Review Article

Review: Pyrimidine Derivatives as Anticancer Agents

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Abstract

Cancer is a disease that can be fatal everywhere. It can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably; they go further than their usual boundaries to attack contiguous parts of the body and/or slap-up meal to other organs. The primary problem facing current treatment techniques, such as chemotherapy and radiation, is multidrug resistance (MDR). Finding a unique and varied structural framework could open the door to the creation of fresh, potent anticancer medications. Also, the knowledge in genomics and molecular sciences has helped in creating drug targets. Pyrimidines, a class of nitrogen-containing heterocyclic compounds, play a significant role in crafting cancer treatment drugs. These synthetic compounds have proven effective against various cancers, including myeloid leukemia, breast cancer, liver cancer, pancreatic cancer, and idiopathic pulmonary fibrosis. This review presents the findings of several investigations conducted between 2006 and 2023 on pyrimidine derivatives and their corresponding anticancer characteristics.
Introduction

According to the World Health Organization (WHO), there are currently 18 million individuals who have cancer, and more than 9 million people have died from this disease. These numbers continue to rise due to the absence of efficacious and targeted anticancer treatments. [1].

Pyrimidine is highly regarded as an essential heterocyclic component due to its wide range of biological and pharmacological functions. The six-membered ring with a 1,3-diazine structure, which has nitrogen atoms at positions 1 and 3, is found in various naturally occurring chemicals including nucleotides, coenzymes, nucleic acids, purines, vitamins, pterins, and uric acids. The widespread therapeutic uses of pyrimidine can be attributed to its existence in the molecular structure of DNA and RNA. This heterocyclic moiety is present in numerous medications such as 5-fluorouracil, methotrexate, stavudine, imatinib, zidovudine, dasatinib, pazopanib, uramustine, nilotinib, cytarabine, tegafur, trimethoprim, sulfamethazine, phenobarbital, minoxidil, primidone, and risperidone. [2, 3]. Moreover, there has been a lot of focus and documentation on the development of pyrimidine-based anticancer agents [4-11].

Cocco and collaborators [12] in 2006 informed the preparation and screening of a series of 2-amino-4-[2-(arylidene)hydrazinyl]-6-(morpholine-4-yl or pyrrolidine-1-yl) pyrimidine-5-carbonitriles (1) for anticancer activity toward nine different categories of human cancers cell lines. Such compounds displayed a good level of cytotoxic activity.

In 2009 [14] an assessment was conducted to determine the inhibitory effects of 2,4,5-substituted pyrimidines on the human hepatocellular carcinoma BEL-7402 cell line. Some derivatives as 3a and 3b demonstrated significant inhibitory effects, with IC50 values less than 0.10 µM.


Moreover, Lin et al [16] documented the synthesis of Certain analogues of 2,7-diaminothiazolo[4,5-d]pyrimidine 7 function as inhibitors of epidermal growth factor receptor (EGFR) tyrosine kinase. The acquired compounds exhibited robust and specific inhibitory effects on EGFR, impeding the spread of EGFR human tumor cells in vitro.

In the same year, [17], it was documented that derivatives 8 of substituted triazolo[4,3-a]pyrimidin-6-sulfonamide had repressing properties against the proliferation of various cancer cell types.
One year later [18], a number of 2-((1H-benimidazol-2-yl)methylthio)-4-(substitutedamino)-6-phenylpyrimidine-5-carbonitriles (9) was prepared and estimated for anticancer activity. They exhibited potent cytotoxic activity against twelve cell lines. The study exposed their noticeable potency when compared with known antitumor drugs as well as that addition of basic groups and moieties at position 4 of the pyrimidine ring has marked effect on the activity.

Edrees et al [19] informed a series of pyrimidines, which assessed for anticancer activity against a panel of 60 human tumor cell lines by the National Cancer Institute (NCI). Some of derivatives of compound 10 showed significant cytotoxicity seen against the tested cell lines.

One year later [20], several trisubstituted pyrimidines were showed good inhibitory effect against phosphatidylinositol 3-kinase (PI3K). Compound 11 displayed strong activity with an IC50 value of 62 nM.

In 2012, Mohammed and his assistants [22] screened a set of 6-aryl-5-cyano-2-thiouracils for their antitumor activity. Compound 13 was found to be the most potent cytotoxic and selective agent toward HCT116 cell line, HepG2 cell line, and MCF7 cell line in comparison with the 5-fluouracil as reference standard.

In the same year [23], 2-anilino-4-(benzimidazol-2-yl)-pyrimidines were assessed for their ability to inhibit the growth of various malignance cell lines. Among these, Compound 14 emerged as the most effective, demonstrating the capability to inhibit numerous cancer cell lines from the NCI panel at concentrations below one micromolar.

In 2014 [24], a team of researchers disclosed their work on preparing and assessing 2,4,6-trisubstituted pyrimidines for their in-vitro cytotoxic and antitumor properties. Following these evaluations, the most effective compounds were also chosen for in-vivo testing. Among the series, only Compound 15 was identified as being notably effective.
Additionally, Ma and his team [25] developed, created, and tested a collection of 1,2,3-triazole-pyrimidines for their anticancer efficacy against four cancer cell lines: MCF-7 (human breast cancer), MGC-803 (human gastric cancer), EC-109 (human esophageal cancer), and B16-F10 (mouse melanoma). The majority of these compounds showed moderate to high effectiveness. Notably, Compound 16 demonstrated the most potent anticancer properties, as evidenced by its IC50 values ranging from 1.42 to 6.52 μM, all in the single-digit micromolar range.

In 2016 [26], Two series of 4-phenyl-5-cyanopyrimidin-6-one derivatives, each featuring different s-alkyl or s-acyl groups at the 2-position, were developed as cytotoxic agents. Anticancer assays were conducted on two distinct cell lines, namely MCF-7 (breast tumor) and HCT-116 (colon tumor), to evaluate the activity of each compound. Among them, Compound 17 stood out as the most effective against the MCF-7 cell line, exhibiting an IC50 value of 18.3 μM.

In 2017, Yousif et al [27] reported the synthesis of a derivatives of pyrazolo[1,5-a]pyrimidines and pyrazolo[3,4-d][1,2,3]triazines and evaluated for their in vitro cytotoxic activities against HepG-2 and MCF-7 cell lines. Compounds 24a (MCF-7 IC50 = 63.2 μg/mL), and 24b (HepG-2 IC50 = 70.3 μg/mL, sequentially), were the most potent in comparison with doxorubicin (MCF-7 IC50 = 65.6 μg/mL and HepG-2 IC50 = 80.9 μg/mL).
Vignaroli's team [30] evaluated the in vitro cytotoxicity of Pyrazolo[3,4-d]pyrimidine derivatives against human glioblastoma (U87) cell line. Compound 25 showed the most strong anticancer activity on U87 after 72 hours (IC\textsubscript{50} = 1.5 µg/mL).

A group of investigators [31] prepared and assessed the anti-proliferative effects of a range of thiazolo[5,4-d]pyrimidine derivatives on several human cancer cell lines. Comparing compound 26 to 5-fluorouracil, which is used as a standard drug. The IC\textsubscript{50} values for MGC-803 and HGC-27, two human stomach cancer cells, were 4.64 and 5.07 µM, respectively, indicating significant suppression.

Felfel et al. [32] produced derivatives of 1-thiaazaspiro[4,5]decane, as well as the corresponding thiazolopyrimidine and 1,3,4-thiadiazole compounds. These compounds were evaluated for their anticancer effectiveness against cell cultures of several human cancer cell lines, including HepG-2, PC-3 and HCT116. Notably, Compound 27 exhibited significant cytotoxic activity against the HCT-116 cell line, surpassing the effectiveness of the standard drug doxorubicin.

In the same year [33] a collection of bis-pyrimidine Schiff base compounds were assessed for their antibacterial and anticancer capabilities. These compounds were specifically evaluated for their effectiveness in combating the HCT-116 human colorectal carcinoma cell line. Among them, Compound 28, with an IC\textsubscript{50} of 0.18 µmol/mL, demonstrated more potent anticancer activity against the HCT-116 cell line compared to the reference drug, 5-fluorouracil.

Hafez and colleagues [34] created a range of 4-substituted thieno[3,2-d]pyrimidine and thienotriazolopyrimidine compounds. These compounds exhibited strong anticancer effects, similar to doxorubicin, on three types of human cancer cells: MCF-7 (breast adenocarcinoma), HeLa (cervical carcinoma), and HCT116 (colonic carcinoma). Compounds 29, 30, and 31 had comparable activity to doxorubicin.

In 2018 [35], a series from thieno[2,3-d] pyrimidines was prepared and assessed for their antitumor activity. Compound 32a exhibited the greatest level of toxicity against the MCF-7 breast cancer cell line, with IC\textsubscript{50} values of approximately 18.87 µg/mL, surpassing the IC\textsubscript{50} values of Paclitaxel, which were around 40.37 µg/mL. The cytotoxicity of paclitaxel was roughly 45.78 µg/mL, while compound 32b showed the highest cytotoxicity against the HeLa cervical cancer cell line, with IC\textsubscript{50} values of around 40.74 µg/mL.
In the same year [36], it was reported that calix[2]arene[2]pyrimidines were designed. Compound 33 exhibited potent inhibitory activity toward MCF-7 cancer cells, and its processes contributed to cell death by halting the cell cycle in the S phase and increasing caspase-3 and caspase-9 cell counts.

Kumar et al. [37] a range of pyrimidine-bridging combretastatin derivatives were developed, followed by testing their effectiveness as anticancer agents against breast cancer (MCF-7) and lung cancer (A549) cell lines. In this series, Compounds 34 and 35 emerged as the most potent, with IC₅₀ values of 4.67 µM and 3.38 µM against MCF7, and 4.63 µM and 3.71 µM against A549 cancer cell lines, respectively. This efficacy was compared to that of colchicine, a reference drug, which showed IC₅₀ values of 5.13 µM and 5.19 µM against the MCF7 and A549 cell lines, respectively.

In a later investigation [38], compound 36 had the most potent anticancer action against CDK2/cyclin E Abl kinases enzymes, displaying notable efficacy against the K-562 and MCF-7 cell lines.

The synthesis and structure-activity relationship (SAR) investigations of pyrimidine derivatives containing a 6′-fluorocyclopentenyl moiety were conducted. For this study, six distinct carcinoma cell lines were utilized: human colorectal carcinoma (HCT-116), gastric carcinoma (SNU-638), lung carcinoma (A-549), prostatic carcinoma (PC-3), liver adenocarcinoma (SK-Hep-1), and breast carcinoma (MDA-MB-231). The human colon cancer and lung cancer cell lines were also included. According to the article, compounds 37a and 37b exhibited promising action, with IC₅₀ values ranging from 1.10 to 2.17 µM and 2.14 to 15.3 µM, respectively [39].
Gilandoust and his colleagues [40] conducted a study of 1,4-disubstituted 1,2,3-triazoles and 1,2,4-triazolo[1, 5-a]pyrimidine derivatives. The compounds were assessed for their ability to prevent breast tumor (MCF-7) cell proliferation. It was observed that compound 38 exhibited selective efficacy against MCF-7 cell lines, displaying an IC\textsubscript{50} value of 1.69 \(\mu\text{M}\). Further examination revealed that Compound 38 also induces cytotoxicity in additional breast cancer cell lines, namely MDA-MB-231 and BT474, with IC\textsubscript{50} values of 4.81 \(\mu\text{M}\) and 4.08 \(\mu\text{M}\), respectively.

In 2018 [41], the cytotoxic activity of many substituted pyrido[2,3-d]pyrimidines was tested in vitro against a range of cancer cell lines, including HepG-2, HCT-116, MCF-7, and PC-3, which represent hepatic, colon, breast, and prostate cancers, respectively. An important finding is that, in comparison to the standard chemotherapy drug doxorubicin, Compound 39 was more successful in reducing the proliferation of HepG-2, PC-3, and HCT-116 tumor cell lines. For HepG-2, PC-3, and HCT-116, the IC\textsubscript{50} values of Compound 39 were 0.3 \(\mu\text{M}\), 6.6 \(\mu\text{M}\), and 7 \(\mu\text{M}\), respectively. In comparison, doxorubicin exhibited IC\textsubscript{50} values of 0.6 \(\mu\text{M}\), 6.8 \(\mu\text{M}\), and 12.8 \(\mu\text{M}\) for the equivalent cell lines.

Concurrently, in the same year [42], thiophene and thienopyrimidine derivatives were developed and evaluated for their effectiveness against numerous malignance cell lines, such as HepG-2, MCF-7, Hep-2, PC-3, HeLa, and epitheloid cervix carcinoma. Compounds 40a-c and 41a-b outperformed the reference medication, doxorubicin, in terms of antineoplastic activity against all of the evaluated cell lines.

Pyrimidine derivatives were created by Ryad et al [43], as potential anticancer compounds. Among these, Compound 42 demonstrated strong \textit{in vitro} cytotoxic effects against leukemia (HL-60) cells, with potent activity at a concentration of less than one micromolar (IC\textsubscript{50}= 0.091 \(\mu\text{M}\), surpassing that of combretastatin A4 (CA-4) (IC\textsubscript{50}= 0.48 \(\mu\text{M}\)). Compound 42 was found to have strong anti-proliferative, pro-apoptotic, and cell cycle arresting properties. An assay focused on \(\beta\)-tubulin polymerization inhibition in HL-60 cells suggested that the anticancer activity of compound 42 is strongly correlated with its ability to inhibit \(\beta\)-tubulin polymerization, showing 66% inhibition compared to 88% for CA-4.

In 2019, two compounds were created and produced. These compounds are derivatives of 2,4-diaminopyrimidine and have either a triazolopiperazine or a 1,4,8-triazaspiro[4.5]decan-3-one structure [44]. At least some of these compounds showed moderate to high efficacy compared to the reference drugs palbociclib and momelotinib against a number of cancer cell lines, including A549, PC-3, HCT-116, and MCF-7, which are human cancer cell lines for lung, prostate, colon, and breast cancers, respectively. In terms of anticancer activity, the two most effective compounds, 43 and 44, respectively, showed IC\textsubscript{50} values of 2.14 \(\mu\text{M}\), 3.59 \(\mu\text{M}\), 5.52 \(\mu\text{M}\), and 3.69 \(\mu\text{M}\) against the A549, HCT-116, PC-3, and MCF 7 cell lines.

During the same year [45], a set of 2,4-disubstituted-2-thiopyrimidine compounds were studied for their potential as VEGFR-2 inhibitors. These compounds were tested against HepG2 and UO-31, two cell lines used to study liver and renal cancer, respectively. Compound 45a and compound 45b were determined to be strong inhibitors of the tyrosine kinase VEGFR-2, with IC\textsubscript{50} values of 1.23 \(\mu\text{M}\), 1.23 \(\mu\text{M}\), 1.23 \(\mu\text{M}\), and 1.23 \(\mu\text{M}\) against the HepG2 and UO-31 cell lines, respectively.
and 3.78 μM, respectively. Additionally, compound 45a had an IC$_{50}$ value of 13.06 μM while compound 45b had an IC$_{50}$ value of 8.35 μM against HepG2. Results from Structure-Activity Relationship (SAR) analyses point to hydrophobic interactions between the thiouracil molecule's phenyl group at position-4 and the substituents at position-2 as the mechanism by which these compounds exert their effects.

\[
45a \text{ R= 4-OCH}_3; \quad 45b \text{ R= 2-OCH}_3
\]

Furthermore [46], a set of 4,6-disubstituted pyrazolo[3,4-d]pyrimidine analogs demonstrated inhibition of CDK2/cyclin E and Abl kinases, along with exhibiting anticancer properties against breast cancer (MCF-7) and leukemia (K-562) cell lines. The most effective compound was 46, which had an IC$_{50}$ value of 19.8 μM for K-562 and 18.9 μM for MCF-7.

Elmetwally and colleagues [47] created a series of thieno[2,3-d]pyrimidine compounds to inhibit tyrosine kinases. In order to ascertain the potential anticancer properties of these compounds, scientists employed a selection of tumor cell lines, including HepG2, HCT-116, MCF-7, and A431 (representing epidermoid carcinoma, breast cancer, and liver cancer cells, respectively). The cell lines were more effectively targeted by compounds 47a-c, as evidenced by IC$_{50}$ values that varied from 7.592 to 16.006 μM. The IC$_{50}$ values of erlotinib, which vary between 4.99 and 13.914 μM, are similar to this performance.

A number of 2,4,6-trisubstituted pyrimidines containing an anthranilic acid ester group were developed and produced by a team of researchers [48]. Using a panel of cancer cell lines, including CEM-13 for leukemia, MDA-MB-231 and BT-474 for breast cancer, U-937 for lymphoma, and DU-145 for prostate cancer, these chemicals were assessed for their antitumor capabilities. The U-937 human monocyte-like cell line was highly selective for Compound 48, which is defined by a 2-amino substitution. The pyrimidines 49a-d, which have a (E)-steryl substituent at the 6-position of the pyrimidine core, showed enhanced efficacy against MDA-MB-231 and BT-474, two breast cancer cell lines, and DU-145, a human prostate cell line. This cell line showed activity that was comparable to doxorubicin.

The anti-liver cancer activity of the pyrimidine pyrazoline-anthracene derivatives (PPADs) discovered by Ahmed and colleagues [49] was evaluated in vitro using the HepG2 and Huh-7 hepatocellular carcinoma cell lines. Out of all of them, Compound 50 was the most effective against the HepG2 and Huh-7 cell lines, with IC$_{50}$ values of 5.34 μg/mL and 6.13 μg/mL, respectively. These values are comparable to the effectiveness of doxorubicin, a standard chemotherapy drug.

As mentioned in the earlier report [50], a group of 2,4,6-trisubstituted pyrimidines and N-alkyl bromide derivatives were made, starting with methoxy substituted azachalcones. The drugs' ability to stop cell growth and kill cells was then tested using screening methods. The anti-proliferative and lethal effects of N-alkyl bromides were different depending on which alkyl chains were added when they were made. In vitro tests were done on different types of cancer cells, such as HeLa, HT29, A549, C6, MCF7, Hep3B, and FL. Compound 51 posed the most potent activity with IC$_{50}$ values were mostly between 2 and 10 μg/mL compared to 5-fluorouracil and cisplatin as reference drugs.
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The possibility of 7H-pyrrolo [2,3-d] pyrimidine derivatives as inhibitors of focal adhesion kinase (FAK) was brought to light in 2019 [51]. Chemical 52 had an IC$_{50}$ of 3.20 μM against breast carcinoma (MDA-MB231) and 17.4 μM against lung cancer (A549) cell lines, respectively.

In 2020, El-Etrawy et al. conducted a study of 5-substituted-2-thiouracils where they tested their effectiveness against a specific cell line [52]. The findings revealed that compounds 53, 54, 55, and 56 have a significant effect on the breast cancer cell line, as indicated by their IC$_{50}$ values of 3.80, 4.00, 4.50, and 4.70 μg/ml, respectively.

The task of inhibiting EGFR tyrosine kinase was taken on by a class of pyrimidine-5-carbonitrile chemicals that imitate the action of ATP. Four human cancer cell lines were used to assess the cytotoxic effects of these drugs in vitro: HCT-116 for colorectal carcinoma, HepG2 for hepatocellular carcinoma, and MCF-7 for breast cancer, and A549 for non-small cell lung cancer. Compound 57 stood out among the others, demonstrating 4.5 to 8.4 times the activity of erlotinib against MCF-7, A549, HepG-2, and HCT-116 cells when tested. Here are the IC$_{50}$ values for this compound: 3.37 μM, 3.04 μM, 4.14 μM, and 2.4 μM [53].

Furthermore, a subset of N'-(2-thiouracil-5-yl)hydrazones by El-Etrawy et al [54] performed MTT assay-based in vitro screening on the MCF-7 human breast cell line. The findings demonstrated that chemicals 58a, 59, 58b, 58c and 58d demonstrate the highest level of effectiveness against breast tumor cell line with IC$_{50}$ values of 3.40, 3.50, 3.60, 3.70 and 3.80 μg/ml, correspondingly.

A number of indolyl-pyrimidine hybrids were designed and produced by Ahmed and colleagues in 2021 [55]. Subsequently, against several malignance cell lines, such as MCF-7 for breast cancer, HepG2 for hepatocellular carcinoma, and HCT-116 for colorectal carcinoma, these compounds were evaluated for their anticancer capabilities. In particular, Compound 60 IC$_{50}$ values of 5.1 μM, 5.02 μM, and 6.6 μM against the MCF-7, HepG2, and HCT-116 cell lines, respectively, demonstrated its strong anticancer activity. When compared to other well-established treatments, such as 5-fluorouracil and erlotinib, these numbers are comparable.

Noemi, et al. reported the design, synthesis, and anti-proliferative activities of aminopyrimidine derivatives [56]. With EC$_{50}$ ranging from 4 to 8 μM, compound 61 was the most intriguing of the derivatives for all the tested tumor cell lines, including triple-negative breast cancer (MDA-MB231), glioblastoma multiforme (U-87 MG), tongue squamous cell carcinoma (CAL27), colon carcinoma (HT-29), and pharynx squamous cell carcinoma (FaDu).
In the same year [57], a group of investigators evaluated the cytotoxic effects of some pyrimidine derivatives against human colon adenocarcinoma HT-29, two breast cancer cell lines (MCF-7, T47D), as well as a mouse embryonic fibroblast cell line, (NIH-3T3). Compound 62 showed the best cytotoxicity against all cell lines with IC\(_{50}\) = 60, and 1.5, 10, 16 µM, respectively.

![Chemical Structure](image)

A study on the cytotoxicity of pyrimidines was conducted by Othman et al [58]. The substances were assessed as potential cytotoxic agents against human breast malignance cells (MCF-7) and hepatocellular carcinoma cells (HepG-2). Compound 63a showed greater potency than 5-flourouracil, while its analogue, compound 63b, was equipotent to it.

![Chemical Structure](image)

Matada et al. [59] developed, and assessed eight pyrimidine derivatives against the MDA-MB-231 and MCF-7 cell lines that cause breast cancer. Compound 64 exhibited notable cytotoxicity against (MDA-MB-231), demonstrating an IC\(_{50}\) value of 18.5 µM.

![Chemical Structure](image)

A unique collection of ten pyrimidine analogues was developed and manufactured by Ashok et al. [60]. A panel of human cancer cell lines, including MCF-7, A-549, Colo-205, and A2780, were used to assess the anticancer potential of a series of chemicals. These cell lines represent breast cancer, non-small cell lung cancer, ovarian cancer, and adenocarcinoma of the colon, respectively. Of these, five Compound 65a-e derivatives showed encouraging anticancer activity in all of the cell lines that were evaluated.

![Chemical Structure](image)

Cherukumalli and co-workers [61] designed and produced a series of urea derivatives of pyrimidine-pyrazole. The tested compounds were evaluated for their anticancer activity against breast cancer cell line (MCF-7), lung cancer cell line (A549), colon cancer cell line (Colo-205) and ovarian cancer cell line (A2780). Compounds 66 exhibited more potent cytotoxicity than standard Etoposide with IC\(_{50}\) values 0.032, 0.01, 0.083 and 0.65 µM respectively.

![Chemical Structure](image)

In 2022 [62], pyrimidinone ring derivatives with a some five-membered heterocycles were created and produced. The MTT test was used to discover the target compounds' in vitro cytotoxic activities against PC-3, HepG-2, and HCT-116 colorectal cancer cell lines. All the investigated compounds showed strong inhibition on PC-3 and HCT-116 but only mild inhibition on HepG-2 cell lines. compound 67 was the most active one on HCT-116 cells showing IC\(_{50}\) = 58.1 µg/mL, higher activity than doxorubicin (IC\(_{50}\) = 73.50 µg/mL).

![Chemical Structure](image)

Modulation of the Monastrol scaffold was conducted by Thabit et al [63] to produce compounds with potent cytotoxic activity. Compound 68 exhibited a notably high level of cytotoxicity against two specific cancer cell lines: colorectal carcinoma (HCT-116) and breast cancer cells (MCF-7), with IC\(_{50}\) values of 3.75–5.13 µM, respectively. In further evaluations of its inhibitory activity against Eg5, a kinesin motor protein, Compound 68 demonstrated potent inhibition with an IC\(_{50}\) of 12.89 µM, outperforming Monastrol, a reference drug, which had a measured IC\(_{50}\) of...
In 2022 [66], a team of researchers successfully prepared \(N-(4\text{-fluorobenzylidene})-2\{[4\text{-oxo-3-phenyl-6,7,8,9-tetrahydro-3H-cyclohepta-[4,5]thieno}[2,3-d]pyrimidin-2-yl]thio\}acetohydrazid (71). The National Cancer Institute (NCI) conducted tests on various cell lines and found that this compound exhibited strong antitumor activity, effectively killing a wide range of cells. In fact, it was 7 times more potent than the standard drug 5-FU, with IC\(_{50}\) values of 50.1. Compound 71 also demonstrated significant inhibitory activity against human dihydrofolate reductase enzyme, with an IC\(_{50}\) value of 0.20 μM. This inhibitory activity was comparable to that of the standard drug methotrexate, which had an IC\(_{50}\) value of 0.22 μM.

Researchers in 2022 tested a number of pyrimidine-2-thiones for their antineoplastic effects on human cancer T-116 and carcinoma of the liver HepG-2 cell lines [64]. Compound 69 was the most active among the selected compounds with IC\(_{50}\) values of 10.72 and 18.95 μM in both HCT-116 A and HepG-2, respectively.

The main objective of Salem et al’s study in 2022 [65] was to prepare, characterize, and estimate the potential anticancer effects of pyrimidine-2-thione analogues. Among these derivatives, compound 70 showed the most promising results with an IC\(_{50}\) value of 2.617 µM on breast cancer cells (MCF-7). Compound 70 was effective in inducing apoptosis in various cancer cell lines and also played a role in suppressing the expression of phosphorylated RAS, JNK proteins, and PI3K/Akt genes. In addition to these actions, Compound 76 increased the levels of the p21 gene and the p53 protein, which are key regulators in cell cycle and apoptosis pathways. Furthermore, it effectively halted the progression of the cell cycle at the sub-G0/G1 phase. Overall, compound 70 showed robust antitumor activity against breast cancer cell growth by specifically targeting the RAS/PI3K/Akt/JNK signaling pathways, which are critical in the development and progression of many cancers.

A group of researchers in 2023 [68] evaluated the cytotoxic effects of compounds belong to the aminopyrimidine-2,4-dione family. They found that compound 73 exhibited a strong cytotoxic activity against breast cancer cells (MDA-MB-231), with IC\(_{50}\) value of 0.78 μM. This potency was compared to methotrexate, a commonly used drug, which had IC\(_{50}\) value of 2.79 μM. Additionally, compound 73 showed significant inhibition of two proteins, bromodomain-containing protein 4 (BRD4) and polo-like kinase 1 (PLK1), with IC\(_{50}\) values of 0.029 μM and 0.094 μM, respectively. These IC\(_{50}\) values were similar to those of volasertib, a known inhibitor of BRD4 and PLK1 (IC\(_{50}\) = 0.017 μM and 0.025 μM, respectively).
Several thiazolopyrimidine derivatives were developed and tested for their ability to destroy cancer cells in the same year [69]. These were tested against three distinct human cancer cell types: MCF-7, A-549, and A-498, which represent non-small cell lung cancer, renal carcinoma, and breast cancer, with IC\textsubscript{50} values of 2 µM for MCF-7 and A-549, and 1 µM for A-498. Compound 74 stood out among these as a very potent anticancer drug. The IC\textsubscript{50} values for the same cell lines were 9 µM, 13 µM, and 7 µM for Doxorubicin, a commonly used anticancer medication, compared to these more favorable results. In addition, with an IC\textsubscript{50} value of 0.23 ± 0.01 µM, Compound 74 showed remarkable potency in inhibiting TopoisoMerase II (Topo II), an enzyme of paramount importance in DNA replication. This level of effectiveness was 1.4 times that of Etoposide and 3.6 times that of Doxorubicin. Compound 74 also showed promise as a potent anticancer agent due to its capability to cause apoptosis and considerably disrupt the cell cycle in A549 cells compared to control cells.

In 2023 [70], a group of investigators tested derivatives based on indazol-pyrimidine for their ability to kill cancer cells. Their efficacy was tested against three different cancer cell lines: MCF-7, A549, and Caco2. Among the compounds tested, 75 and 76 showed the strongest ability to kill cancer cells, with IC\textsubscript{50} values of 1.629 and 1.841 µM, respectively, compared to Staurosporine as a reference drug with an IC\textsubscript{50} value of 8.029 µM. These two compounds, 75 and 76, were further investigated to understand how they work. It was discovered that they can activate caspase-3/7, which leads to apoptosis.

The synthesis of a series of tetrasubstituted pyrimidines was followed by an evaluation of their capacity to suppress cell proliferation in four distinct human cancer cell lines: MGC-803, Eca-109, PC-3, and MCF-7 [71]. Most of the compounds demonstrated varying degrees of effectiveness in inhibiting cell growth in all four cancer cell lines. Compound 77 exhibited the strongest inhibitory effect on MGC-803 cells, with an IC\textsubscript{50} value of 2.98 µM, which was significantly better than the positive control, 5-FU. Further investigation into the mechanism of action revealed that compound 77 not only suppressed colony formation and cell migration in MGC-803 cells, but also arrested the cell cycle in the G0/G1 phase and induced apoptosis.

Chiral pyrimidine derivatives were produced and tested for anticancer properties in a recent study [72]. These chemicals were selected for comprehensive testing against 60 distinct human cancer cell lines by the National Cancer Institute (NCI). Compound 78 was exceptionally effective against cancer, with an average tumor growth suppression rate of 59.61% across all types of cancer. The MCF-7 and MDA-MB-468 breast cancer cell lines were inhibited by this chemical at concentrations of 94.62% and 85.81%, respectively. In addition, the compound 78 IC\textsubscript{50} values for the most sensitive cell lines were found to be 11.96 µM for leukemia (HL-60), 9.46 µM for ovarian cancer (SK-OV-3), and 6.68 µM for breast carcinoma (MCF-7). Also, compound 78 showed strong suppression of COX-2 (Cyclooxygenase-2) activity, with an IC\textsubscript{50} value of 69.79 µM, which makes it similar to celecoxib, the reference medication (IC\textsubscript{50} = 53.76 µM). Furthermore, compound 84 was found to limit cell division while the cell is in the S and G2/M stages, suggesting that it may activate apoptosis or programmed cell death. In light of these findings, compound 78 may warrant additional investigation as a potential anticancer agent.

Conclusion

It is clear from the recent advancements mentioned in this study that pyrimidine analogues provide attractive prospects for cancer treatment. Pyrimidine's heterocyclic nitrogen-containing rings are widely utilized in drug research and development due to its strong coordination abilities and involvement in diverse biological activities. Furthermore, the pyrimidine analogues have exhibited
significant biological efficacy against a diverse array of cancer targets, in addition to providing ample opportunities for chemical modification. The method of substituting various rings and functional groups on the core structure was employed to obtain a variety of pyrimidine analogues and pyrimidine complexes. In light of the polypharmacological trend, we conducted a process of combining pyrimidine basic structures with readily available bioactive substances to create compounds with diverse chemotherapeutic applications.

References


60. Ashok N, Madhukar J, Sridhar G. Design, synthesis and biological evaluation of 1, 2, 4-oxadiazole linked 1, 2, 4-thiadiazole-pyrimidines as anticancer agents. Chemical Data Collections. 2021;32:100653.


