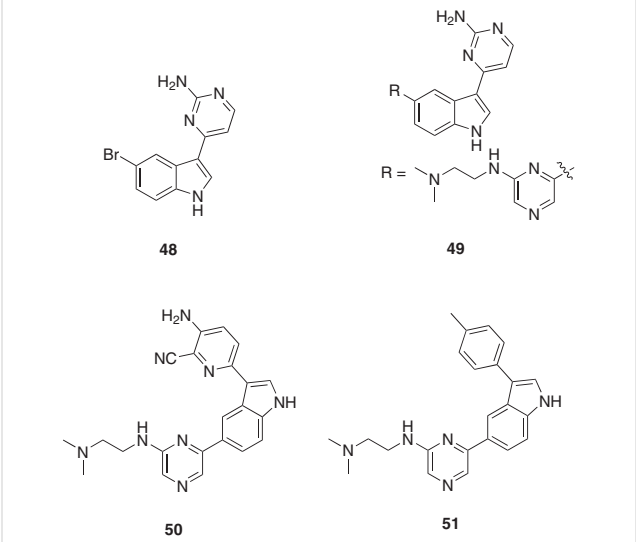


Figure 18

The FDA or China Food and Drug Administration has approved five HDAC inhibitors: vorinostat, belinostat, romidepsin, panbinostat, and chidamide. Dai and co-workers synthesized and evaluated a series of hydroxamic acid-based HDAC inhibitors with an indole amide residue at the terminus.[50] Compound **52** (Figure 19) proved to be the most efficacious chemical with a nanomolar IC_{50} value of 3.1 nM against a mixture of HDACs (mostly HDAC1/2, K562 cell extracts) about 40 times more active than SAHA which had an IC_{50} value of 143 nM. It showed sub micromolar IC_{50} values against the human HT1080 cell line (fibrosarcoma; IC_{50} = 0.12 μM) and the human MDA435 cell line (breast cancer; IC_{50} = 0.13 μM) which are more than ten times more potent than SAHA.

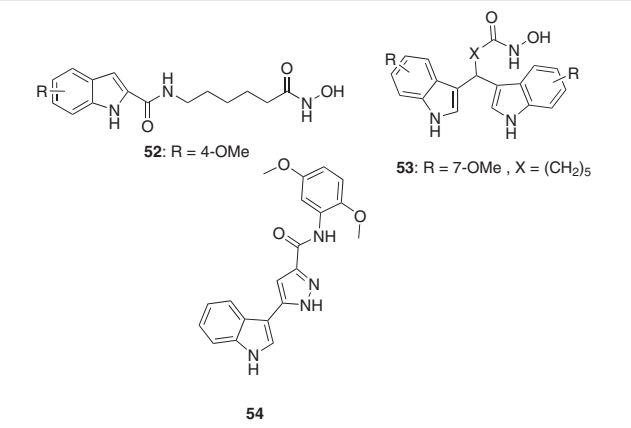


Figure 19

Giannini et al.[51] designed and synthesized a series of SAHA derivatives bearing the bis(indolyl)methane (BIM) moiety and against the HCT116 and H460 tumor cell lines, compound **53** (Figure 19) exhibited remarkable antiproliferative properties (IC_{50} = 0.41 and 0.55 μM, respectively). SAR demonstrated that linker length affects HDAC inhibition with pentamethylene linkers being the most effective. The monoindolyl methane derivatives were not as potent as the target compounds containing the BIM moiety.

2.3.1 Novel Indole-Pyrazole Hybrids as Potential Tubulin-Targeting Agents

Compound **54** (Figure 19) demonstrated a moderate level of inhibition against tubulin polymerization (IC_{50} = 19 μM) and excellent efficacy against hepatocellular carcinoma (HCC) cell lines with IC_{50} values in the range of 0.6–2.9 μM.[52]

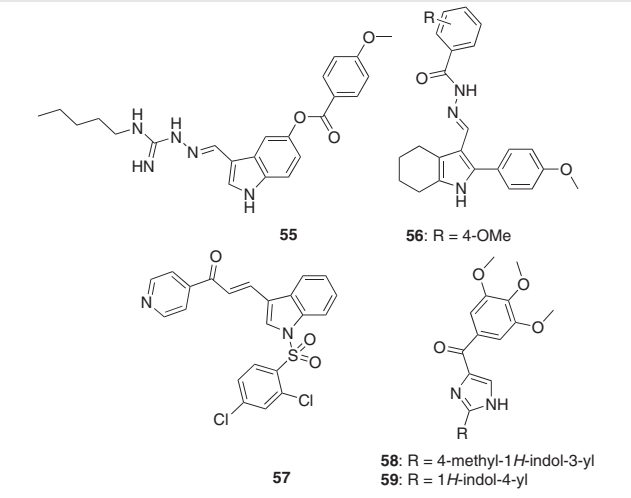


Figure 20

(*E*)-3-(2-{[(*N*-Pentylcarbamimidoyl)hydrazono]methyl}-1*H*-indol-5-yl)-4-methoxybenzoate (**55**) possesses and excellent IC_{50} value of 0.042 μM against SMMC-7721 cells (Figure 20).[53] However, compound **55** exhibited no cytotoxicity when tested against normal cells, such as HEK293 and HEK293T cells.

2-Phenyl-4,5,6,7-tetrahydro-1*H*-indole derivative **56** (Figure 20),[54] with a 4-methoxyphenylhydrazone moiety, is a tubulin polymerization inhibitor and it was tested for its antiproliferative activity *in vitro* against human breast cancer cell line (MCF-7) and human lung adenocarcinoma cell line (A549). With an IC_{50} value of 1.77 ± 0.37 μM against MCF-7 and 3.75 ± 0.11 μM against A549, it demonstrated remarkable anticancer activity and had a significant inhibitory effect on tubulin polymerization akin to that of colchicine. Compound **56** exhibited a similar inhibitory effect on tubulin polymerization as colchicine and molecular docking analysis demonstrated that compound **56** possesses a high binding affinity for the tubulin binding pocket of colchicine.[55]

The inhibitory efficacy of compound **57**, a sulfonamide derivative of pyridyl-indole-based chalcone (Figure 20), is an efficient carbonic anhydrase inhibitor; it was tested against the human carbonic anhydrase IX isoform.[56] Studies on fluorescence binding and molecular docking were employed. Utilizing MCF-7 and HepG-2 cell lines, its anticancer efficacy was investigated. Compound **57** with an IC_{50} value of 0.13 μM, demonstrates remarkable anticancer efficacy.

Li, Li, and co-workers, in 2019, examined indole-imidazole hybrids as powerful tubulin inhibitors and found that 2-(4-methyl-1*H*-indol-3-yl)imidazole **58** and 2-(1*H*-indol-4-yl)imidazole **59** (Figure 20) were very powerful with IC_{50} = 1.6 to 3.7 nmol/L, which is two to three times greater than the reference drug ABI-231.[57]

Compound **60** is a thiosemicarbazone derivative containing an indole group (Figure 21).[58] Compound **60** exhibits remarkable anticancer properties as evidenced by its IC_{50} values of 0.14 ± 0.02 μM for PC3 and 9.85 ± 0.26 μM for WPMY-1. Compound **60** effectively causes apoptosis and

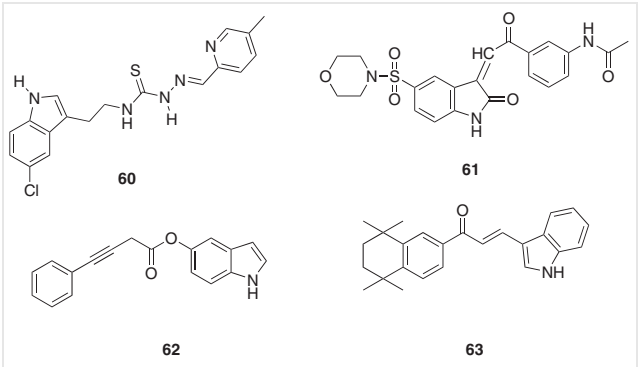


Figure 21

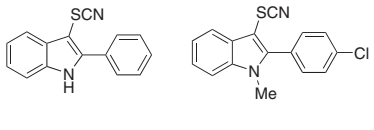
inhibits PC3 cell colonization and proliferation. In PC3 cells, compound **60** demonstrated increased selectivity towards two normal WPMY-1 and GES-1.

Ammar, Belal, and co-workers synthesized a novel series of indole derivatives and evaluated their anticancer activity using HepG-2, HCT-116, and MCF-7 cell lines;[59] compound **61** (IC_{50} <10 μM) demonstrated broad spectrum anticancer action on all three tested cell lines (Figure 21). Compound **61** exhibits superior antitumor activity compared to lapatinib. Molecular docking was utilized to investigate the binding mechanism, amino acid interactions, and free binding energy of chemical **61**.

Compound **62**, an indole and pyranoindole derivative possesses good antitumor activity (Figure 21).[60] Compound **62** demonstrated its inhibitory action on the target protein tubulin and exhibited strong anticancer activity against the HeLa cell line (IC_{50} = 3.6 ± 0.5). No cytotoxicity was observed by **62** towards normal cells. Data confirmation was achieved using silico assay.

Indole retinoid compound **63** (Figure 21) exhibits antiproliferative properties in cell lines of liver, breast, and colon cancer.[61] Compound **63** prevents the proliferation of all breast cancer cell lines with extremely low IC_{50} values. In Huh7 cell line, compound **63** has the highest anticancer activity (IC_{50} <0.01 μM). Docking and molecular dynamics experiments on RXRα and RXRγ were conducted with compound **63**.

The antiproliferative activity of compounds **64** and **65** (Figure 22), which are 3-thiocyanato-1*H*-indole derivatives, was assessed against four human cancer cell lines: HL60, HEP-2, NCI-H292, and MCF-7.[62] The reference drug utilized was doxorubicin. Compound **64** antiproliferative activity was measured with IC_{50} values of 1.43 μM, 2.79 μM, 2.07 μM, and 3.95 μM against HL60, HEP-2, NCI-H292, and MCF-7, respectively. With an IC_{50} value of 1.10 μM against HL60, 2.80 μM against HEP-2, 2.07 μM against NCI-H292 and 4.05 μM against MCF-7, compound **65** also showed strong antiproliferative activity.



64 65

Figure 22

2.4 Pyrimidine Derivatives as Anticancer Agents

It is commonly recognized that pyrimidine derivatives have pharmacological properties. Numerous medications containing pyrimidine group, such as thioguanine, tegafur, and 5-fluorouracil (5-FU) (Figure 23) were synthesized and employed as anticancer treatments. Pyrimidines and their derivatives have a wide range of biological properties including antibacterial, analgesic, antiviral, and anticancer properties. As a result of the assessment of pyrimidines as a novel class of highly effective anticancer agents, hundreds of compounds, such as 2-cyanopyrimidines, hydrazino pyrimidine-5-carbonitriles, 1,3-dialkylated pyrimidine-2,4-diones, and 4-anilino-2-(2-pyridyl)pyrimidines, have been prepared and evaluated for their anticancer activity.[63] It is acknowledged as the most significant substance in the treatment of cancer because of its structural similarity to the nucleotide base pair found in both DNA and RNA.[64]

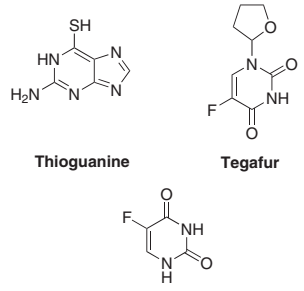


Figure 23 Pyrimidine-based anticancer drugs

Sharma and co-workers reviewed the anticancer activity of pyrimidine with key emphasis on SAR in 2021.[64] Recent advances on pyrimidine derivatives as anticancer agents was reviewed in 2023 by Mahdy, Elnagar, and Sakr.[65]

2.4.1 Pyrimidine-Containing Compounds as Adenosine Receptor Antagonists

In 2022, Li et al. synthesized a number of dual A2A/A2B adenosine receptor (AR) antagonists based on the triazole-pyrimidine-methylbenzonitrile core.[66] Compound **66** (Figure 24) had remarkable inhibitory effect on A2B AR with an IC_{50} = 14.12 nM.

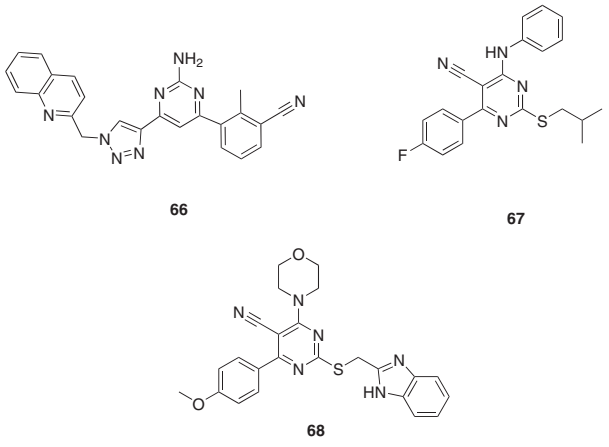


Figure 24

2.4.2 Pyrimidine-Containing Compounds as COX-2 Selective Inhibitors

Alam and co-workers synthesized fluorophenyl-substituted cyanopyrimidines in 2020 and assessed them as COX-2 selective inhibitor anticancer medicines.[67] Compound **67** (Figure 24) demonstrated remarkable anticancer efficacy against ovarian cancer (GI_{50} = 0.33 μM and selectivity index of 4.84), in contrast to 5-fluorouracil (5-FU) (GI_{50} = 4.43 μM). Compound **67** was more specific for COX-2 than COX-1 and exhibited broad antitumor action.

2.4.3 Cyanopyrimidines

In 2020, Alam and co-workers synthesized many analogues of benzimidazole-pendant cyanopyrimidine derivatives which were assessed for their *in vitro* anticancer properties against NCI-60 cancer cell lines at the National Cancer Institute (NCI) in the United States.[68] Of all the compounds produced, compound **68** (Figure 24) exhibited the highest level of activity.

2.4.4 Disubstituted Pyrimidines

Chen and co-workers, in 2020, synthesized 2,4-disubstituted pyrimidines (Figure 25)[69] and they were tested for antiproliferative activity using MTT assay with VX-680 as positive control against the cell lines A549 (IC_{50} = 12.05 ± 0.45 μM), HTC-116 (IC_{50} = 1.31 ± 0.41 μM), and MCF-7 (IC_{50} = 20.53 ± 6.13 μM); compound **69** exhibited moderate to high levels of activity. Compounds **70** (IC_{50} = 2.14 to 5.52 μM) and **71** (IC_{50} = 1.98 to 4.27 μM) differed in their substitution on the aromatic ring and terminal aniline on the pyrimidine moiety and demonstrated excellent activity against the PC-3, A549, MCF-7, and HCT-16 cancer cell lines.[70]

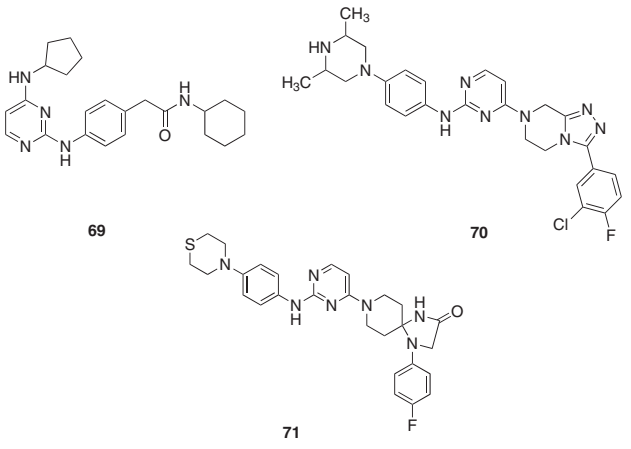


Figure 25

2.4.5 Trisubstituted Pyrimidines

2.4.5.1 2,4,5-Trisubstituted Pyrimidines

2,4-Diaminopyrimidines are highly effective and specific inhibitors of Aurora A kinase. Using the MTT assay, the compound outstanding activity was evaluated against HeLa, A-549, HCT-8, and Hep-G2 cells and contrasted with VX-680, a positive control. Compound **72** (Figure 26) demonstrated a cytotoxicity IC_{50} = 0.5–4.0 μM indicating good activity.[71] HeLa cells in the G2/M phase experience cell cycle arrest due to compound **72**.

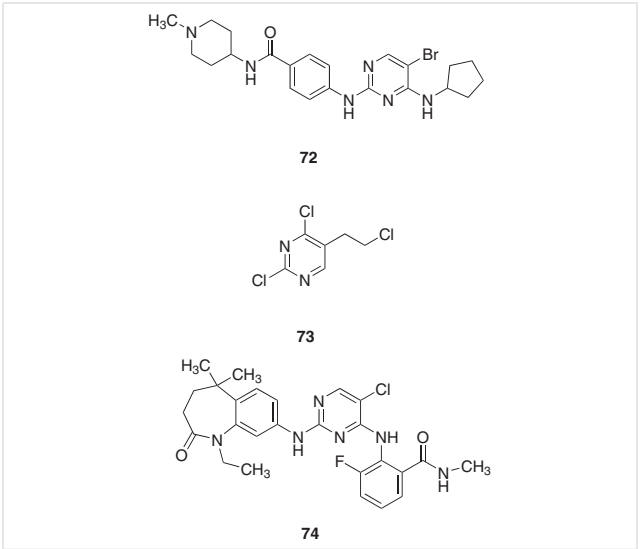


Figure 26

Cytostatic activities of alkyl 5-alkylpyrimidines, alkyl *N*-(methoxymethyl)pyrimidines, and 5,6-dihydrofuro[2,3-*d*]pyrimidines were described (Figure 26) using 5-FU as the positive control.[72] With an IC50 of 0.8 ± 0.2 mM, 5-(2-chloroethyl)-2,6-dichloropyrimidine (**73**) had a cytostatic impact on the HCT-116 cancer cell line, resulting in cell cycle arrest at the G2/M phase due to DNA damage. In cellular and enzymatic experiments, 2-(arylamino)pyrimidines with a 2-amino-*N*-methylbenzamide at C4 and chlorine at C5 shown to be good c-Met inhibitors.[73] Excellent c-Met inhibition was demonstrated by pyrimidines bearing a C2 benzazepinone; the best analogue was compound **74**, which had an IC_{50} value of 10 nM; C3 of the aminobenzamide moiety contains fluorine, which gives c-Met kinase selectivity.

2.4.5.2 2,4,6-Trisubstituted Pyrimidines

2,4,6-Trisubstituted pyrimidine **75** (Figure 27) demonstrated outstanding efficacy in inhibiting the U937 cell line, with an IC_{50} value of 12.2 nM. It inhibited the growth of cancer cells by causing polyploidy (4N, 8N, and 16N) by disruption of both chromosomal and spindle formation.[74]

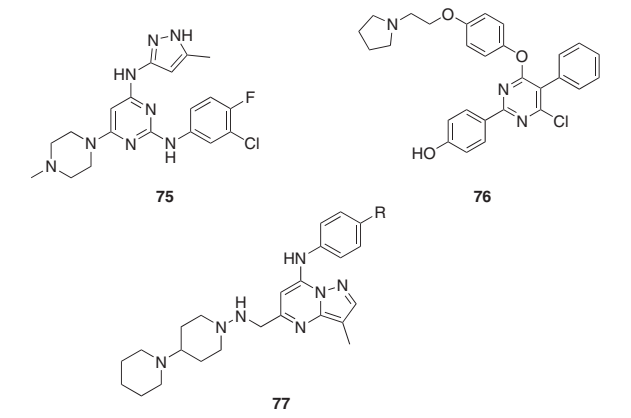


Figure 27

2.4.6 2,4,5,6-Tetrasubstituted Pyrimidines

The MCF-7 cancer cell lines were examined with 2,4-disubstituted pyrimidine derivatives which are ERα and VEGFR-2 ligands. Compound **76** (Figure 27) demonstrated inhibitory efficacy against VEGFR-2 with an IC_{50} value of 0.085 μM and an ERα binding affinity of 1.64 μM.[75]

2.4.7 Pyrazolo[1,5-*a*]pyrimidines and Pyrazolo[4,3-*d*]-pyrimidines

The anticancer activity of the pyrazolo[1,5-*a*]pyrimidine derivatives with a nitrogen mustard moiety was evaluated using the MTT assay against the cell lines A549, SH-SY5Y, HepG2, MCF-7, and DU145. Compound **77** (Figure 27) brought the cell cycle to a stop at the G1 phase with an IC_{50} = 0.2–8.3 μM causing apoptosis in each of the five cancer cell lines.[76]

Pyrazolo[4,3-*d*]pyrimidines were examined for their anticancer action both *in vivo* and *in vitro* and they demonstrated CDK inhibition when the appropriate substitutions were made at C3, C5, and C7.[77] Compound **78** (Figure 28) demonstrated remarkable inhibition of CDK2, CDK5, and CDK9 with IC_{50} = 0.002 μM.

Pyrazolo[4,3-*d*]pyrimidine, a bioisostere of roscovitine, was evaluated for both CDK inhibition and antiproliferative activity. 5-Substituted 3-isopropyl-7-[(4-(2-pyridyl)benzyl)amino]-1(2)*H*-pyrazolo[4,3-*d*]pyrimidine **79** (Figure 28) demonstrated excellent suppression of CDK2 (IC_{50} = 21 nM) and CDK5 (IC_{50} = 35 nM).[78]

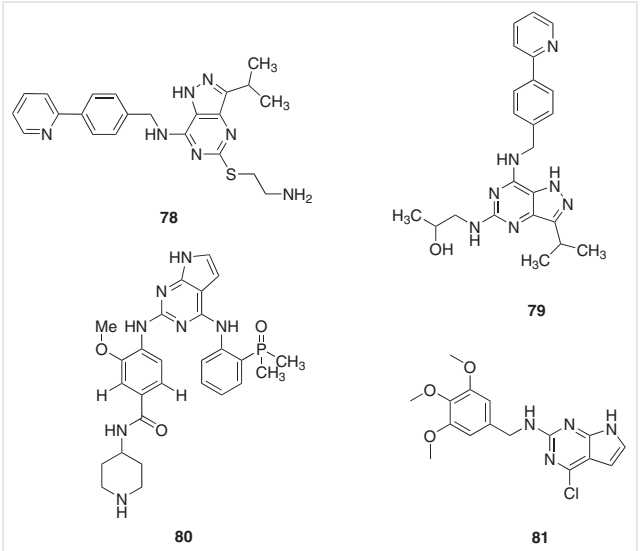


Figure 28

2.4.8 Pyrrolo[2,3-*d*]pyrimidines

Derivatives of pyrrolo[2,3-*d*]pyrimidines exhibit possible inhibitory effects on FAK. Compound **80** (Figure 28) demonstrated the suppression of MDA-MB231 and A549 cancer cell lines with the IC_{50} range of 3.20 ± 0.41 to 17.41 ± 1.3 μM, respectively and lowered the FAK enzymatic action at IC_{50} = 5.4 nM.[79]

When tested against the human cancer cell lines MCF-7 (breast), HCT116 (colorectal), and HepG2 (liver), compound **81** (Figure 28) demonstrated cytotoxic action.[80] When tested for its ability to inhibit EGFR-TK (epidermal growth factor receptor tyrosine kinase), it demonstrated outstanding inhibitory effects with IC_{50} values as low as 0.107 μM.

2.5 Pyridine Derivatives as Anticancer Agents

Pyridine is a well-known primary heterocyclic organic compound.[81] Pyridine derivatives have a broad range of biological and medicinal applications, including antiviral,[82,83] antibacterial,[83] antifungal,[83] anti-inflammatory,[83] anticancer,[83] antineuropathic, antihypertensive,[81] antidiabetic,[83] antitubercular,[83] antiparasitic,[81] antihistaminic,[81] and several other activities. Pyridine-related drugs have high therapeutic properties which persuade medicinal chemists to produce many newly chemotherapeutic agents. Pyridines constitute the class of nitrogenous heterocycles that undergo different chemical synthesis routes for generation of novel compounds possessing anticancer/antitumor properties.[84] Pyridine derivatives are important class of anticancer drug as they possess tendency to inhibit kinases, androgen receptors, tubulin polymerization, topoisomerase, enzyme, human carbonic anhydrase.[85] Sorafenib, regorafenib, vis-

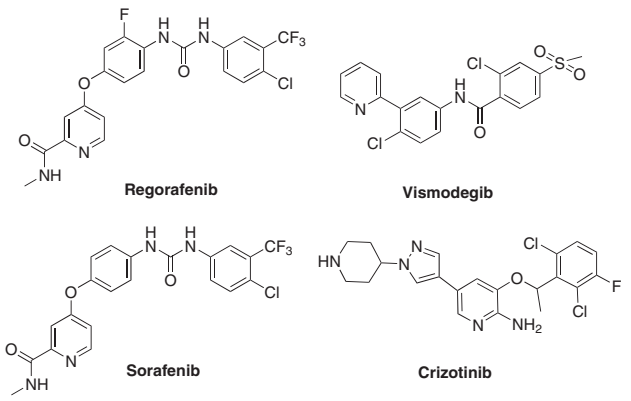


Figure 29 Pyridine-based anticancer drugs

modegib are pyridine based small molecules that have been approved as anticancer drugs (Figure 29).

Three relevant reviews appeared in 2022. Alrooqi et al. reviewed pyridine-based heterocyclic compounds as potent anticancer agents from 2017 to 2021.[81] Marinescu and Popa reviewed pyridine compounds with antimicrobial and antiviral activities.[82] Finally De, Kumar S K, and co-workers examined the clinical diversity of the pyridine scaffold.[83]

2.5.1 Pyridine-Ureas as Potential Anticancer Agents

1-[4-Chloro-3-(trifluoromethyl)phenyl]-3-[6-(4-methoxyphenyl)-2-methylpyridin-3-yl]urea (82) (Figure 30) and 1-[3-(trifluoromethyl)phenyl]-1-(6-(4-methoxyphenyl)-2-methylpyridin-3-yl)urea (83) are two new pyridine-ureas.[86] 3-[3-(Trifluoromethyl)phenyl]urea 83 was tested for its ability to suppress the proliferation of the MCF-7 breast cancer cell line *in vitro*. Compounds 82 and 83 were assessed for their *in vitro* anticancer activity utilizing the US-NCI procedure. Comparing compound 82 to the reference medication doxorubicin (IC_{50} = 1.93 μM), compound 82 is a more potent and essential congener against MCF7 cells (IC_{50} = 0.22 μM).

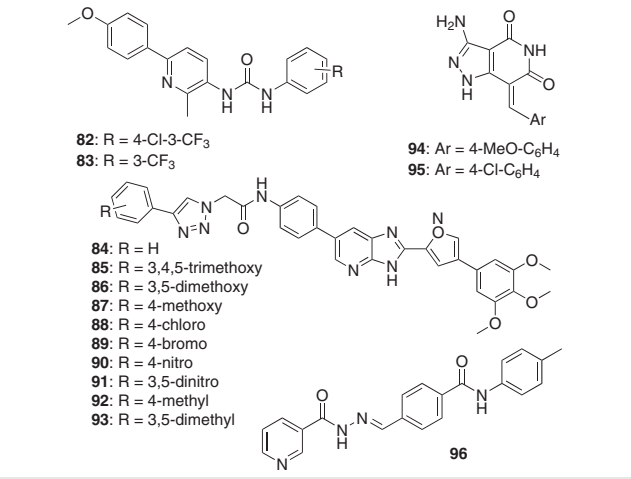


Figure 30

2.5.2 Pyridine Derivatives Containing Triazole and Benzimidazole Moieties

A series of *N*-{4-[2-(1-ammoniaylidyne-4-(3,4,5-trimethoxyphenyl)-1*H*-furan-2-yl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl]phenyl}-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetamide derivatives **84**–**93** were designed and synthesized (Figure 30).[87] These compounds anticancer properties were tested against A549 Colon-20, A2780, and MCF-7 and their results were contrasted with those of the reference medication, etoposide. Compounds **85**–**89** and **93** exhibited remarkable anticancer properties.

2.5.3 Pyridine Derivatives Containing a Pyrazole Moiety

The anticancer activities of pyridine derivatives (*Z*)-3-amino-7-(4-methoxybenzylidene)-1,7-dihydro-4*H*-pyrazolo[4,3-*c*]pyridine-4,6(5*H*)-dione (**94**) and (*Z*)-3-amino-7-(4-chlorobenzylidene)-1,7-dihydro-4*H*-pyrazolo[4,3-*c*]pyridine-4,6(5*H*)-dione (**95**) were studied (Figure 30).[88] Comparing compound **94** to the reference medication doxorubicin (IC_{50} = 4.749 and 2.527 μg/mL, respectively) showed that compound **94** had excellent cytotoxic action against the liver and breast cancer cell line. Comparing compound **95** to doxorubicin (IC_{50} = 3.641 μg/mL), compound **95** is more effective against colon cancer cell lines (IC_{50} = 2.914 μg/mL).

2.5.4 Pyridine Derivatives Containing Acylhydrazone and Benzamide Moieties

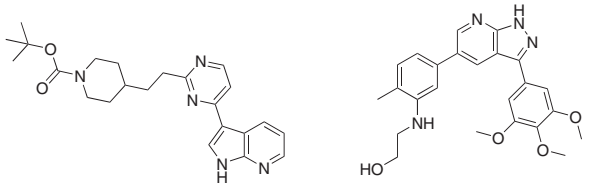
Novel compound (*E*)-4-[(2-pyridylcarbonyl)diazanylidene)methyl]-*N*-(*p*-tolyl)benzamide (**96**) (Figure 30) was tested against two human cancer cell lines and one human normal cell line to determine its antiproliferative properties.[89] Compound **96** exhibits remarkable antiproliferative efficacy against RPMI8226 cells with an IC_{50} of 0.12 ± 0.09 μM. Comparing compound **96** to imatinib, it was less hazardous. Compound **96** effectively inhibits cell growth as demonstrated by flow cytometry analysis, stopping the cell cycle at the G0 and G1 phases, which leads to the apoptosis of RPMI8226 cells by facilitating the release of mitochondrial ROS.

2.5.5 Pyridine Derivatives Containing a Pyrrole Moiety

The *in vitro* biological activities of pyridine derivatives containing a pyrrole moiety were assessed against maternal embryonic leucine zipper kinase (MELK). Compound **97**

(Figure 31) demonstrated a strong antiproliferative activity on MDA-MB-231, MCF-7, and A549 cell lines with IC_{50} = 0.109–0.245 μM.[90] showed outstanding enzyme inhibition at IC_{50} = 32 nM. Compound **97** effectively stops A549 cells in the G0/G1 phase and causes apoptosis in a dose-dependent manner according to flow cytometry studies.

2.5.6 3,5-Disubstituted 1H-Pyrazolo[3,4-b]pyridines as Multiacting Inhibitors



97 98

Figure 31

Against Microtubule and Kinases

Compound **98** showed excellent antiproliferative activities towards many cancer cell lines.[91] In both enzymatic and cellular experiments, compound **98** (Figure 31) demonstrated a substantial inhibition of tubulin assembly and a potent inhibition towards FLT3 and Abl1. Compound **98** severely interfered with HUVEC tube formation and resulted in a cell cycle arrest at G2/M phase. Compound **98** at 10 mg/kg, suppressed tumor growth on the K562 leukemia xenograft model according to in vivo effectiveness tests.

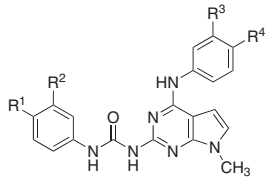
2.6 Pyrrole Derivatives as Anticancer Agents

A prospective scaffold for antibacterial, antiviral, antimalarial, antitubercular, anticancer, and anti-inflammatory is the class of physiologically active heterocyclic molecules known as pyrrole derivatives.[92] By establishing hydrogen bonds with DNA, chemicals containing heteroatoms, like nitrogen, sulfur, and oxygen, strengthen the complex.[93] Typically, the anticancer activity of a chemical is correlated with the force of its contact with DNA. In addition, the intercalating chromophore has a polarized characteristic property and the best contact occurs when the chemical structure contains one or more nitrogen heteroatoms. Prodigiosin is well known anticancer drug containing pyrrole moiety.

In 2020, Raimondi and co-workers reviewed bioactive pyrrole-based compounds with target selectivity.[94]

2.6.1 Pyrrole-Pyrimidine with Urea Derivatives

In 2019, Kilic-Kurt and co-workers[95] synthesized pyrrolo[2,3-*d*]pyrimidines with a urea moiety at C2 (Figure 32) that show cytotoxic action against A549, PC-3, and MCF-7 cell lines. Cytotoxicity was impacted by the design of the scaffold. IC_{50} values for compounds **99**, **100**, and **101** of 0.35, 1.48, and 1.56 μM, respectively, showed that the A549 cells were very responsive to the therapy.

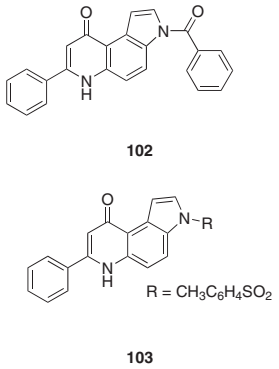


99: R^1 = H, R^2 = CF_3, R^3 = Cl, R^4 = F
100: R^1 = F, R^2 = CF_3, R^3 = Br, R^4 = H
101: R^1 = F, R^2 = R^3 = H, R^4 = Cl

Figure 32

2.6.2 Phenylpyrroloquinolinone Derivatives

Carta et al.,[96] in 2017, examined the ability of new phenylpyrroloquinolinones (PPyQs) to inhibit the growth of a variety of solid tumor and leukemic cell lines (Figure 33). Instead of having a sulfonyl or carbamoyl moiety at the pyrrole nitrogen, compound **102** has a benzoyl group. Compound **102** showed the best effect with GI_{50} = 0.2 nM against HeLa, 0.1 nM against HT-29, and 0.2 nM against MCF-7 cell lines while compound **103** which is a sulfonyl derivative was less potential as compared to compound **102**. Compound **102** displayed good potential in blocking tubulin assembly (IC_{50} = 0.84 mM).



102

R = $CH_3C_6H_4SO_2$

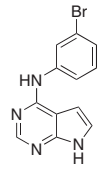
103

Figure 33

2.6.3 Pyrrolo[2,3-*d*]pyrimidines

Kurup et al.,[97] in 2018, reported the synthesis of eighteen pyrrolo[2,3-*d*]pyrimidines, dual inhibitors of both EGFR and Aurora kinase A (AURKA). These are involved in

the control of several critical processes such as cell migration, differentiation, proliferation, and survival. All substances were tested for their potential to inhibit kinases using enzymatic assays. The findings demonstrated micromolar and nanomolar inhibition of AURKA and EGFR. Compound **104** (Figure 34) showed excellent dual activity with IC_{50} of 1.99 mM against AURKA and 3.76 nM against EGFR.



104

Figure 34

2.6.4 Pyrrolo[3,2-*c*]pyridines

In 2018, El-Gamal and Oh reported the synthesis of a number of pyrrolo[3,2-*c*]pyridines and tested their inhibition of FMS kinase. With IC_{50} values of 60 and 30 nM, respectively compounds **105** and **106** (Figure 35) demonstrated remarkable activity.[98] The antiproliferative properties of **106** were assessed against 13 cancer cell lines (breast, prostate, and ovarian), demonstrating selectivity for cancer cells over normal fibroblasts with an IC_{50} ranging from 0.15 to 1.78 μM. With an IC_{50} value of 84 nM, a strong effect was also seen against macrophages generated from bone marrow, blocking their CSF-1-induced proliferation.

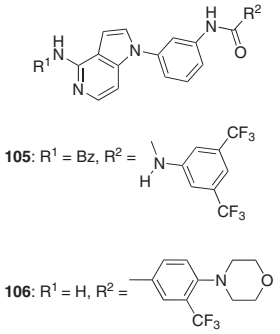


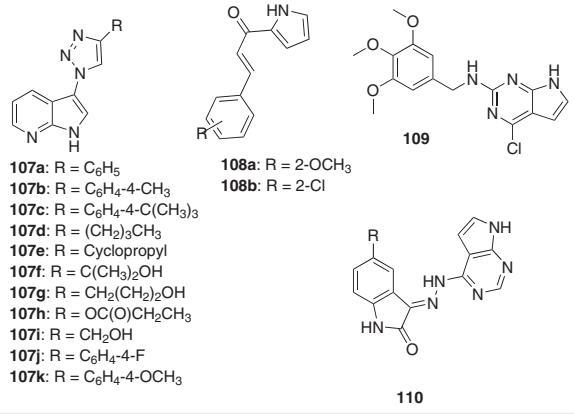
Figure 35

2.6.5 Piperidine-3,4-diol and Piperidin-3-ol with Pyrrolotriazine Derivatives

Mesaros et al.,[99] in 2015, produced pyrrolo[2,1-*f*][1,2,4]triazine derivatives via diastereoselective synthesis and these compounds demonstrated good *in vitro* ALK inhibitory activity in both an enzyme assay (IC_{50} = 3–57 nM) and a cell-based assay (IC_{50} = 30–500 nM).

2.6.6 Pyrrolo[2,3-*b*]pyridines

In 2016, Kondapalli and co-workers[100] developed novel pyrrolo[2,3-*b*]pyridines and tested their antitumor efficaciousness against the human cancer cell lines MDA-MB-231, HeLa, and A549. Compounds **107a–k** (Figure 36) exhibited the greatest inhibition of growth at doses ranging from 0.17 to 25.9 μM.



107a: R = C_6H_5
107b: R = C_6H_4-4-CH_3
107c: R = C_6H_4-4-$C(CH_3)_3$
107d: R = $(CH_2)_3CH_3$
107e: R = Cyclopropyl
107f: R = $C(CH_3)_2OH$
107g: R = $CH_2(CH_2)_2OH$
107h: R = $OC(O)CH_2CH_3$
107i: R = CH_2OH
107j: R = C_6H_4-4-F
107k: R = C_6H_4-4-OCH_3

108a: R = 2-OCH_3
108b: R = 2-Cl

110

Figure 36

2.6.7 Pyrrole Derivatives as CYP Inhibitors

A superfamily of enzymes known as cytochrome-P450 (CYP) includes members that are in charge of phase 1 metabolism.[94] Compound **108b** (Figure 36) preferentially inhibits CYP1B1 with IC_{50} = 0.21 μM while compound **108a** inhibits all CYP1 isoforms with almost identical potency (IC_{50} = 0.9–1.1 μM).[101]

2.6.8 Pyrrolo[2,3-*d*]pyrimidin-2-amines

The *in vitro* cytotoxic activity of compound **109** (Figure 36) was assessed against the human cancer cell lines HepG2 (liver), HCT116 (colorectal), and MCF-7 (breast). The epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitory action of compound **109** was investigated and this compound displayed good inhibitory effect with IC_{50} = 0.107 μM.[80]

2.6.9 Pyrrole-Pyrimidine Derivatives as Multi-Kinase Inhibitors

The inhibitory effects of various compounds **110** (Figure 36) on protein kinases were assessed.[102] Compound **110** (R = OMe) as compared to the reference drugs demonstrated good multi-kinase inhibitory activities in nanomolar range against EGFR, Her2, VEGFR2, and CDK2 protein kinases. Further evaluation of compound **110** revealed the ability to suppress cycle progression and induce programmed cell death.

2.7 Sulfonamides linked with heterocycles as Anticancer Agents

Belinostat, ABT-199, and amsacrine are anticancer drugs containing the sulfonamide moiety that have been approved by FDA.[118] Belinostat is a histone deacetylase inhibitor, ABT-199 is a Bc1-2 inhibitor, and amsacrine is a topoisomerase II inhibitor. The general structure of sulfonamides is of type RSO_2NH_2 where R may be an aliphatic or aromatic moiety, see, for example **111** (Figure 37).[119] This structure has served as an essential fighting platform for a number of illnesses.

2.7.1 Sulfonamide Benzoquinazolinones

The strong growth inhibitory effect of benzoquinazolines and sulfonamides against several cancer cells and TK enzymes motivated Soliman and co-workers to work on their molecular hybridization, which may result in a scaffold with promising anticancer activity (Figure 37).[120] Compound **112** was used as reference in this study and anthraquinone derivative **113** showed excellent activity against HER2 with IC_{50} = 3.20 μM.

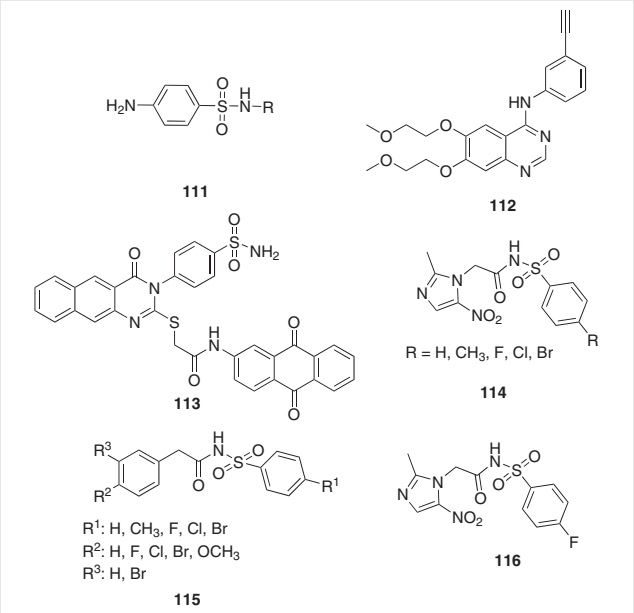


Figure 37

2.7.2 Metronidazole Acid Acyl and Phenylacetyl Benzenesulfonamide Derivatives

A family of *N*-acylsulfonamides of metronidazole was created by Zhu and co-workers as EGFR modulators.[121] Metronidazole belongs to the nitroimidazole family chemically. Protein and nucleic acid are readily damaged by its action which entails penetration and accumulation in the tumor region followed by bioreduction that produces electrophilic chemicals. The good biological activity and low toxicity of acyl sulfonamides prompted Zhu and co-workers to synthesize metronidazole acid sulfonamide derivatives **114** (Figure 37). Using the same lengths of the phenylacetic acid and metronidazole side chains, a series of phenylacetyl benzene sulfonamides **115** was created. Compounds with a metronidazole skeleton had superior EGFR inhibitory activity (IC_{50} = 0.39–38.52 μM), whereas compounds containing phenylacetic acid have moderate EGFR inhibitory activity (IC_{50} = 5.17–38.52 μM). Excellent anticancer (IC_{50} = 1.26 μg/mL for A549 and IC_{50} = 0.35 μg/mL for B16-F10) and EGFR inhibition (IC_{50} = 0.39 μM for EGFR and 1.53 μM for HER-2) activities were demonstrated by molecule **116**.

2.7.3 Quinazoline Sulfonamide Derivatives

Compounds **117** (Figure 38) had remarkable cytotoxic activity against MCF-7, EGFR, and VEGFR with IC_{50} = 0.0977 μM, 0.0728 μM, and 0.0523 μM, respectively.[122] Compound **117** could bind to the ATP-binding site of EGF and VEGF receptors thereby decreasing their function as determined using molecular docking. The clinical significance of 4-anilinoquinazoline derivatives such as vandetanib, WHI-P180, gefitinib, lapatinib, afatinib, and erlotinib lies in their ability to decrease tumor growth by targeting either the VEGFR-2 or EGFR signaling pathways.

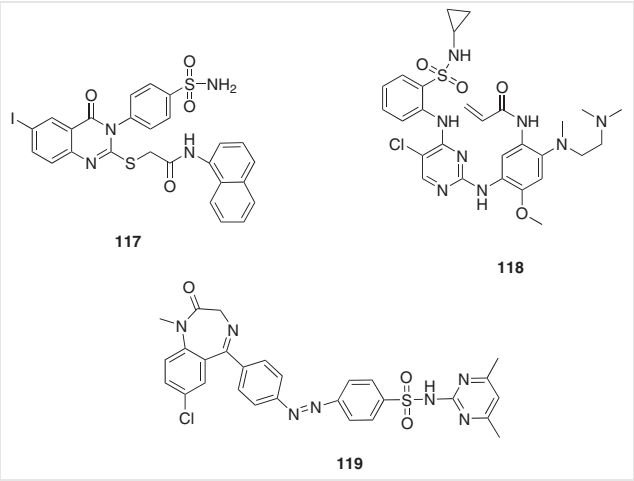


Figure 38

2.7.4 Sulfonamide-Pyrimidine Derivatives

Compound **118** (Figure 38) showed excellent activity with IC_{50} = 0.0215 μM against H1975 cancer cell lines ($EGFR^{T790M/L858R}$ high express) and 0.011 μM against H2228 cells (ALK rearrangement).[123] The terminal amino group of the sulfonamide is a secondary amine with potent antican-

cer action. Its sulfonamide moiety has a cyclopropyl group attached to it. Compound **118** demonstrated strong kinase inhibitory activity with IC_{50} = 3.31 nM against EML4-ALK rearrangement and 17.74 nM against $EGFR^{T790M/L858R}$ mutation. The acrylamide moiety of **118** interacts with the cysteine residues in EGFR kinase, effectively inhibiting $EGFR^{T790M/L858R}$. In order to assess the cytotoxicity of **118**, two cell types were chosen: renal tubular cells (HK-2) and umbilical vein endothelial cells (EA.hy926). The MTT method was utilized for this purpose. Compound **118** has high selectivity for EA.hy926 normal cells with the selective ratio of 74.83 (IC_{50} of H1975 cells/IC_{50} of EA.hy926 cells = 1.609 μM/0.0215 μM) and 146.27 (1.609 μM/0.011 μM) to H1975 and H2228 cancer cell lines, respectively.

2.7.5 Diazepam-sulfonamides

Compound **119** (Figure 38), which is a diazepam-bearing sulfonamide moiety, was evaluated for its anticancer activity against HepG2, HCT-116, and MCF-7 cell lines.[124] Compound **119** shown remarkable efficacy against cancer cell lines HepG2, HCT-116, and MCF-7 with IC_{50} = 8.98 ± 0.1 μM, 7.77 ± 0.1 μM, and 6.99 ± 0.1 μM, respectively. Compound **119** showed worse activity against the HCT116 cancer cell line but it displaced more activity than sorafenib against HepG2 and MCF-7. It showed superior activity against the HCT-116 cancer cell line but less activity against the HepG2 and MCF-7 cell lines when compared to doxorubicin. Compound **119** had remarkable efficacy against VEGFR-2, displaying IC_{50} = 0.10 ± 0.01 μM.

2.7.6 Chromone-Oxime Sulfonamide Derivatives

A chromone-oxime derivative containing a piperazine sulfonamide moiety was evaluated against indoleamine 2,3-dioxygenase 1 (IDO_1).[125] Compound **120** (Figure 39) demonstrated strong inhibitory activity with IC_{50} = 0.64 μM against hIDo1 and 1.04 μM against HeLa IDO_1. A direct interaction between compound **120** and IDO_1 protein was confirmed using surface plasmon resonance analysis. In MTT assay compound **120** displayed no cytotoxicity.

2.7.7 Tertiary Sulfonamide–Benzimidazole Derivatives

Compound **121**, a tertiary sulfonamide derivative with a benzimidazole moiety (Figure 39), showed good antiproliferative action against cell lines MGC-803, HGC-27, and SGC-7901 with IC_{50} = 1.02 μM, 1.61 μM, and 2.30 μM, respectively.[126] Compound **121** demonstrated strong cell-cancer and normal cell selectivity. Compound **121** was shown to interact with gastric cancer cell lines by disrupting the AKT/mTOR and RAS/Raf/MEK/ERK pathways, as evidenced by the decrease in p-Akt and p-c-Raf.

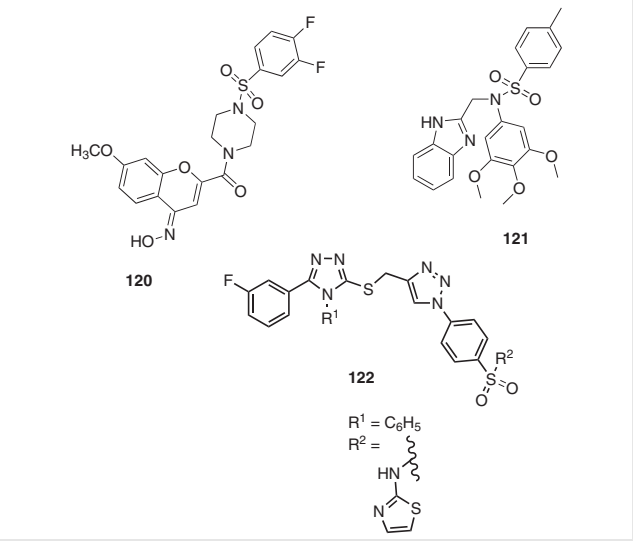


Figure 39

2.7.8 Sulfonamide-Isomeric Triazole Hybrids

Aouad, Teleb, and co-workers synthesized a number of new sulfonamide-tethered isomeric triazole hybrids.[127] Of these, **122** (Figure 39) was an excellent and the safest anticancer agent with IC_{50} values in nanomolar range of 7.37–11.96 nM. Compound **122** had IC_{50} = 5.66 nM against MMP-2 and 6.65 nM against VEGFR when compared to the reference MMP-2 inhibitor NNGH (IC_{50} = 299.50 nM) and the VEGFR-2 inhibitor sorafenib (IC_{50} = 4.92 nM). Compound **122** showed encouraging ligand efficiency metrics and in silico ADMET characteristics.

2.7.9 2-Phenylquinoline-4-carboxamides Bonded to Benzene

Sulfonamide containing quinolines were investigated for their inhibitory potential against four human (h) carbonic anhydrase (CA) isoforms hCA I, II, IX, and XII.[128] Compounds **123**, **124**, and **125** (Figure 40) showed excellent inhibitory potential and their IC_{50} values in the nanomolar range are given in Table 3; the standard drug chosen was acetazolamide (AAZ).

2.7.10 Carbazole Sulfonamide Derivatives

Compounds **126**, **127**, and **128** (Figure 41) are N-substituted carbazole sulfonamide derivatives.[129] Compound **126** possesses excellent anticancer activity with IC_{50} = 19 nM against HepG2 whereas compound **127** and **128** also possess good anticancer activity with IC_{50} = 4.13 μM and 1.12 μM, respectively, against HepG2.

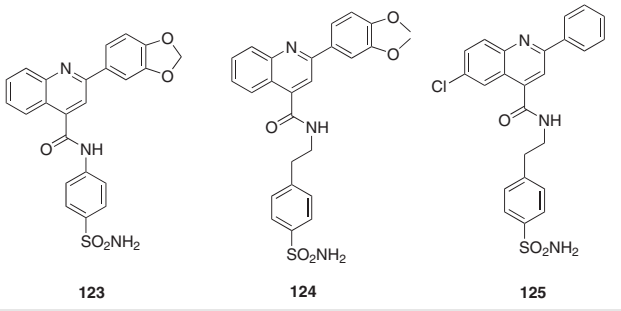


Figure 40

Table 3 IC_{50} Values of Compounds **123–125**

Cancer cell line	Compd **123** (nM)	Compd **124** (nM)	Compd **125** (nM)	AAZ (nM)
hCA I	255.8	91.8	1889	250
hCa II	7.1	35.2	42.9	12.1
hCA IX	6.5	9.7	47.6	25.8
hCA XII	72.1	88.5	6.7	5.7

2.7.11 Cinnamic Acyl Sulfonamide Derivative

Compound **129** (Figure 41), a cinnamic acyl sulfonamide derivative with a 1,3-benzodioxole group, is an excellent tubulin inhibitor with IC_{50} = 0.88 μM.[130] Docking simulations and 3D-QSAR of compound **129** were carried out.

2.8 Oxadiazole and Its Derivatives as Anticancer Compounds

Zibotentan, an oxadiazole based anti-cancer drug candidate developed by AstraZeneca is used for the treatment of prostate cancer.[131] Because it has unique pharmacokinetic properties and boosts the lipophilicity of the drug, 1,3,4-oxadiazole, one of the isomers of oxadiazole, has attracted the attention of researchers. The characteristics of this molecule help in the transmembrane diffusion of the medication to the target location.[132] Recently new topsentin-linked 1,3,4-oxadiazoles and indole-linked 1,3,4-oxadiazoles have demonstrated anticancer potential via tubulin polymerization inhibition.[133,134]

2.8.1 1,3,4-Oxadiazoles Compounds Containing N-Heterocycles

Bhat et al. synthesized a series of 2-(*N*-heterocycle)-substituted 1,3,4-oxadiazoles.[135] Of these, 5-bromo-1-((4-chlorophenyl){[5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl]-

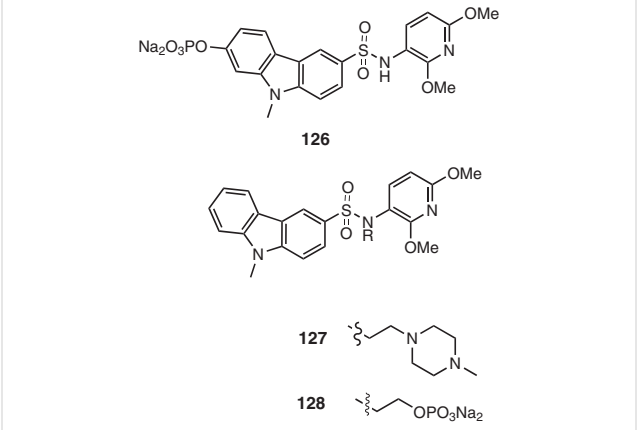


Figure 41

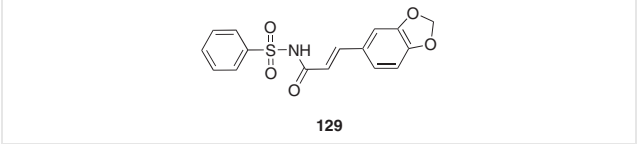


Figure 42

amino}methyl)indoline-2,3-dione (**130**, Figure 43) displayed good cytotoxicity with IC_{50} = 0.78 μM against HT-29 and 0.26 μM against HepG2 by inhibiting EGFR and CDK2 kinases.

2.8.2 Amine Derivatives of 5-[5-(Chloromethyl)-1,3,4-oxadiazol-2-yl]-2-(4-fluorophenyl)pyridine

Vinayak et al. reported that {5-[6-(4-fluorophenyl)pyridin-3-yl]-1,3,4-oxadiazol-2-ylmethyl}phenylamine (**131**, Figure 43) possesses cytotoxic activity with IC_{50} = 2.3 μM against Caco-2 cell lines.[136]

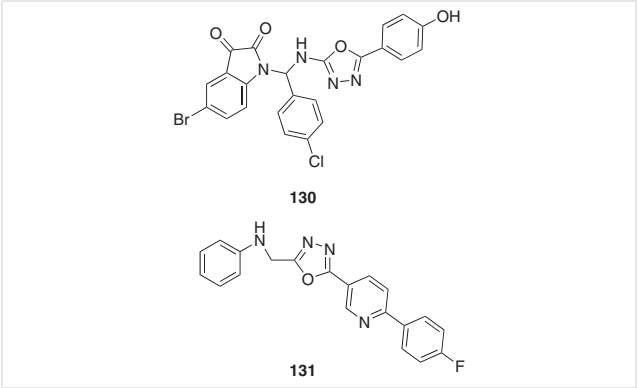
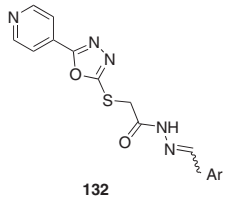


Figure 43

2.8.3 5-Pyridyl-1,3,4-oxadiazoles

Khalil and co-workers reported that *N*′-[(*Z*/*E*)-(3-indolyl)methylene]-2-{[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]-sulfanyl}acetohydrazide (**132**, Figure 44) possesses an anticancer effect with IC_{50} = 0.010 μM through inhibition of EGFR.[137]



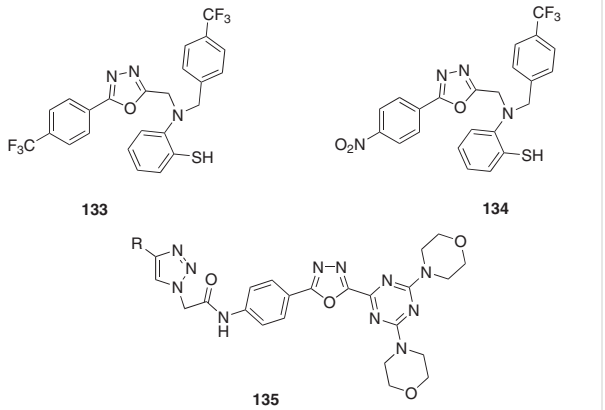
132

Ar: 3-indolyl

Figure 44

2.8.4 1,3,4-Oxadiazole Derivatives as Tubulin Inhibitors

Compounds **133** and **134** (Figure 45) shown superior sensitivity and good IC_{50} = 3.19–8.21 μM against colorectal HCT116, liver HepG2, and breast MCF-7 cancer cell lines when compared to colchicine.[138] Compounds **133** and **134** demonstrated exceptional IC_{50} = 7.95 and 9.81 nM, respectively, when evaluated for enzymatic activity against the tubulin enzyme.



R: pyridin-4-yl

Figure 45

2.8.5 1,2,3-Triazoles Containing 1,3,4-Oxadiazoles and 1,3,5-Triazines

1,2,3-Triazoles are nitrogen-containing five membered heterocyclic aromatic scaffolds with great significance in medicine. They demonstrated various biological activities, such as anticancer,[139] antimalarial,[140] antitubercular,[141] anti-HIV,[142] antifungal,[143] antibacterial,[144] antidiabetic,[145,146] and antineoplastic.[147,148]

A new library of 1,2,3-triazole-incorporated 1,3,4-oxadiazole-triazine derivatives was designed, synthesized, and tested *in vitro* for anticancer activity against A549 (lung cancer), MCF-7 (breast cancer), and PC3 and DU-145 (prostate cancer) cell lines. The assessment employed the MIT assay with etoposide serving as the control medication.[149] With IC_{50} values ranging from 0.16 ± 0.083 μM to 11.8 ± 7.46 μM, the compounds demonstrated excellent anticancer efficacy. Compound **135** (Figure 45) containing a 4-pyridyl moiety exhibits exceptional anticancer activity with IC_{50} = 0.17 ± 0.063 μM, 0.19 ± 0.075 μM, 0.51 ± 0.083 μM, and 0.16 ± 0.083 μM against PC3, A549, MCF-7, and DU-145 cell lines, respectively.

2.8.6 Oxadiazole Derivatives as HDAC Inhibitors

In 2022, Singh and co-workers reviewed oxadiazole derivatives as histone deacetylase inhibitors in anticancer therapy and drug discovery.[150]

In 2014, Mai and co-workers synthesized a series of 1,3,4-oxadiazole derivatives (Figure 46) and these were evaluated on different types of HDAC enzymes.[151] (*E*)-*N*-(2-Aminophenyl)-3-(4-{[5-(naphthalen-1-ylmethyl)-1,3,4-oxadiazol-2-yl]methyl}phenyl)acrylamide (**136**) was found to be most potent and selective against HDAC1. Compound **136** exhibited remarkable antiproliferative properties against the five cancer cells associated with leukemia. Comparing compound **137**, **138**, and **139** to SAHA, they demonstrated superior HDAC1 inhibitory action. Hydroxamic acid derivatives **137** and **138** exhibited greater potency towards HDAC4/6 in comparison benzamide derivatives **136** and **139**. Compound **136** displayed good activity with IC_{50} = 0.2 μM against HDAC1, 0.89 μM against HDAC6, 1.8 μM against U937, 2.8 μM against HL-60, 2 μM against HEL, 1.8 μM against KG1, and 1.6 μM against MOLM13, while compound **137** exhibits favorable IC_{50} = 0.2 μM for HDAC1, 0.03 μM for HDAC6, 2.6 μM for KG1, and 2.2 μM for MOLM13. Compound **138** had an IC_{50} = 0.2 μM against HDAC1 and 1.2 μM.

2.9 Benzothiazole-Triazole Hybrids as Anticancer Compounds

Benzothiazoles are an important class of heterocyclic compounds that have attracted great attention due to their antimicrobial,[152] antileishmanial,[153] antitumor,[154] and antiviral[155] properties. Many modified benzothiazole derivatives (Figure 47) that inhibit topoisomerase II (compound **140**),[156] β-glucoronidase (compound **141**),[157] CYP1A1 of cytochrome P450 enzyme,[158] and tyrosine kinase histone deacetylase[159] enzymes have been reported. Compound **142** is a topo I inhibitor with IC_{50} = 8.2 μM. Compound **143** is a

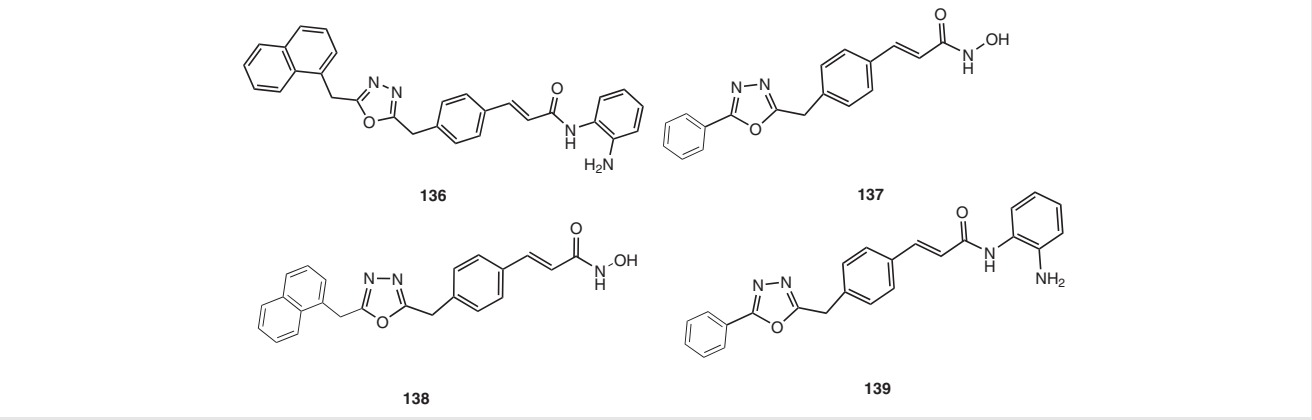


Figure 46

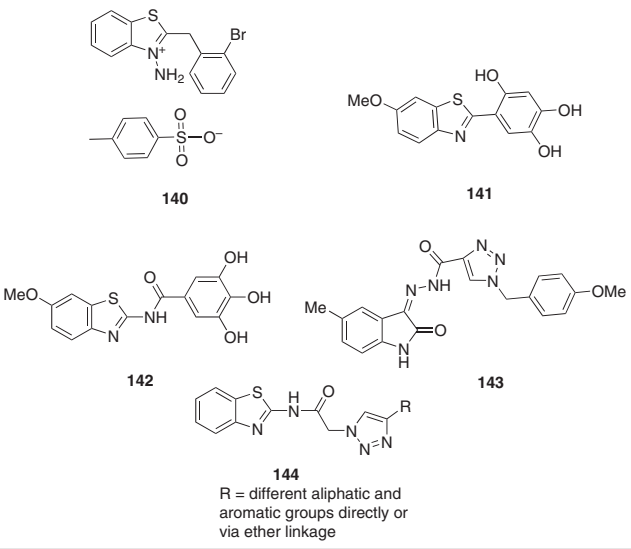


Figure 47

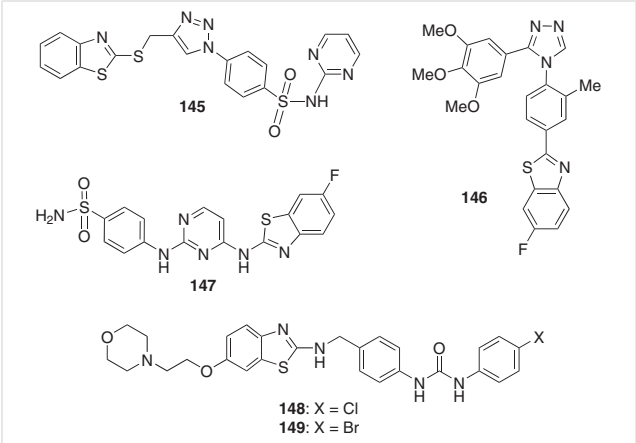


Figure 48

MARK4 inhibitor with IC_{50} = 8.4 μM. Compound **144** is a benzothiazole-triazole hybrid that possess anticancer activity, reported by Rawat et al.[160]

2.9.1 Benzothiazole and Isatin Coupled to a 1,2,3-Triazole Moiety as EGFR Inhibitors

A number of medications including benzothiazole/isatin coupled to the 1,2,3-triazole moiety and sulfonamides were created and tested for their ability to kill a variety of cancer cell types.[161] Comparing compound **145** (Figure 48) to erlotinib, it demonstrated better EGFR activity (IC_{50} = 103 vs 67.6 nM). Under HepG2 model testing, compound **145** demonstrated potent inhibition of tumor growth, a strong induction of cancer cell death and suppression of cell cycle progression leading to DNA fragmentation.

2.9.2 Apoptosis Inducing and Tubulin Polymerization-Inhibiting Compounds: Benzothiazole Incorporated with Triazole and Tetrazole Rings

The combretastatin pharmacophore was modified to synthesize a series of colchicine site binding tubulin inhibitors.[162] In order to limit the *cis* orientation of the olefinic bond, the triazole and tetrazole rings, which bore structural similarities to combretastatin, a tubulin inhibitor, were added. Compound **146** (Figure 48) was the most effective molecule, exhibiting an antiproliferative action similar to CA-4 with an IC_{50} = 0.04 μM against the human lung cancer cell line (A549). Hoechst staining was used in compound **146** investigations to verify that the chemical caused apoptotic cell death.

2.9.3 Benzothiazole-Pyrimidine Derivatives

Diao et al. reported 2-aminobenzothiazole derivatives based on pyrimidines as strong anticancer agents. The selection process yielded the following five human anticancer cell lines: MCF-7, HeLa, PC-3, MDA-MB-231, and HCT116. The most effective molecule was discovered to be compound **147** which showed IC_{50} = 0.45, 0.70, 0.92, and 1.80 μM against HeLa, HCT116, PC-3, and MDA-MB-231, respectively.[163]

2.9.4 Benzothiazole-Amino Derivatives

Lee et al. reported the discovery of 2-aminobenzothiazole compounds that exhibit anticancer action and serve as Aurora B kinase inhibitors. A series of derivatives inhibitory activity against Aurora B kinase was assessed based on the activity of the enzyme at various concentrations. When evaluated at enzyme concentrations of 1 μM, compounds **148** and **149** (Figure 48), which contain chlorine and bromine groups at the *para*-position of the phenyl ring, demonstrated excellent inhibitory activity against Aurora B kinase with IC_{50} = 0.12 and 0.09 μM.[164]

2.9.5 Amino-benzothiazole Urea Derivatives

Xie et al. reported the powerful anticancer, mTOR, and PI3K inhibitor properties of amino-benzothiazole urea derivatives. These compounds had a substituted pyridine ring at C6 of the 2-aminobenzothiazole. The HCT116, MCF-7, U87 MG, and A549 cancer cell lines were utilized to assess the anticancer efficacy of each derivative. In comparison to HCT116, MCF-7, U87 MG, and A549, compound **150** (Figure 49) showed IC_{50} = 0.30 μM, 0.32 μM, 0.39 μM, and 0.45 μM, respectively.[165]

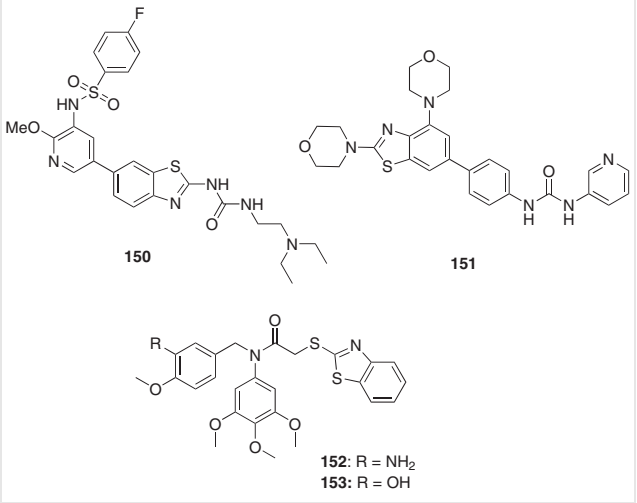


Figure 49

2.9.6 Morpholine-Substituted Benzothiazoles

Cao et al. demonstrated the use of benzothiazole derivatives as a powerful PI3K inhibitor and anticancer drug. The derivatives IC_{50} values against the cancer cell lines A549, MCF7, DU145, PC-3, and HepG2 were found to be between 0.35 and 10.93 μM. The results showed that **151** (Figure 49) was the most effective against the human cancer cell lines PC-3, MCF7, DU145, HepG2, and A549 with IC_{50} = 0.35 μM, 0.36 μM, 0.62 μM, 3.43 μM, and 3.48 μM, respectively.[166]

2.9.7 Benzothiazole-Tertiary Amide Derivatives

Song et al. created tertiary amide compounds with a 2-mercaptobenzothiazole moiety that are powerful anticancer drugs. MGC803, HCT-116, and PC-3 are human cancer cell lines that were chosen because they showed good anticancer inhibitory potency with an IC_{50} value range of 0.035–16.4 μM. It was discovered that compounds **152** and **153** (Figure 49) were highly effective against the HCT-116 cell line with IC_{50} = 0.491 μM, and 0.182 μM, respectively.[167]

2.9.8 Benzothiazole-Acylhydrazones

Osmaniye et al. reported a number of compounds of mercaptobenzothiazole acylhydrazones (Figure 50) as effective anticancer drugs. They were tested on four human cancer cell lines: A549, C6, MCF-7, and HT-29 and had an IC_{50} value of less than 1.50 μM. Testing compound **154** against the cancer cell lines MCF-7, C6, and HT-29 it showed IC_{50} = 0.10 μM, 0.03 μM, and 0.30 μM, respectively. In contrast, compound **155** showed IC_{50} values against NIH3T3, A549, C6, and MCF-7 cell lines of 0.01 μM, 0.03 μM, 0.03 μM, and 0.30 μM, respectively.[168]

2.9.9 Benzothiazole-Pyrazoles

Belal and Abdelgawad created a number of unique benzothiazole-pyrazole hybrids as anticancer agents. Three distinct human cancer cell lines were chosen namely A549, Hep3B (hepatoma cells), and MCF-7. Compound **156** (Figure 50) had remarkable inhibitory efficacy against the A549 cell line, demonstrating IC_{50} = 2.35 μM.[169]

2.9.10 Comberstatin-Benzothiazole Hybrids

Comberstatin-benzothiazole hybrids (Figure 50) which are strong tubulin inhibitors, are structurally linked to the benzothiazole molecule by a 1,2,4-triazole bridge. Compound **157**, with a methoxy group at C6 of the benzothiazole ring, showed strong inhibitory potency against the A549 cell line (IC_{50} = 0.054 μM) while against the HeLa, DU145, HepG2, and MCF-7 cancer cell line (IC_{50} = 0.16 μM, 0.48 μM, 0.67 μM, and 1.13 μM, respectively). Compound **158** the most potent of the series, was shown to exhibit re-

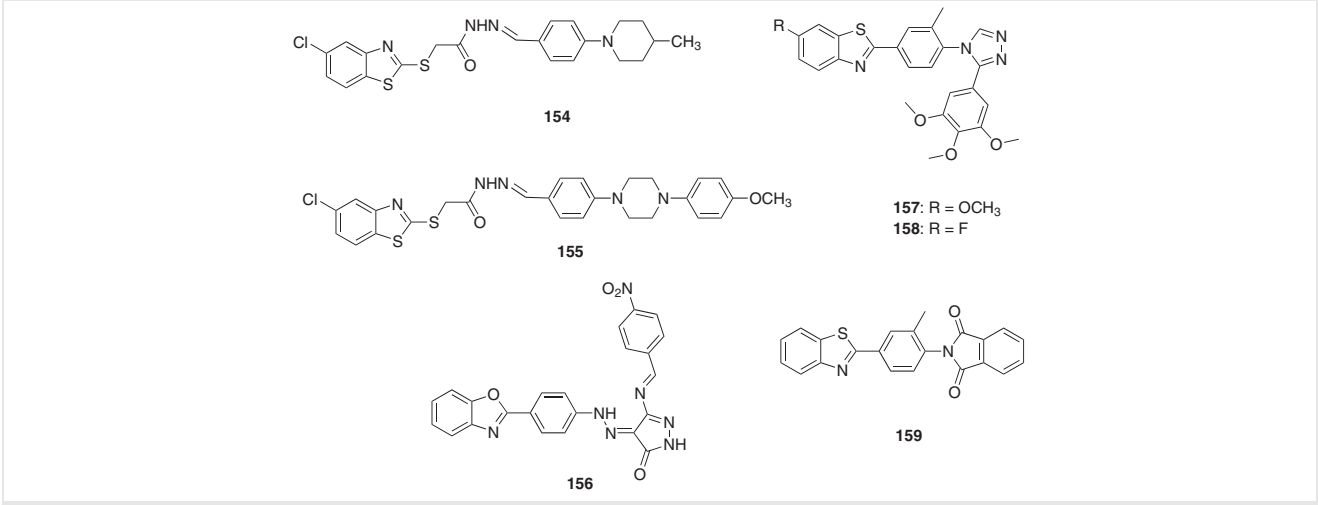


Figure 50

markable anticancer activity against A549, HeLa, and DU-145, with IC_{50} = 0.048 μM, 0.15 μM, and 0.28 μM, respectively. Compound **158** was substituted with a fluorine at C6 of the benzothiazole moiety.[170]

2.9.11 Benzothiazole-Phthalimides

Benzothiazole-phthalimide hybrids as potent anticancer agents were reported by Philoppes and Lamie.[171] Compound **159** (Figure 50) has IC_{50} = 0.098 μM, 28.82 μM, and 0.006 μM against the cancer cell lines HepG2, WI-38, and MCF-7, respectively.

3 Conclusion

Heterocyclic compounds are the most important organic compounds as they play an important role in preparation of drugs. A summary of biological activity of various heterocyclic anticancer compounds has been presented in this review. The major motivation for creating this review is to assist researchers in this field, as the abundance of studies conducted both historically and presently on the development of heterocyclic anticancer drugs underlines the importance of these molecules.

Conflict of Interest

The authors declare no conflict of interest.

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