
Section B: Organic, Analytical and Pharmaceutical Chemistry.

Review Article

Review: Pyrimidine Derivatives as Anticancer Agents

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Abstract

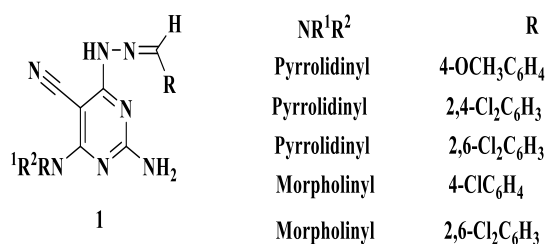
Cancer is a disease that can be fatal everywhere. It can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably; they go further than their usual boundaries to attack contiguous parts of the body and/or slip-up meal to other organs. The primary problem facing current 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

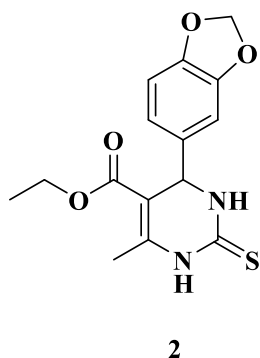
According to the World Health Organization (WHO), there are currently 18 million individuals who have cancer, and more than 9 million people have died from this disease. These numbers continue to rise due to the absence of efficacious and targeted anticancer treatments. [1].

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].

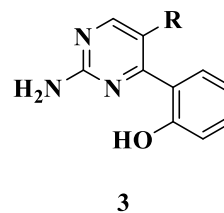
Cocco and collaborators [12] in 2006 informed the preparation and screening of a series of 2-amino-4-[2-(arylidene)hydrazinyl]-6-(morpholine-4-yl or pyrrolidine-1-yl) pyrimidine-5-carbonitriles (1) for anticancer activity toward nine different categories of human cancers cell lines. Such compounds displayed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



In that year, a team of researchers [13] presented their work on synthesizing and evaluating a series of thiopyrimidines for their capability to inhibit the growth of seven different tumor cell lines. Among these, Compound 2 demonstrated strong anticancer effects on breast cancer MCF-7 and colon cancer HCT-29 cell lines, showing half maximal inhibitory concentrations (IC₅₀) of 1.9 µg/mL and 2.5 µg/mL, respectively.

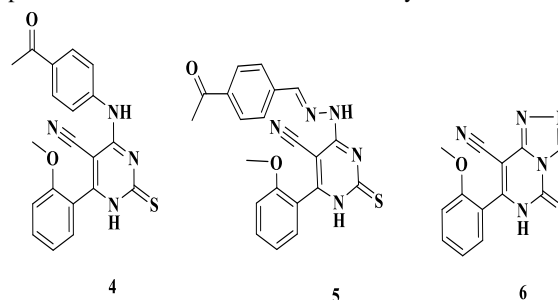


In 2009 [14] an assessment was conducted to determine the inhibitory effects of 2,4,5-substituted pyrimidines on the human hepatocellular carcinoma BEL-7402 cell line. Some derivatives as **3a** and **3b** demonstrated significant inhibitory effects, with IC₅₀ values less than 0.10 µM.

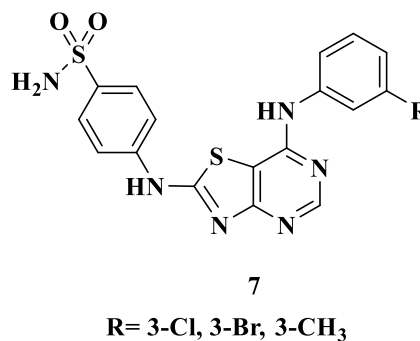


R= a) 4-SCH₃C₆H₅; b) OC₂H₅

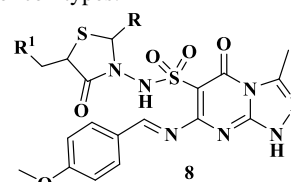
Fathalla and co-workers [15] registered the estimation of a series of pyrimidine derivatives for anticancer and antibacterial activity. Some derivatives 4-6 exhibited potent anticancer and antibacterial activity.



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.



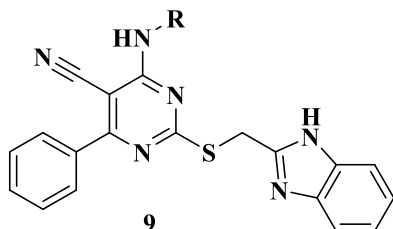
In the same year, [17], it was documented that derivatives 8 of substituted triazolo[4,3-a]pyrimidin-6-sulfonamide had repressing properties against the proliferation of various cancer cell types.



R= 4-CH₃OC₆H₄, 2-C₄H₉S

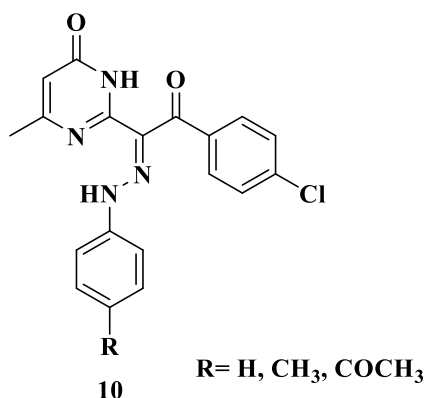
R¹= 4-CH₃NC₄H₈N, NC₄H₈O

One year later [18], a number of 2-((1H-benzimidazol-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.

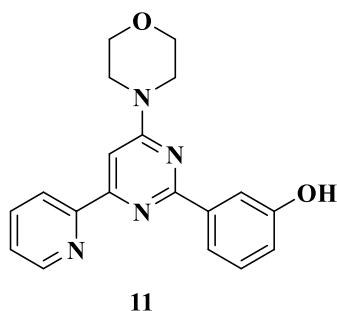


R = NH₂, -NHC₆H₅, -C₅H₄N, -C₃H₂NS, -CONH₂

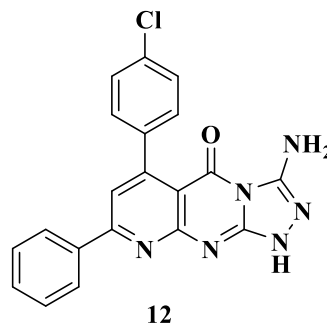
Edrees et al [19] informed a series of pyrimidines, which assessed for anticancer activity against a panel of 60 human tumor cell lines by the National Cancer Institute (NCI). Some of derivatives of compound 10 showed significant cytotoxicity seen against the tested cell lines.



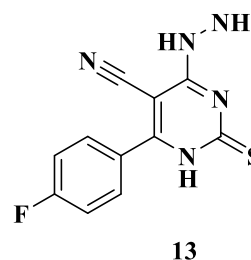
One year later [20], several trisubstituted pyrimidines were showed good inhibitory effect against phosphatidylinositol 3-kinase (PI3K). Compound 11 displayed strong activity with an IC₅₀ value of 62 nM.



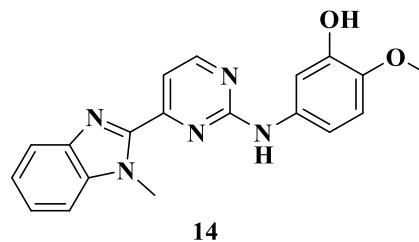
In 2011 [21], certain pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-ones have been screened for their antitumor activity against adenocarcinoma MCF7. Several compounds exploited significant antitumor activity, particularly compound 12. The study reported that derivatives bearing thioxo, alkylthio or amino group at position 3 increased antitumor activity.



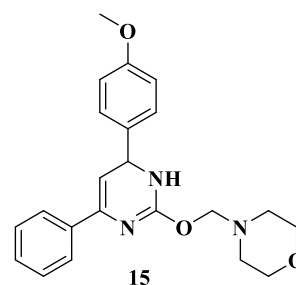
In 2012, Mohammed and his assistants [22] screened a set of 6-aryl-5-cyano-2-thiouracils for their antitumor activity. Compound 13 was found to be the most potent cytotoxic and selective agent toward HCT116 cell line, HEPG2 cell line, and MCF7 cell line in comparison with the 5-fluorouracil as reference standard.

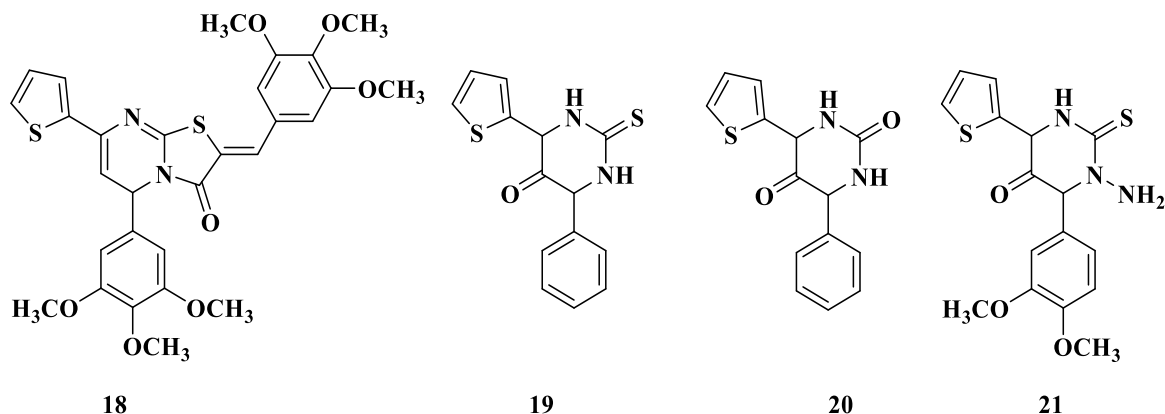


In the same year [23], 2-anilino-4-(benzimidazol-2-yl)-pyrimidines were assessed for their ability to inhibit the growth of various malignance cell lines. Among these, Compound 14 emerged as the most effective, demonstrating the capability to inhibit numerous cancer cell lines from the NCI panel at concentrations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

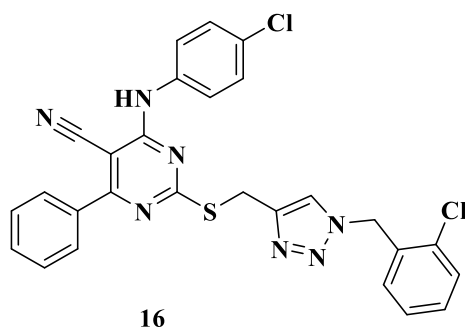


In 2014 [24], A team of researchers disclosed their work on preparing and assessing 2,4,6-trisubstituted pyrimidines for their in-vitro cytotoxic and antitumor properties. Following these evaluations, the most effective compounds were also chosen for in-vivo testing. Among the series, only Compound 15 was identified as being notably effective.

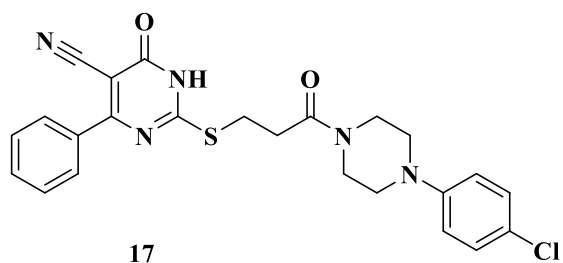




Additionally, Ma and his team [25] developed, created, and tested a collection of 1,2,3-triazolo-pyrimidines for their anticancer efficacy against four cancer cell lines: MCF-7 (human breast cancer), MGC-803 (human gastric cancer), EC-109 (human esophageal cancer), and B16-F10 (mouse melanoma). The majority 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.



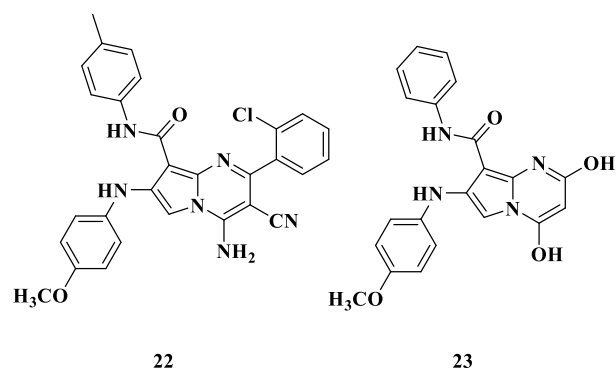
In 2016 [26], Two series of 4-phenyl-5-cyanopyrimidin-6-one derivatives, each featuring different *s*-alkyl or *s*-acyl groups at the 2-position, were developed as cytotoxic agents. Anticancer assays were conducted on two distinct cell lines, namely MCF-7 (breast tumor) and HCT-116 (colon tumor), to 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.



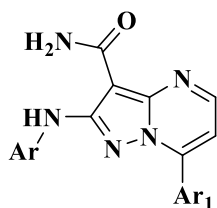
In 2017, Yousif et al [27] They produced bicyclic thiazolopyrimidine compounds and iminopyrimidine, thioxopyrimidine, and functionalized pyrimidine derivatives. Also, substituted arylidene derivatives of

thiazolopyrimidine compounds were made, and their ability to fight cancer was tested on different types of human cancer cells, such as HepG-2 liver cancer cells, PC-3 prostate cancer cells, and HCT-116 colon cancer cells. Compounds 18, 19, and 20 exhibited significant activity against PC-3 cancer cells, with IC₅₀ values of 66.5, 69.6, and 65.8 μg/mL, respectively. Furthermore, compounds 20 and 21 showed notably higher activity against the HCT-116 cell line, with IC₅₀ values of 58.2 and 60.9 μg/mL, respectively, when compared to the reference drug doxorubicin.

In the same year, a group of researchers [28] designed and produced a series of pyrazolo[1,5-a]pyrimidine derivatives and Schiff bases and assayed for their *in vitro* cytotoxic effects on HepG-2, PC-3, and HCT116 cancer cell lines. Two compounds showed significant antitumor efficacy against HCT-116 and PC-3 cells. which are compound 22 (IC₅₀= 59.18 and 67.27 μg/mL, sequentially), and compound 23 (IC₅₀= 58.44 and 64.58 μg/mL, sequentially), in comparison to doxorubicin as a reference drug (IC₅₀ = 73.50 and 75.24 μg/mL, sequentially).



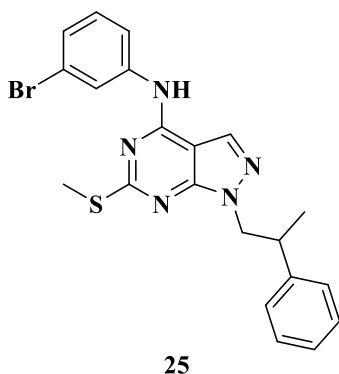
Hassan and collaborators [29] reported the synthesis of a derivatives of pyrazolo[1,5-a]pyrimidines and pyrazolo[3,4-d][1,2,3]triazines and evaluated for their *in vitro* cytotoxic activities against HepG-2 and MCF-7 cell lines. Compounds 24a (MCF-7 IC₅₀ = 63.2 μg/mL), and 24b (HepG-2 IC₅₀ = 70.3 μg/mL, sequentially), were the most potent in comparison with doxorubicin (MCF-7 IC₅₀ = 65.6 μg/mL and HepG-2 IC₅₀ = 80.9 μg/mL).



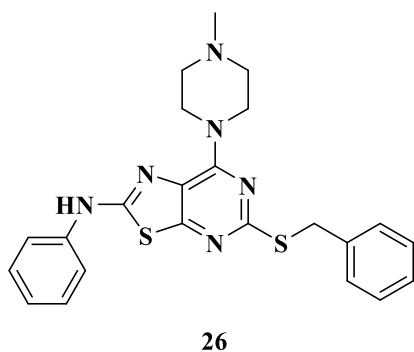
24a Ar = C₆H₅, Ar₁ = 4-Cl-C₆H₄

24b Ar = 4-OCH₃-C₆H₄, Ar₁ = 4-Br-C₆H₄

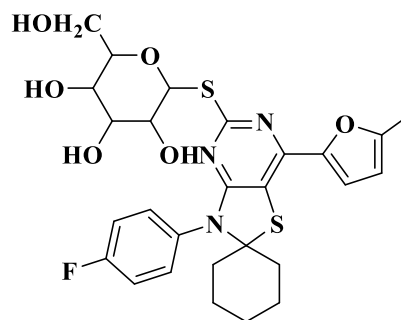
Vignaroli's team [30] evaluated the in vitro cytotoxicity of Pyrazolo[3,4-d]pyrimidine derivatives against human glioblastoma (U87) cell line. Compound 25 showed the most strong anticancer activity on U87 after 72 hours (IC₅₀ = 1.5 µg/mL).



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 IC₅₀ values for MGC-803 and HGC-27, two human stomach cancer cells, were 4.64 and 5.07 µM, respectively, indicating significant suppression.

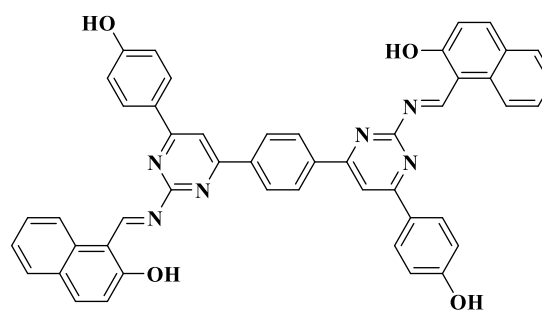


Felfel *et al.* [32] produced derivatives of 1-thia-azaspiro[4.5]decane, as well as the corresponding thiazolopyrimidine and 1,3,4-thiadiazole compounds. These compounds were evaluated for their anticancer effectiveness against cell cultures of several human cancer cell lines, including HepG-2, PC-3 and HCT116. Notably, Compound 27 exhibited significant cytotoxic activity against the HCT-116 cell line, surpassing the effectiveness of the standard drug doxorubicin.



27

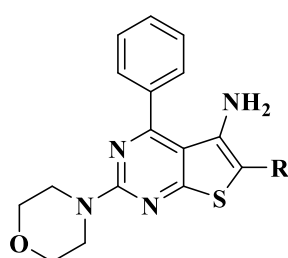
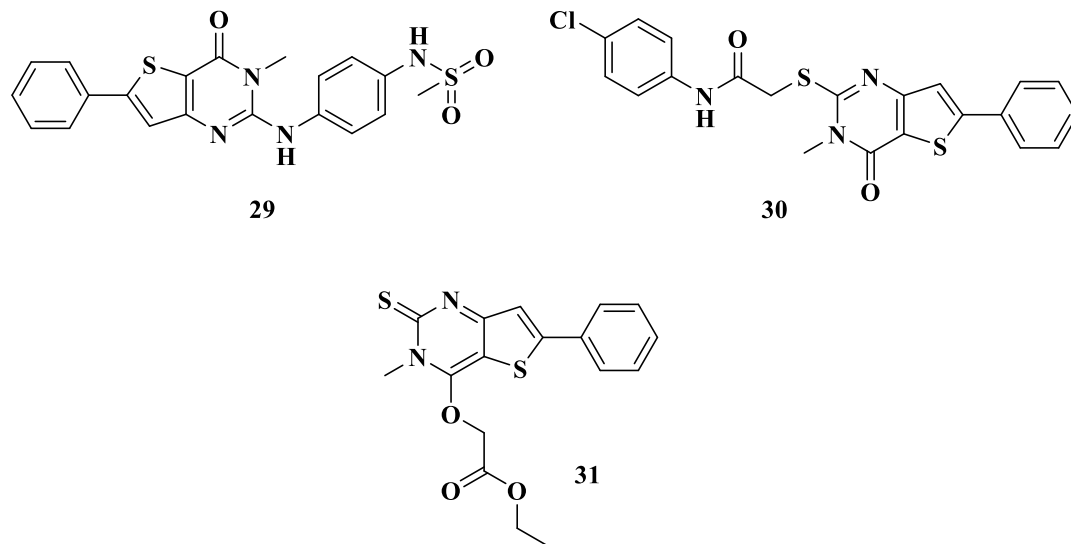
In the same year [33] a collection of bis-pyrimidine Schiff base compounds were assessed for their antibacterial and anticancer capabilities. These compounds were specifically evaluated for their effectiveness in combating the HCT-116 human colorectal carcinoma cell line. Among them, Compound 28, with an IC₅₀ of 0.18 µmol/mL, demonstrated more potent anticancer activity against the HCT-116 cell line compared to the reference drug, 5-fluorouracil.



28

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.

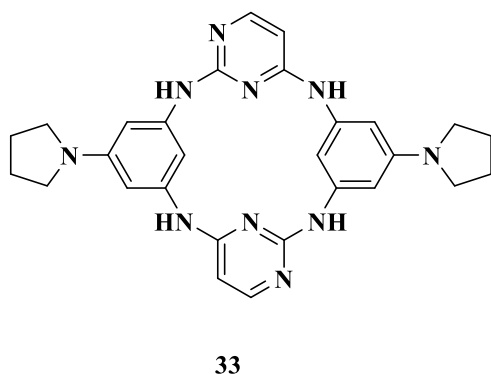
In 2018 [35], a series from thieno[2,3-d] pyrimidines was prepared and assessed for their antitumor activity. Compound 32a exhibited the greatest level of toxicity against the MCF-7 breast cancer cell line, with IC₅₀ values of approximately 18.87 µg/mL, surpassing the IC₅₀ values of Paclitaxel, which 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 IC₅₀ values of around 40.74 µg/mL..



32a R= CONHC₆H₄-4-Cl

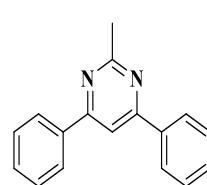
32b R= COC₆H₅

In the same year [36], it was reported that azacalix[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.

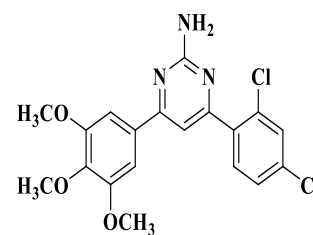


33

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.

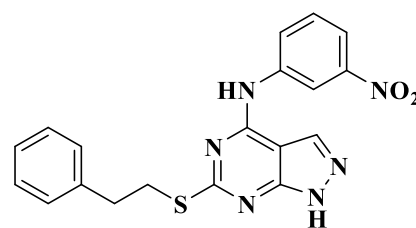


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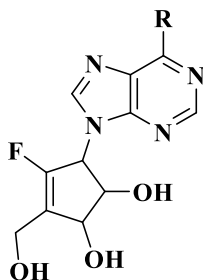
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In a later investigation [38], compound **36** had the most potent anticancer action against CDK2/cyclin E Abl kinases enzymes, displaying notable efficacy against the K-562 and MCF-7 cell lines.

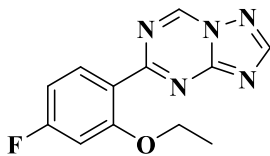


36

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].

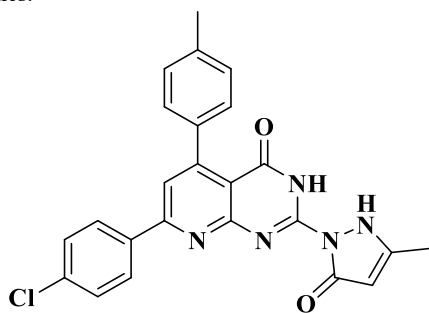
37a R= NH₂, 37b R= NH-CH₃

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 IC₅₀ value of 1.69 μM. Further examination revealed that Compound **38** also induces cytotoxicity in additional breast cancer cell lines, namely MDA-MB-231 and BT474, with IC₅₀ values of 4.81 μM and 4.08 μM, respectively.



38

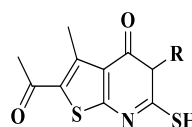
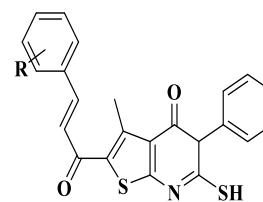
In 2018 [41], The cytotoxic activity of many substituted pyrido[2,3-*d*]pyrimidines was tested *in vitro* against a range of cancer cell lines, including HepG-2, HCT-116, MCF-7, and PC-3, which represent hepatic, colon, breast, and prostate cancers, respectively. An important finding is that, in comparison 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 IC₅₀ values of Compound **39** were 0.3 μM, 6.6 μM, and 7 μM, respectively. In comparison, doxorubicin exhibited IC₅₀ values of 0.6 μM, 6.8 μM, and 12.8 μM for the equivalent cell lines.



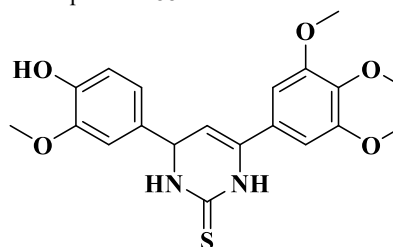
39

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.

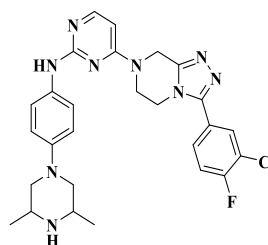
40a R= C₆H₅40b R= 4-Cl-C₆H₄40c R= CH₂-C₆H₅41a R= 4-CH₃41b R= 3,4,5-OCH₃

Pyrimidine derivatives were created by Ryad *et al* [43], as potential anticancer compounds. Among these, Compound **42** demonstrated strong *in vitro* cytotoxic effects against leukemia (HL-60) cells, with potent activity at a concentration of less than one micromolar (IC₅₀= 0.091 μM), surpassing that of combretastatin A4 (CA-4) (IC₅₀= 0.48 μM). Compound **42** was found to have strong anti-proliferative, pro-apoptotic, and cell cycle arresting properties. An assay focused on β-tubulin polymerization inhibition in HL-60 cells suggested that the anticancer activity of compound **42** is strongly correlated with its ability to inhibit β-tubulin polymerization, showing 66% inhibition compared to 88% for CA-4.

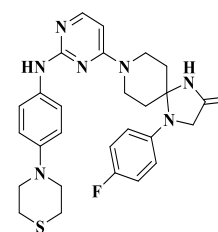


42

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 IC₅₀ values of 2.14 μM, 3.59 μM, 5.52 μM, and 3.69 μM against the A549, HCT-116, PC-3, and MCF 7 cell lines.



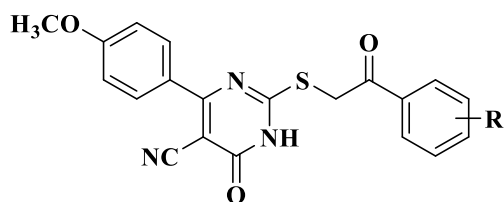
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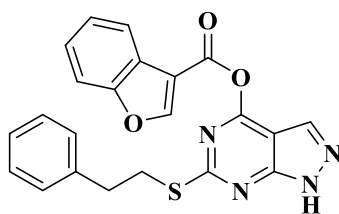
During the same year [45], a set of 2,4-disubstituted-2-thiopyrimidine compounds were studied for their potential as VEGFR-2 inhibitors. These compounds were tested against HepG2 and UO-31, two cell lines used to study liver and renal cancer, respectively. Compound **45a** and compound **45b** were determined to be strong inhibitors of the tyrosine kinase VEGFR-2, with IC₅₀ values of 1.23 μM

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.



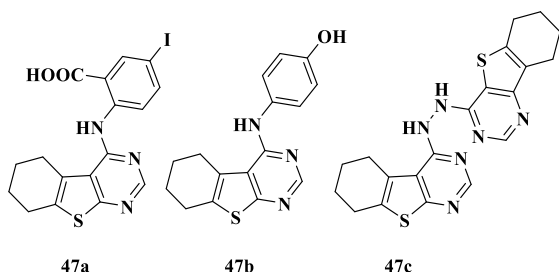
45a R= 4-OCH₃; **45b** R= 2-OCH₃

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.



46

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.



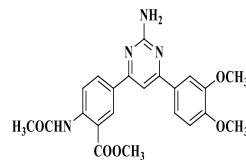
47a

47b

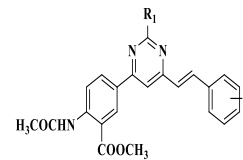
47c

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*)-styryl 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.

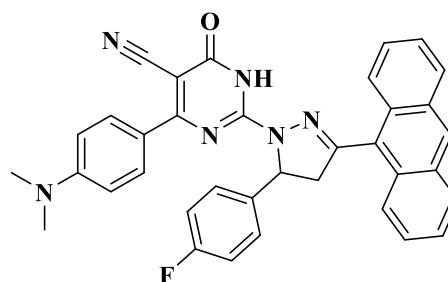


48



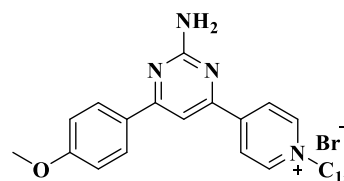
49a R = 2,3-OCH₃, R₁ = CH₃
49b R = 2,3-OCH₃, R₁ = C₆H₅
49c R = 2,5-OCH₃, R₁ = CH₃
49d R = 3,4-OCH₃, R₁ = CH₃

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 $\mu\text{g/mL}$ and 6.13 $\mu\text{g/mL}$, respectively. These values are comparable to the effectiveness of doxorubicin, a standard chemotherapy drug.



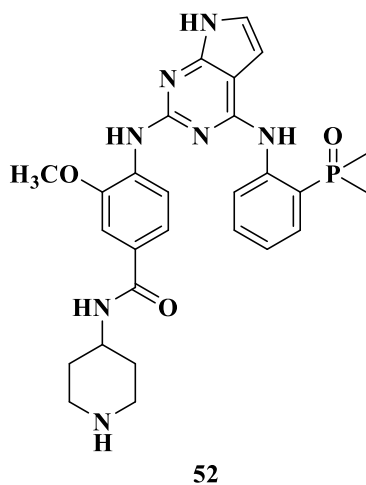
50

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 $\mu\text{g/mL}$ compared to 5-fluorouracil and cisplatin as reference drugs.

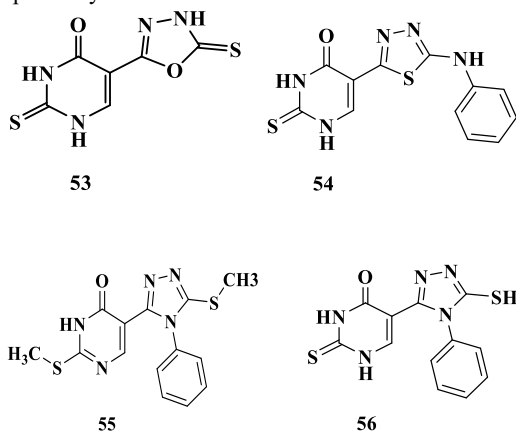


51

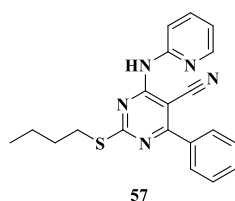
The possibility of 7H-pyrrolo [2,3-*d*] pyrimidine derivatives as inhibitors of focal adhesion kinase (FAK) was brought to light in 2019 [51]. Chemical **52** had an IC₅₀ of 3.20 μM against breast carcinoma (MDA-MB231) and 17.4 μM against lung cancer (A549) cell lines, respectively.



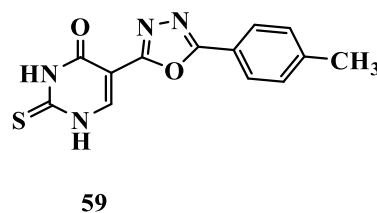
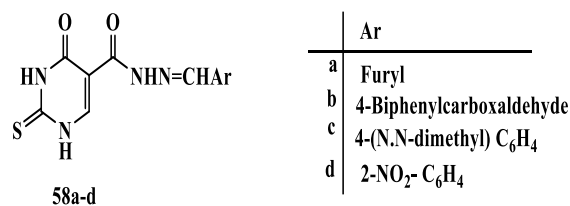
In 2020, El-Etrawy *et al.* conducted a study of 5-substituted-2-thiouracils where they tested their effectiveness against a specific cell line [52]. The findings revealed that compounds **53**, **54**, **55**, and **56** have a significant effect on the breast cancer cell line, as indicated by their IC₅₀ values of 3.80, 4.00, 4.50, and 4.70 μg/ml, respectively.



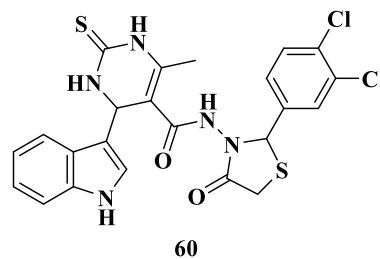
The task of inhibiting EGFR tyrosine kinase was taken on by a class of pyrimidine-5-carbonitrile chemicals that imitate the action of ATP. Four human cancer cell lines were used to assess the cytotoxic effects of these drugs *in vitro*: HCT-116 for colorectal carcinoma, HepG-2 for hepatocellular carcinoma, 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 IC₅₀ values for this compound: 3.37 μM, 3.04 μM, 4.14 μM, and 2.4 μM [53].



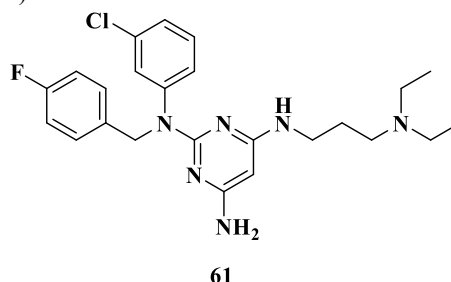
Furthermore, a subset of N¹-(2-thiouracil-5-oyl)hydrazones by El-Etrawy *et al.* [54] performed MTT assay-based *in vitro* screening on the MCF-7 human breast cell line. The findings demonstrated that chemicals **58a**, **59**, **58b**, **58c** and **58d** demonstrate the highest level of effectiveness against breast tumor cell line with IC₅₀ values of 3.40, 3.50, 3.60, 3.70 and 3.80 μg/ml, correspondingly.



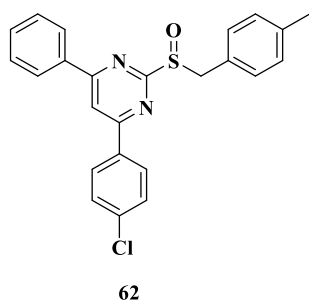
A number of indolyl-pyrimidine hybrids were designed and produced by Ahmed and colleagues in 2021 [55]. Subsequently, against several malignance cell lines, such as MCF-7 for breast cancer, HepG2 for hepatocellular carcinoma, and HCT-116 for colorectal carcinoma, these compounds were evaluated for their anticancer capabilities. In particular, Compound **60** IC₅₀ 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.



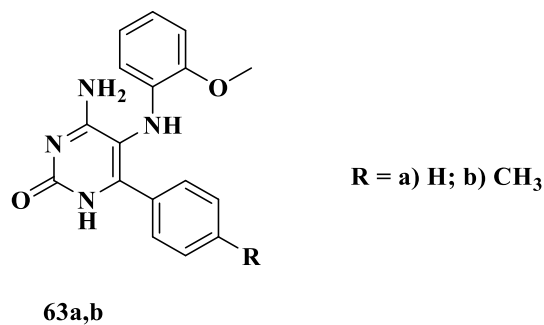
Noemi, *et al.* reported the design, synthesis, and anti-proliferative activities of aminopyrimidine derivatives [56]. With EC₅₀ ranging from 4 to 8 μM, compound **61** was the most intriguing of the derivatives for all the tested tumor cell lines, including triple-negative breast cancer (MDA-MB231), glioblastoma multiforme (U-87 MG), tongue squamous cell carcinoma (CAL27), colon carcinoma (HT-29), and pharynx squamous cell carcinoma (FaDu).



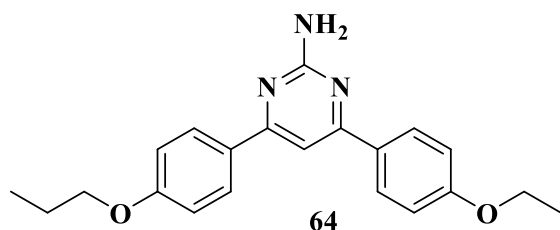
In the same year [57], a group of investigators evaluated the cytotoxic effects of some pyrimidine derivatives against human colon adenocarcinoma HT-29, two breast cancer cell lines (MCF-7, T47D), as well as a mouse embryonic fibroblast cell line, (NIH-3T3). Compound **62** showed the best cytotoxicity against all cell lines with $IC_{50} = 60, \text{ and } 1.5, 10, 16 \mu\text{M}$, respectively.



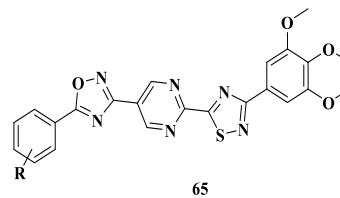
A study on the cytotoxicity of pyrimidines was conducted by Othman *et al* [58]. The substances were assessed as potential cytotoxic agents against human breast malignance cells (MCF-7) and hepatocellular carcinoma cells (HepG-2). Compound **63a** showed greater potency than 5-flourouracil, while its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



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 $18.5 \mu\text{M}$.

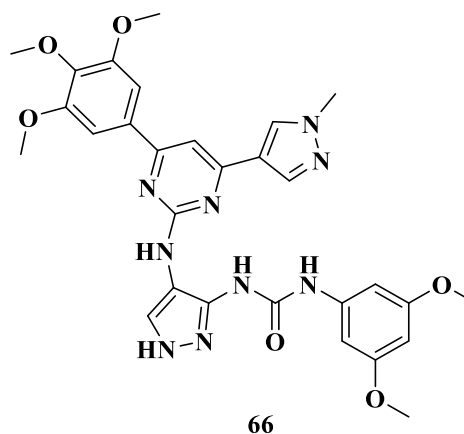


A unique collection of ten pyrimidine analogues was developed and manufactured by Ashok *et al.* [60]. A panel of human cancer cell lines, including MCF-7, A-549, Colo-205, and A2780, were used to assess the anticancer potential of a series of chemicals. These cell lines represent breast cancer, non-small 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.

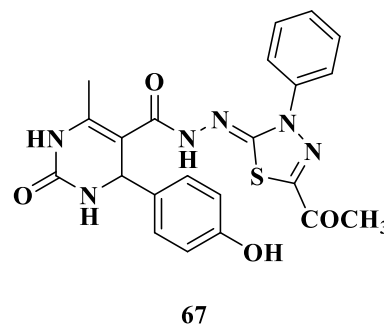


$R = \text{a) } 3,4,5\text{-tri OCH}_3; \text{ b) } 3,5\text{-di OCH}_3; \text{ c) } 4\text{-OCH}_3; \text{ d) } 4\text{-CH}_3; \text{ e) } 4\text{-NH(CH}_3)_2$

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.

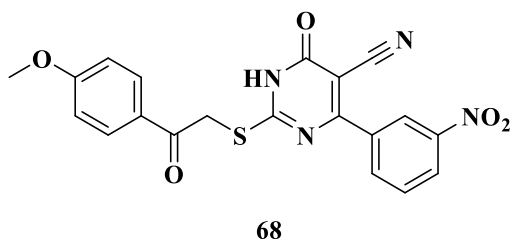


In 2022 [62], pyrimidinone ring derivatives with a some five-membered heterocycles were created and produced. The MTT test was used to discover the target compounds' *in vitro* cytotoxic activities against PC-3, HepG-2, and HCT-116 colorectal cancer cell lines. All the investigated compounds showed strong 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 $IC_{50} = 58.1 \mu\text{g/mL}$, higher activity than doxorubicin ($IC_{50} = 73.50 \mu\text{g/mL}$).

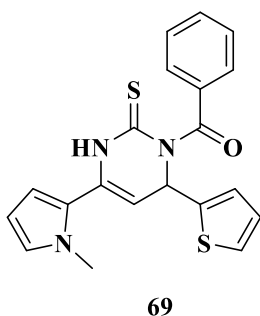


Modulation of the Monastrol scaffold was conducted by Thabit *et al* [63] to produce compounds with potent cytotoxic activity. Compound **68** exhibited a notably high level of cytotoxicity against two specific cancer cell lines: colorectal carcinoma (HCT-116) and breast cancer cells (MCF-7), with IC_{50} 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

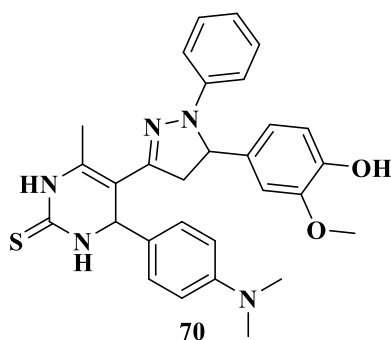
14.89 μM . Furthermore, a considerable apoptotic effect was observed along with a cell cycle arrest at the G2/M phase when HCT-116 cells treated with Compound **68** were observed to have this distribution.



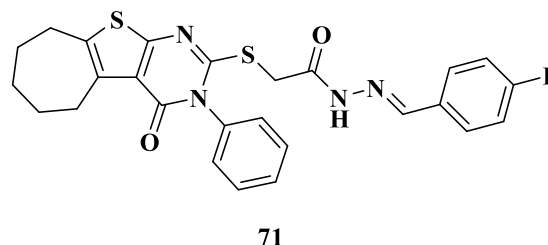
Researchers in 2022 tested a number of pyrimidine-2-thiones for their antineoplastic effects on human cancer T-116 and carcinoma of the liver HepG-2 cell lines [64]. Compound **69** was the most active among the selected compounds with IC_{50} (10.72 and 18.95) μM in both HCT-116 A and HepG-2, respectively.



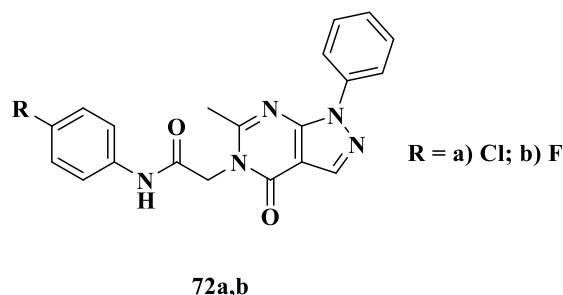
The main objective of Salem *et al's* study in 2022 [65] was to prepare, characterize, and estimate the potential anticancer effects of pyrimidine-2-thione analogues. Among these derivatives, compound **70** showed the most promising results with an IC_{50} value of 2.617 μM on breast cancer cells (MCF-7). 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 **70** 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.



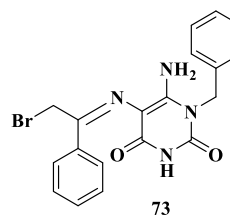
In 2022 [66], a team of researchers successfully prepared *N'*-(4-fluorobenzylidene)-2-[(4-oxo-3-phenyl-6,7,8,9-tetrahydro-3*H*-cyclohepta-[4,5]thieno[2,3-*d*]pyrimidin-2-yl)thio]acetohydrazid (**71**). The National Cancer Institute (NCI) conducted tests on various cell lines and found that this compound 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 LC_{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 .



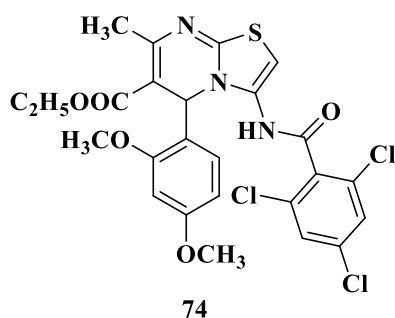
N^5 -substituted-pyrazolo[3,4-*d*]pyrimidinone derivatives were synthesized and assessed as anticancer agents against colorectal carcinoma (HCT-116) and liver carcinoma (HepG-2) cell lines in a study conducted by Zaki *et al.* [67]. Additional analysis of compounds **72a** and **72b**, the most promising cytotoxic agents in the study on both cell lines, revealed that these derivatives inhibit CDK2 kinase. Regarding CDK2 inhibitory action, compound **72b** was more effective than the reference drug roscovitine (IC_{50} values: 0.21 and 0.25 μM , respectively).



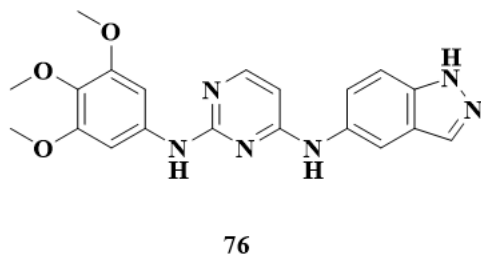
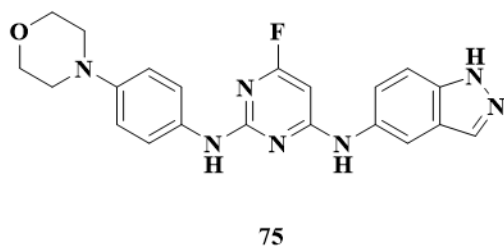
A group of researchers in 2023 [68] evaluated the cytotoxic effects of compounds belong to the aminopyrimidine-2,4-dione family. They found that compound **73** exhibited a strong cytotoxic activity against breast cancer cells (MDA-MB-231), with IC_{50} value of 0.78 μM . This potency was compared to 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).



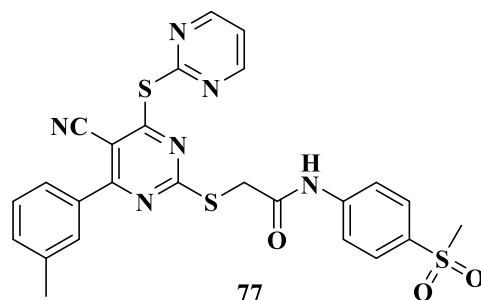
Several thiazolopyrimidine derivatives were developed and tested for their ability to destroy cancer cells in the same year [69]. These were tested against three distinct human cancer cell types: MCF-7, A-549, and A-498, which represent non-small cell lung cancer, renal carcinoma, and breast cancer, with IC_{50} values of 2 μ M for MCF-7 and A-549, and 1 μ M for A-498, Compound **74** stood out among these as a very potent anticancer drug. The IC_{50} values for the same cell lines were 9 μ M, 13 μ M, and 7 μ M for Doxorubicin, a commonly used anticancer medication, compared to these more favorable results. In addition, with an IC_{50} value of 0.23 ± 0.01 μ M, 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.



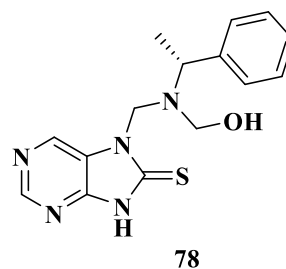
In 2023 [70], a group of investigators tested derivatives based on indazol-pyrimidine for their ability to kill cancer cells. Their efficacy was tested against three different cancer cell lines: MCF-7, A549., and Caco2. Among the compounds tested, **75** and **76** showed the strongest ability to kill cancer cells, with IC_{50} values of 1.629 and 1.841 μ M, respectively, compared to Staurosporine as a reference drug with an IC_{50} value of 8.029 μ M. 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_{50} value of 2.98 μ M, 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_{50} values for the most sensitive cell lines were found to be 11.96 μ M for leukemia (HL-60), 9.46 μ M for ovarian cancer (SK-OV-3), and 6.68 μ M for breast carcinoma (MCF-7). Also, compound **78** showed strong suppression of COX-2 (Cyclooxygenase-2) activity, with an IC_{50} value of 69.79 μ M, which makes it similar to celecoxib, the reference medication ($IC_{50} = 53.76$ μ M). 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.

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