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Heteroarylpyrimidine Ring As An Anticancer Agent: A Review

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ABSTRACT

Background: Cancer is a broad collection of illnesses that can begin in practically any organ or tissue of the body. These illnesses are brought on when abnormal cells grow out of control, cross their normal boundaries to infect nearby body parts and/or spread to other organs. The latter process, known as metastasizing, is a significant contributor to cancer-related mortality.

Main text: The Heteroarylpyrimidine ring system has garnered significant interest in medicinal chemistry due to its potential as an anticancer agent. In the past several years, a large number of brand-new pyrimidine derivatives have been created and studied for their anticancer activities. The current review attempts to concentrate on the relationship between pyrimidine derivatives structure and activity in relation to biological response as an anticancer agent throughout the past ten years.

Conclusion: This review aims to aid in the creation of pyrimidine scaffold-based anticancer medications that are more effective and potent. This review article discusses the 4-heteroarylpyrimidine ring's reported anticancer activity on a variety of cancer cell lines. This review aims to provide an overview of the recent advancements and studies regarding the use of this ring system in anticancer drug development.

KEYWORDS:Cancer, Pyrimidine, Anticancer activity, Structure activity relationship, Heterocyclic compound.

INTRODUCTION

Cancer is the unchecked spread of aberrant cells throughout the body. Cancer cells, malignant cells, or tumor cells are names for these aberrant cells. These cells are able to invade healthy body tissues. The name of the tissue from which the aberrant cells originated helps to further identify many tumors and the abnormal cells that make up the cancer tissue (for example, breast cancer, lung cancer and colorectal cancer). The terms "neoplasm" and "malignant tumor" are also used to describe cancer. An estimated 9.6 million deaths, or one in every six deaths, were attributed to cancer in 2018, making it the second highest cause of death worldwide. Men are more likely to develop lung, prostate, colorectal, stomach and liver cancer than women,

who are more likely to develop breast, colorectal, lung, cervical and thyroid cancer. The physical, psychological and financial toll that cancer takes on people, families, communities and health systems around the world keeps rising. Numerous low- and middle-income countries' health systems are ill-equipped to handle this burden and many cancer patients worldwide lack access to prompt, effective diagnosis and treatment. Because of readily available early detection, high-quality treatment and survivorship care, the survival rates of many forms of cancer are increasing in nations with robust health systems. In the United States, the top three malignancies affecting men, women and children are as follows: Males: colorectal, lung and prostate women: colorectal, lung and breast cancer Leukemia, brain tumor sand lymphoma in children Numerous variables, including age, gender, race, local environmental factors, food and genetics, have an impact on the occurrence of cancer and the different forms of cancer. As a result, these varying factors have an impact on both the incidence of cancer and the forms of cancer. The World Health Organization (WHO), for instance, offers the general knowledge below regarding cancer globally: The top cause of death in the world is cancer. According to the most recent WHO data, it was responsible for 8.2 million deaths, or around 22% of all deaths that were not caused by infectious diseases. The greatest cancer-related fatalities each year are caused by lung, stomach, liver, colon and breast cancer. It is anticipated that there would be 13.1 million cancer-related deaths worldwide in 2030, which would represent a 70% increase. There may be malignancies that are more or less common in some parts of the world than in the United States. For instance, while stomach cancer is uncommon in the United States, it is frequently seen there. This typically denotes a confluence of hereditary and environmental variables.

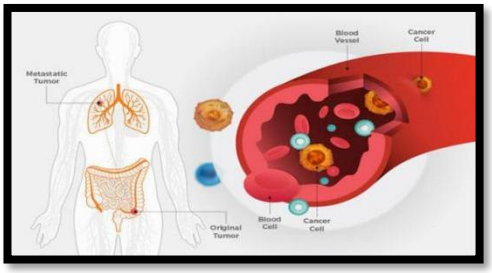


Figure1: Cancer

The three types of cancer that affects Americans most frequently—men, women and kids:

1. Men: Prostate, longhand colorectal.
2. Women: Breast, lung and colorectal.
3. Children: Leukemia, brain tumor and lymphoma.

The following table (National Cancer Institute 2022) gives the estimated numbers of new cases and deaths for each common cancer type:[1]

Cancer Type	Estimated New Cases	Estimated Deaths
Bladder	76960	17100
Breast	287,850	43250
Colon & Rectal	151030	52580
Endometrial	65950	12550
Kidney	79000	13920
Leukemia	60650	24000
Lung	236740	130180
Melanoma	99780	7650
Non Hodgkin Lymphoma	80,470	20,250
Pancreatic	62210	49830
Prostate	268490	34500

Table 1: A rough estimate of the number of new cases and fatalities for common cancer types

Prevention of Cancer

Between 30% and 50% of cancer-related fatalities could be prevented by changing or removing important risk factors and putting into practice currently advised evidence-based prevention strategies. Through early cancer detection and patient management, the burden of cancer can also be decreased. The most economical long-term approach to the control of cancer is prevention.

• Steer clear of tobacco products, such as cigarettes and smokeless tobacco.
• Continue to be a healthy weight.

• Consume a balanced diet that includes lots of fruit and vegetables.
• Regular exercise.
• Drink in moderation.
• Engage in discreet sex.
• Obtain vaccinations against the human papillomavirus and hepatitis B. (HPV).
• Limit your exposure to UV radiation.
- Reduce exposure to ionizing radiation (e.g. minimize occupational exposure; ensure safe and appropriate medical use of radiation in diagnosis and treatment).
- To lessen smoke and urban air pollution, refrain from burning solid fuels in your home.
- Avoid using solid fuels in your home to reduce smoke and urban air pollution.
- Get regular medical care.
- Some persistent infections can increase your risk of developing cancer. Chronic infections increase the risk of cancer development in people living in low- and middle-income nations.

Figure 2: Symptoms of Cancer

Figure 3: Signs of Cancer

Management for Cancer

When cancer is detected early, it is more likely to respond to appropriate treatment, increasing the likelihood of survival as well as reducing morbidity and treatment costs. Early detection is encouraged by two different tactics:

1. Early diagnosis locates cancer instances with symptoms at the earliest opportunity.
2. The goal of screening is to find people who have anomalies that could be signs of a particular disease or pre-cancer but who have not yet shown any symptoms so that a rapid diagnosis and treatment can be made.

Surgery, cancer medications and/or radiotherapy, either alone or in combination, are available as treatment options. Based on tumor kind, cancer stage, clinical and other characteristics, a multidisciplinary team of cancer experts suggests the optimal treatment strategy. Patients' wishes should be taken into account, as well as the capabilities of the healthcare system. A crucial part of cancer treatment is palliative care, which aims to enhance the quality of life for patients and their families. A comprehensive plan for tracking cancer recurrence and spotting new cancers, evaluating and treating the long-term side effects of cancer and/or its treatment and services to meet the needs of cancer survivors is all included in survivorship care.[2]

ACTIVITIES OF 4-HETEROARYLPYRIMIDINE

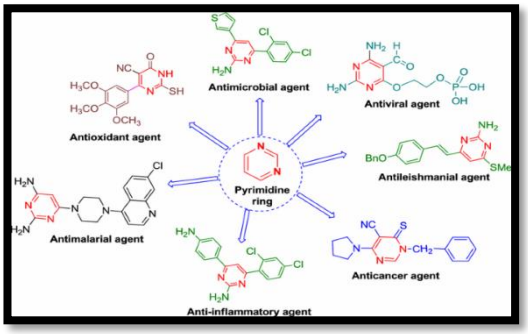


Figure 4: Activities of 4-heteroarylpyrimidine

The activities of 4-heteroarylpyrimidine compounds span a wide range of biological effects, with many exhibiting significant potential as therapeutic agents. Some of the key activities associated with these compounds include:

1. Anticancer Activity: Perhaps the most widely studied activity of 4-heteroarylpyrimidine compounds is their anticancer potential. These compounds often target specific molecular pathways involved in cancer progression, such as receptor tyrosine kinases (e.g., EGFR, VEGFR), protein kinases (e.g., Bcr-Abl, c-Met) and other signaling molecules critical for tumor growth and survival. By inhibiting these targets, 4-heteroarylpyrimidines can induce apoptosis, inhibit cell proliferation and suppress angiogenesis, thereby exhibiting potent anticancer effects.

2. Antimicrobial Activity: Some 4-heteroarylpyrimidine derivatives have shown promising antimicrobial activity against a variety of pathogens, including bacteria, fungi and parasites. These compounds may target essential enzymes or processes vital for microbial survival and replication, making them potential candidates for the development of new antimicrobial agents to combat drug-resistant infections.

3. Antiviral Activity: Certain 4-heteroarylpyrimidines exhibit antiviral activity against a range of viruses, including HIV, hepatitis C virus (HCV), herpes simplex virus (HSV) and respiratory viruses such as influenza. These compounds may interfere with viral replication, entry, or assembly, offering potential as therapeutic agents for viral infections.

4. Anti-inflammatory Activity: Several studies have reported the anti-inflammatory properties of certain 4-heteroarylpyrimidine derivatives. These compounds may modulate inflammatory pathways and cytokine production, thereby attenuating inflammatory responses implicated in various diseases, including rheumatoid arthritis, inflammatory bowel disease and neuroinflammatory disorders.

5. Antioxidant Activity: Some 4-heteroarylpyrimidine compounds possess antioxidant properties, which may help mitigate oxidative stress and cellular damage associated with various pathological conditions, including neurodegenerative diseases, cardiovascular disorders and aging-related disorders.

6. Enzyme Inhibition: Certain 4-heteroarylpyrimidines act as enzyme inhibitors, targeting enzymes involved in diverse biological processes such as kinases, proteases and metabolic enzymes. Modulating the activity of these enzymes can impact various cellular functions and pathways, making them potential therapeutic targets for various diseases.
Overall, the diverse range of biological activities exhibited by 4-heteroarylpyrimidine compounds underscores their potential as versatile pharmacological agents for the treatment of various diseases. Further research in the anticancer activity is greatly influenced by substitutions at the pyrimidine core's C-2, C-4and C-6 positions, particularly a thio or amino group at C-2 and a modified phenyl group at C-4. In comparison to six member rings like pyrido and quinazoline, pyrididine fused with five member rings such as pyrazolo, pyrrolo, triazolo, imidazole, oxazolo, thiazoloand thieno demonstrated more distinct anticancer action. Inhibition of kinase (erbB2, raf, CDK, Src, etc.) enzymes, cell cycle arrest, activation of oncogenes, reduction of mitochondrial membrane potential, increase of ROS and induction of apoptosis by up-regulation of apoptotic and down-regulation of anti-apoptotic proteins are just a few of the diverse mechanisms by which pyrimidine analogues work as anticancer agents. This will help scientists and researchers from all around the world to choose and optimize certain targets for the future creation of powerful lead compounds as anticancer medicines. [4]

HETEROARYLPYRIMIDINE DERIVATIVES AS ANTIPROLIFERATIVE AGENTS:
Mohammed Albratty et al. highlight the significance of pyridine and pyrimidine analogues in anticancer drug development, emphasizing their diverse applications and potential therapeutic benefits in various types of cancer. Here's a summary of the key points discussed in the review:

1. **Class of Heterocyclic Compounds:** Pyridines and pyrimidines are heterocyclic nitrogenous compounds that have demonstrated significant potential in anticancer drug development. Their structural diversity and ability to interact with biological targets make them attractive candidates for the treatment of various types of cancer.

2. **Applications in Cancer Therapy:** Pyridine and pyrimidine analogues have been explored as potent compounds for the treatment of several types of cancer, including breast cancer, myeloid leukemia, pancreatic cancer, liver cancer and idiopathic respiratory fibrosis. These compounds may exhibit anticancer properties through various mechanisms, such as inhibition of key signaling pathways, interference with DNA replication or repair, induction of apoptosis and modulation of cellular metabolism.

3. **In Vitro and In Silico Studies:** The review enumerates the results of studies published over the past three years (2019–2021) that have investigated the anticancer properties of pyridine and pyrimidine analogues. These studies may involve in vitro experiments using cancer cell lines to assess cytotoxicity, cell proliferation, apoptosis induction and other relevant endpoints. Additionally, in silico studies, such as molecular docking, virtual screening and quantitative structure-activity relationship (QSAR) analyses, provides insights into the molecular interactions and pharmacological profiles of these compounds.

4. **Recent Advances:** The review highlights recent advances in the development of pyridine and pyrimidine analogues as potential anticancer agents. These advances may include the discovery of novel compounds with improved efficacy, selectivity and pharmacokinetic properties, as well as insights into their mechanisms of action and therapeutic potentials.

5. **Future Opportunities:** The promising results from studies on pyridine and pyrimidine analogues underscore the appealing opportunities for cancer therapy. Further research and development efforts in this field may lead to the identification of new lead compounds, optimization of existing compounds and eventual translation into clinical applications for the treatment of cancer.[5]
Abdel-Maksoud MS et al . reported the design, synthesis and evaluation of a new series of 4-(1H-benzo[d]imidazol-1-yl)pyrimidin-2-amine linked sulfonamide derivatives as potential V600E BRAF inhibitors.

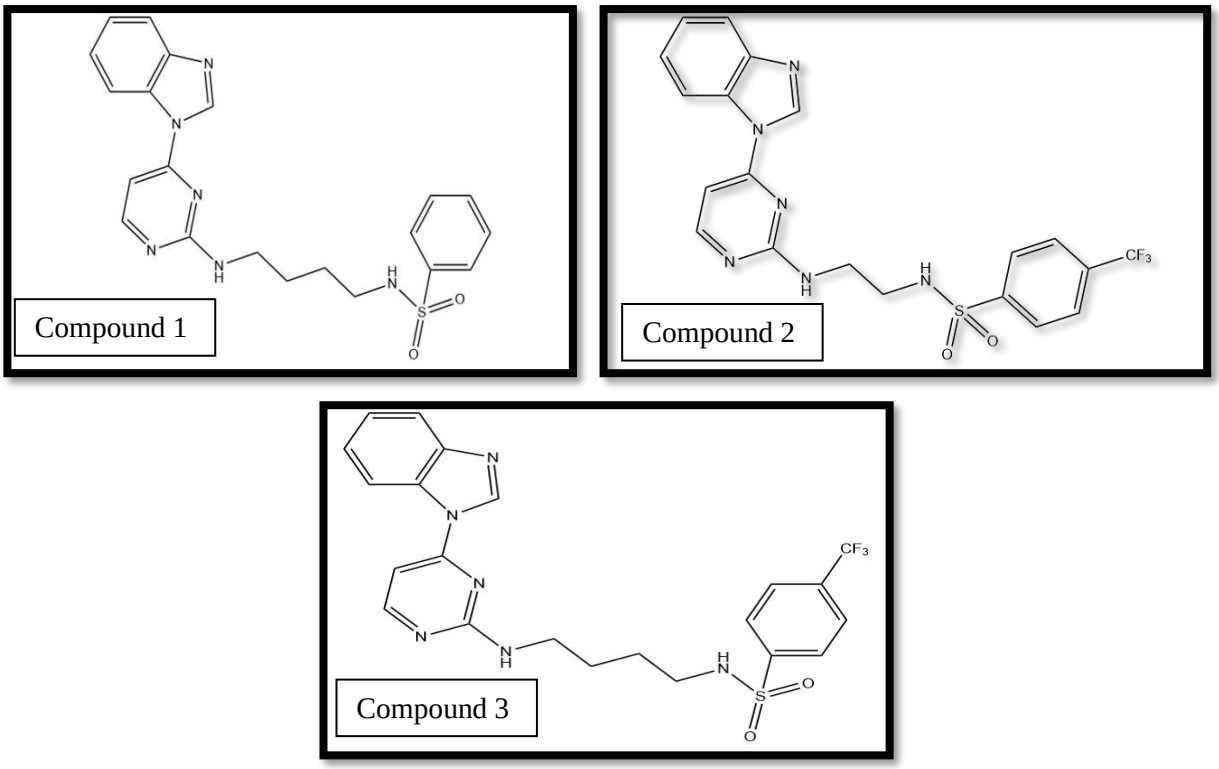
1. **Design and Synthesis:** The compounds were designed based on the structure of established V600E BRAF inhibitors. The sulfonamide moiety was linked to the pyrimidine ring via ethylamine or propylamine bridges. The synthesis likely involved standard organic chemistry techniques for building the desired molecular structures.

2. **Evaluation of Inhibitory Activity:** The synthesized compounds were tested at a fixed concentration (1 µM) against V600E BRAF. Among the tested compounds 1, 2 and 3 exhibited the strongest inhibitory activity, with compound 3 showing the lowest IC50 value of 0.49 µM. This indicates their potential as V600E BRAF inhibitors.

3. **Screening on NCI 60 Cancer Cell Lines:** The most promising compound 1 was further evaluated for its growth inhibition activity against multiple cancer cell lines using the NCI 60 panel. This panel consists of 60 human cancer cell lines representing nine different tumor types and is commonly used for anticancer drug screening.

4. **Cell Cycle Analysis:** Cell cycle analysis of compound 1 was conducted to investigate its effect on cell cycle progression. This analysis likely involved techniques such as flow cytometry to assess the distribution of cells in different phases of the cell cycle (G1, S and G2/M).

5. **Virtual Docking Studies:** Virtual docking studies were performed to gain insights into the plausible binding modes of vemurafenib (a known V600E BRAF inhibitor) and the most potent compounds. Molecular docking is a computational technique used to predict the binding affinity and orientation of small molecules within the active site of a target protein, providing valuable information for drug design and optimization.[6]



Compound 1: N-(2-((4-(1H-benzo [d]imidazol-1-yl) pyrimidin-2-yl) amino)ethyl)-4-(trifluoromethyl)benzenesulfonamide.
Compound 2: N-(3-((4-(1H-benzo [d]imidazol-1-yl) pyrimidin-2-yl) amino)propyl)-4-fluorobenzenesulfonamide.
Compund 3: N-(3-((4-(1H-benzo [d]imidazol-1-yl) pyrimidin-2-yl) amino)propyl)-4-(trifluoromethyl) benzenesulfonamide.

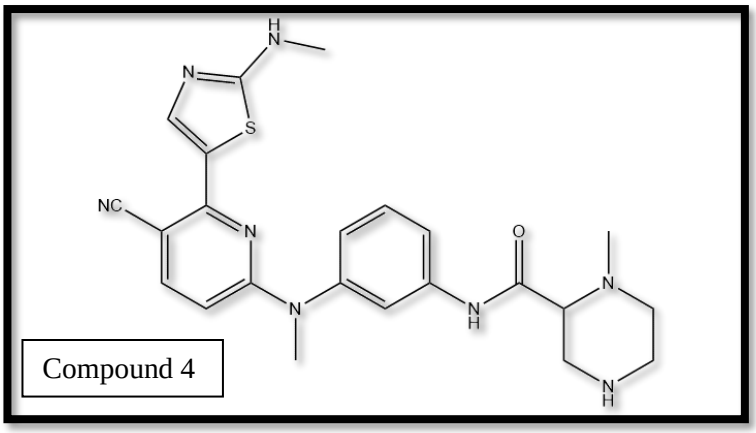
Hao et al. Reported synthesis and characterization of a series of 2, 4,5-trisubstituted pyrimidines with potent CDK inhibition and anti-proliferative activities. Here's a breakdown of the key findings and analyses:
1. **Synthesis and Characterization:** The 2, 4,5-trisubstituted pyrimidines were synthesized and thoroughly characterized using various spectroscopic and analytical techniques to confirm their chemical structures and purities.

2. **CDK Inhibition and Anti-proliferative Activities:** The synthesized compounds were evaluated for their inhibitory activity against cyclin-dependent kinases (CDKs) and their ability to inhibit cell proliferation. This likely involved biochemical assays to measure CDK activity and cell viability assays using cancer cell lines.

3. **Structure-Activity Relationship (SAR) Analysis:** The structure-activity relationship of the synthesized compounds was analyzed to understand the impact of different substituent on their CDK inhibition and anti-proliferative activities. This analysis may involve correlating structural features of the compounds with their biological activities to identify key motifs or functional groups crucial for potency and selectivity.

4. **Rational for CDK9 Selectivity:** The study discusses the rationale behind the observed selectivity of certain compounds, such as compound 4, for CDK9 over other CDKs. This may involve molecular modeling studies, docking simulations, or biochemical assays aimed at understanding the interactions between the compounds and the CDK active sites, as well as the structural differences between CDK isoforms that confer selectivity.

5. **Mechanism of Action:** Compound 4, which exhibits appreciable selectivity for CDK9, is capable of activating caspase 3, reducing the level of Mcl-1 anti-apoptotic protein and inducing cancer cell apoptosis. This suggests that the compound may exert its anti-proliferative effects through the induction of apoptosis via modulation of key apoptotic proteins and pathways.[7]



Compound 4: 3-(5-Cyano-4-(4-methyl-2-(methylamino) thiazol-5-yl) pyrimidin-2-ylamino)-N-(1-methylpiperidin-4-yl) benzamide.

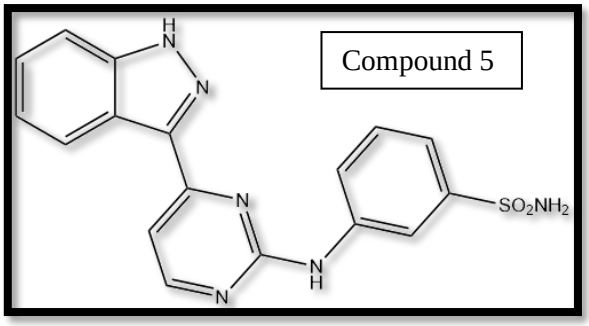
Lukasik, P. M et al. describes the synthesis and evaluation of three series of compounds—N-phenyl-imidazo[4,5-b]pyridin-2-amines, 4-indazolyl-N-phenylpyrimidin-2-aminesand N-phenyl-4-pyrazolo[3,4-b]pyridin-pyrimidin-2-amines—for their anti-proliferative activities against HCT-116 human colon carcinoma and MCF-7 breast carcinoma cell lines. Here's a breakdown of the key findings:

1. **Synthesis:** The compounds were synthesized using appropriate synthetic routes and characterized using spectroscopic techniques to confirm their structures.
2.
3. **Evaluation of Anti-Proliferative Activities:** The synthesized compounds were tested for their ability to inhibit cell proliferation using HCT-116 and MCF-7 cell lines. This likely involved cell viability assays to measure the effect of the compounds on cell growth and proliferation.

4. **CDK9 Inhibitory Activities:** Many of the synthesized compounds exhibited potent CDK9 inhibitory activities. This suggests that their anti-proliferative effects may, in part, be mediated through the inhibition of CDK9, a kinase involved in cell cycle regulation and transcriptional control.

5. **Lead Compound Identification:** Compound 5 emerged as a lead compound due to its potent anti-proliferative activities and CDK9 inhibitory properties. This compound demonstrated the ability to reduce the level of Mcl-1 anti-apoptotic protein, activate caspase 3/7and induce cancer cell apoptosis.

6. **Mechanism of Action:** The ability of compound 5 to reduce Mcl-1 levels, activate caspase 3/7and induce cancer cell apoptosis suggests that it may exert its anti-proliferative effects through the modulation of apoptotic pathways. Mcl-1 is an anti-apoptotic proteinand its down regulation can lead to apoptosis induction, while cascade activation is a key event in the execution of apoptosis.[8]



Compund 5: 3-(4-(1H-Indazol-1-yl)pyrimidin-2-ylamino) benzenesulfonamide.

Ahmed, N.M. et al.describes the synthesis and evaluation of novel indolyl-pyrimidine hybrids as potential antitumor agents. Here's a breakdown of the key findings and methodologies:

1. **Synthesis of Indolyl-Pyrimidine Hybrids:** The novel compounds were synthesized using appropriate synthetic routes and characterized using spectroscopic techniques to confirm their structures.

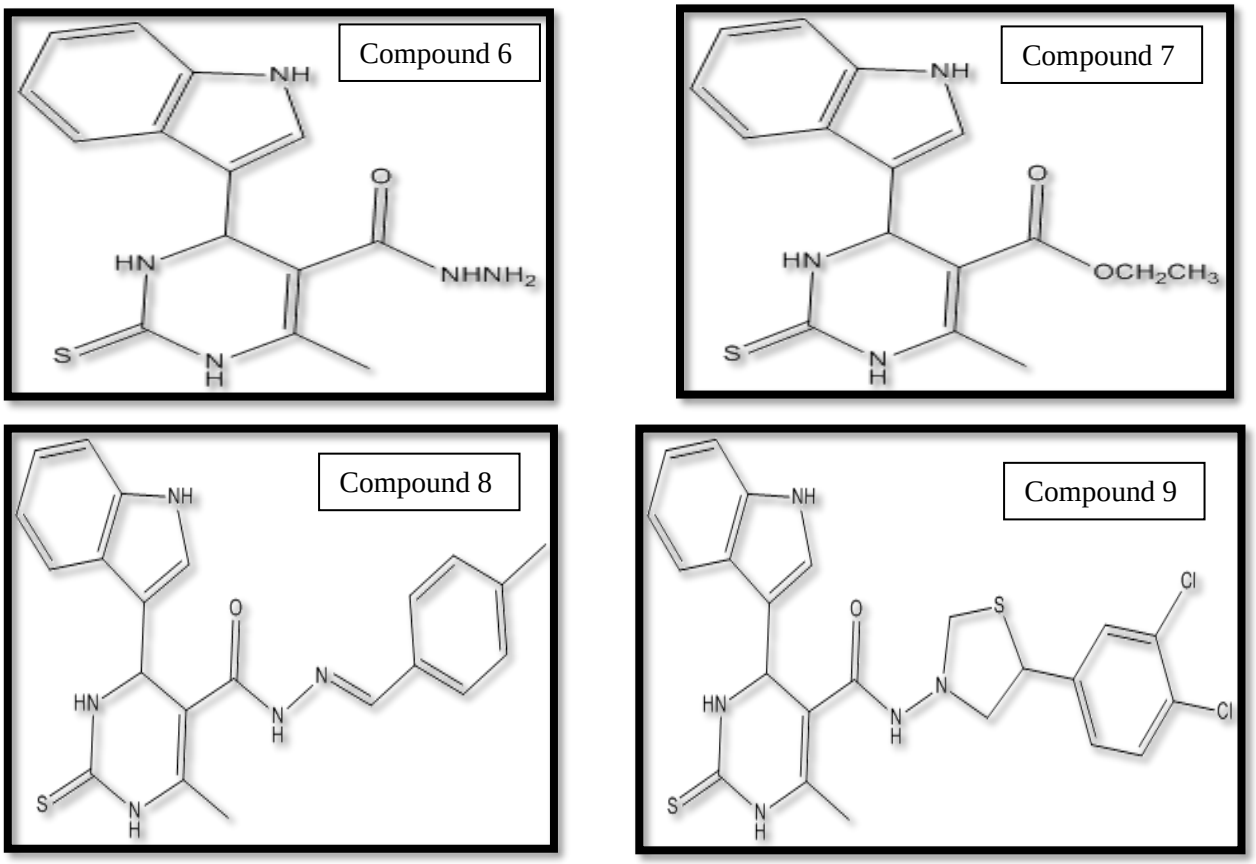
2. **In Vitro Antiproliferative Activity:** The synthesized compounds were evaluated for their ability to inhibit cell proliferation using MCF-7 (breast cancer), HepG2 (liver cancer) and HCT-116 (colon cancer) cell lines, as well as WI38 normal cells as a control. The antiproliferative activity was determined using the resazurin assay, which measures cell viability.

3. **Identification of Potent Compounds:** Compounds 6-9 exhibited broad-spectrum cytotoxic activity against all tested cancer cell lines compared to normal cells. Among them, compound 4g demonstrated potent antiproliferative activity with IC50 values of 5.1 µM (MCF-7), 5.02 µM (HepG2)and 6.6 µM (HCT-116), comparable to standard treatments (5-FU and erlotinib).

4. **In Vivo Antitumor Efficacy:** The most promising compounds were further evaluated for their in vivo antitumor efficacy using EAC (Ehrlich Ascites Carcinoma) tumor-bearing mice. Compound 4g exhibited the most potent in vivo antitumor activity.

5. **EGFR Inhibitory Activity:** The most active compounds were evaluated for their inhibitory activity against EGFR (Epidermal Growth Factor Receptor), a target commonly implicated in cancer. Compound 4g showed significant EGFR inhibitory activity with an IC50 value of 0.25 µM, comparable to erlotinib, a reference treatment. Molecular modeling studies confirmed proper binding of compound 4g within the EGFR active site, similar to erlotinib.

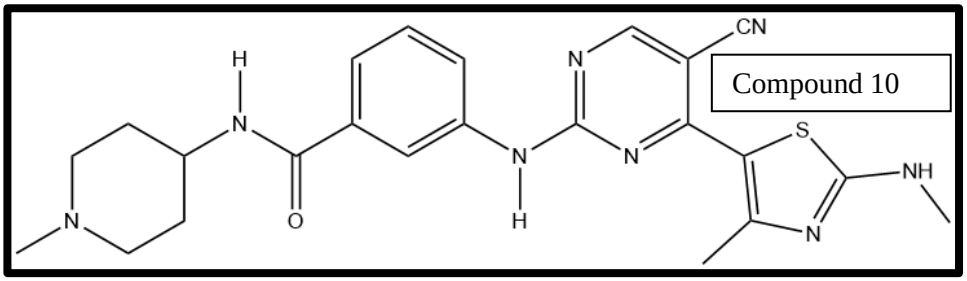
6. **Potential as Anticancer Agent:** Based on the in vitro and in vivo antitumor efficacy, as well as EGFR inhibitory activity and molecular modeling results, compound 9 is identified as a potential anticancer agent.[9]



Compound 6: Ethyl 4-(1H-indol-3-yl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-Carboxylate.
Compound 7: 4-(1H-indol-3-yl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide.
Compound 8: 4-(1H-indol-3-yl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylic acid (4-methyl-benzylidene)-hydrazide.

Compound 9: N-(2-(3, 4-dichlorophenyl)-4-oxothiazolidin-3-yl)-4-(1H-indol-3-yl)-6-methyl-2-thioxo1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide.

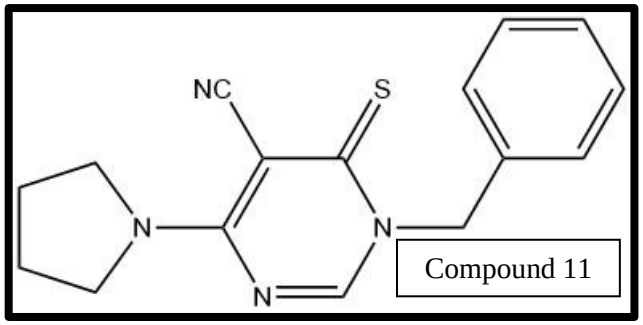
Shao et al. focused on the synthesis and evaluation of new derivatives of 2,4,5-trisubstituted pyrimidine CDK inhibitors as potential anti-tumour agents against various cancer cell lines, including colorectal, breast, lung, ovarian, cervical and pancreatic cancer cells. Among the synthesized derivatives, compound 10 stood out for its significant selectivity for CDK9 over other CDKs. Additionally, compound 10 demonstrated the ability to activate cascade 3, which is an enzyme involved in apoptosis (programmed cell death). It also exhibited the capacity to reduce the level of Mcl-1, an anti-apoptotic protein often overexpressed in cancer cells, thereby promoting cancer cell apoptosis.[10]



Compound 10: 3-((5-cyano-4-(4-methyl-2-(methylamino)thiazol-5-yl)pyrimidin-2-yl)amino)-N-(1-methylpiperidin-4-yl)benzamide.

Compound	**Human Cancer Cell Lines**		
	Type of Cancer	**Cell Line**	**IC_{50} (µM)**
10	Colon	HCT-116	0.79±0.08
	Breast	MCF-7	0.64±0.08
		MDA-MB468	1.51±0.34
	Lung	A549	2.01±0.55
	Ovarian	A2780	1.00±0.11
	Cervical	HeLa	0.90±0.07
	Pancreatic	Miacapa-2	1.25±0.26
11	CNS	SF-268	2.95
		SF-295	9.79
		SF-539	3.99
		SNB-19	5.42
		SNB-57	2.49
		U-251	3.38
	Ovarian	IGROV1	7.71
		OVCAR-3	6.34
		OVCAR-4	3.42
		OVCAR-8	4.92
15	Prostate	A-549	3.36±0.39
		PC-3	1.54±0.19
16	Prostate	A-549	0041±0.03
		PC-3	0.36±0.02
17	Leukaemia	HL-60	0.08
18	Leukaemia	HL-60	0.21

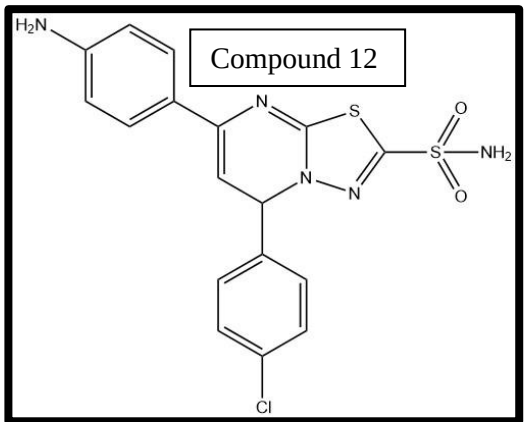
Cocco et al. conducted research on the synthesis of a novel class of 6-thioxopyrimidine derivatives. The molecular structures of these derivatives were confirmed through various analytical techniques such as infrared spectroscopy (IR), nuclear magnetic resonance (NMR)and elemental analyses. The synthesized derivatives were then evaluated for their in vitro anticancer potential against multiple panels of 60 human cancer cell lines using the Sulforhodamine B assay, a method commonly employed to assess cytotoxicity. Notably, compound 11 demonstrated the most significant cytotoxicity among the tested derivatives.[11]

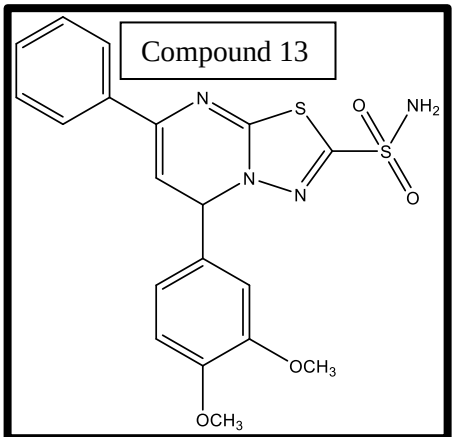


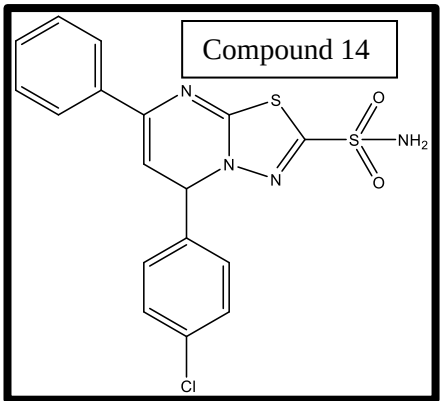
Compound 11: 1-benzyl-4-(pyrrolidin-1-yl)-6-thioxo-1,6-dihydropyrimidine-5-carbonitrile.

Table 2: Anti-cancer activity of compound 10,11,15-18 in human cancer cell lines

El-Sayed et al. synthesized a new library of sulfonamide derivatives and evaluated their potential as anti-tumor agents both in vitro and in vivo. In their preliminary biological study, they found that compounds 12, 13 and 14 exhibited notable characteristics. These compounds showed the highest affinity to DNA, suggesting a possible mechanism of action involving DNA interaction. Additionally, when tested in vivo using a mouse model inoculated with Ehrlich ascites cells, compounds 12, 13 and 14 demonstrated a significant increase in the lifespan of the mice compared to 5-fluorouracil, which was used as the standard drug for comparison.[12]







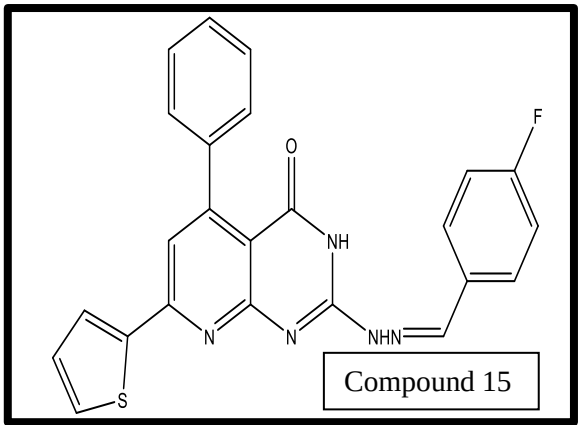
Compound 12: 7-(4-aminophenyl)-5-(4-chlorophenyl)-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-2-sulfonamide.

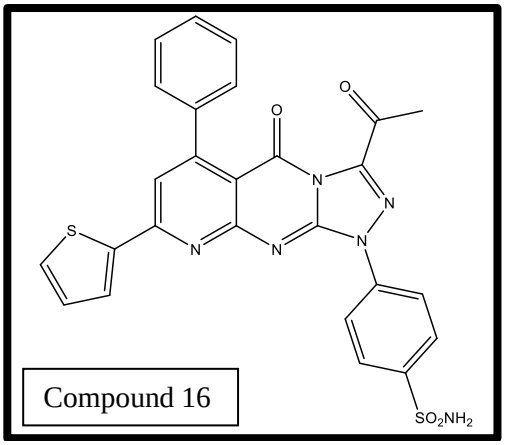
Compound 13: 5-(3,4-dimethoxyphenyl)-7-phenyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-2-sulfonamide.

Compound 14: 5-(4-chlorophenyl)-7-phenyl-5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-2-sulfonamide.

Fares et al. synthesized two new classes of compounds: pyrido[2,3-d]pyrimidine and pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidines. The molecular structures of these synthesized derivatives were confirmed through various physicochemical properties and spectral data analysis methods, including infrared spectroscopy (IR), nuclear magnetic resonance (NMR), mass spectrometry (Mass)and elemental analyses. These synthesized compounds were then screened for their anticancer activity against human cancer cell

lines, specifically PC-3 prostate cancer cells and A-549 lung cancer cells. Among the tested compounds, some demonstrated high growth inhibitory potential against PC-3 cells. Notably, compounds 15 and 16 exhibited relatively potent antitumor activity.[13]

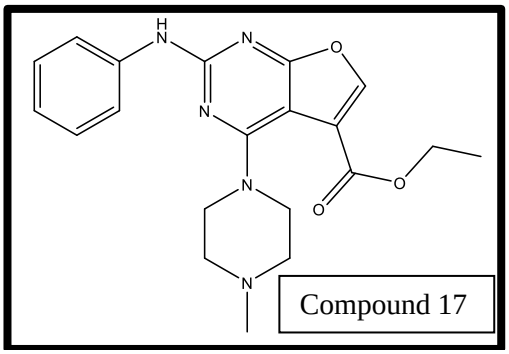




Compound 15: (E)-2-(2-(4-fluorobenzylidene)hydrazineyl)-5-phenyl-7-(thiophen-2-yl)pyrido[2,3-d]pyrimidin-4(3H)-one.

Compound 16: 4-(3-acetyl-5-oxo-6-phenyl-8-(thiophen-2-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-1(5H)-yl)benzenesulfonamide.

Hu et al. developed a new library of 2,4-diaminofuro[2,3-d]pyrimidine compounds and evaluated there in vitro anti-cancer activity against A459 and SPC-A-1 cancer cell lines. The structures of these compounds were confirmed using various analytical techniques such as 1H-NMR, electron ionization mass spectrometry (EI-MS), infrared spectroscopy (IR)and elemental analysis. Among the synthesized compounds, compound 17, specifically identified as ethyl-6-methyl-4-(4-methylpiperazin-1-yl)-2-(phenylamino)furo[2,3-d]pyrimidine-5-carboxylate, exhibited the most potent anticancer activity against the lung cancer cell line A459.[14]



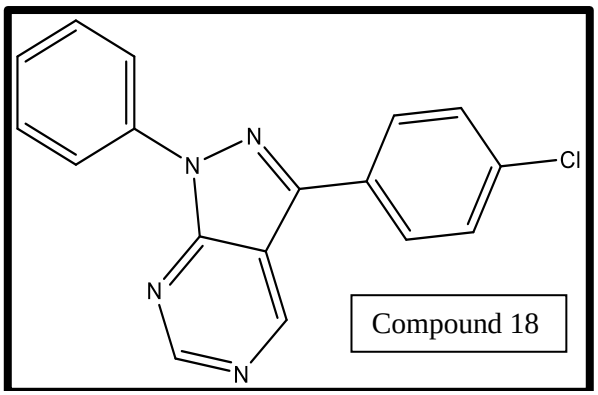
Compound 17: ethyl 4-(4-methylpiperazin-1-yl)-2-(phenylamino)furo[2,3-d]pyrimidine-5-carboxylate.

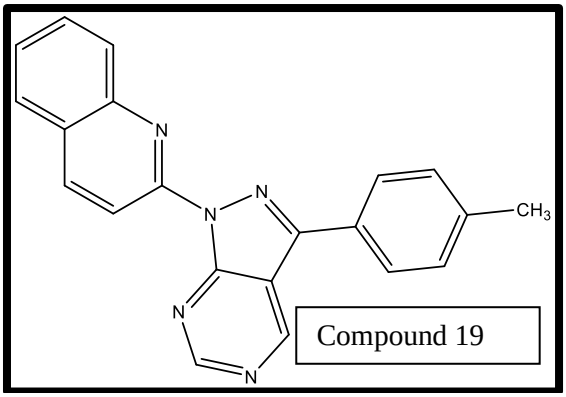
Compound	Human Cancer Cell Lines		
	Type of Cancer	Cell Line	GI_{50} (µM)
17	Lung	A549	0.8
18	Lung	NCl-H226	18
		NPC-TW01	23
19	Lung	NCl-H226	29
		NPC-TW01	30
20	Nasopharyngeal	NCl-H226	39
		NPC-TW01	35
21	Nasopharyngeal	NCl-H226	37
		NPC-TW01	36

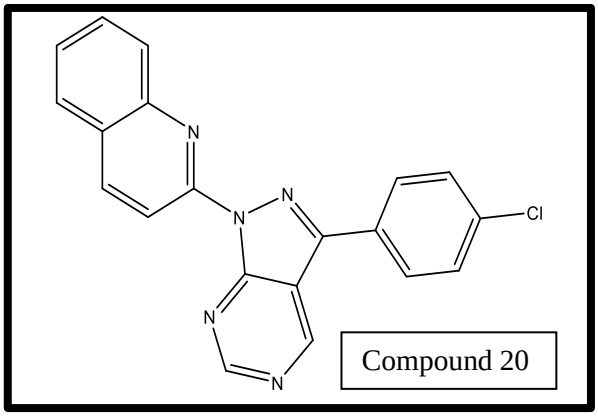
Table 3: Anti-cancer activity of compound 17-21 in human cancer cell lines

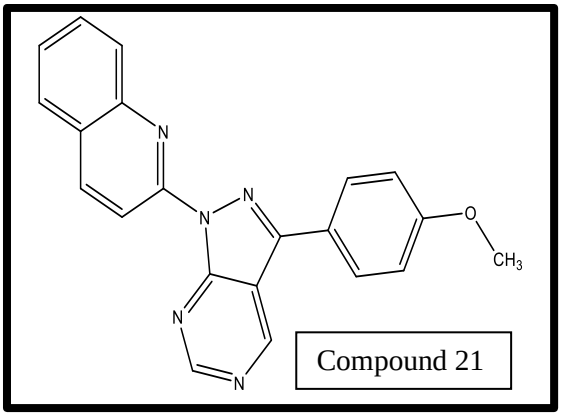
Huang et al. developed a novel series of pyrazolo[3,4-d]pyrimidines using 5-aminopyrazoles with formamide in the presence of PBr3 as the coupling agent. The chemical structures of these synthesized compounds were characterized using various analytical techniques including infrared spectroscopy (IR), proton (1H) and

carbon-13 (13C) nuclear magnetic resonance (NMR), mass spectrometry (Mass)and elemental analyses. Among the series of compounds tested, compounds 18, 19, 20 and 21 demonstrated superior potency against both NCI-H226 and NPC-TW01 cancer cells. [15]



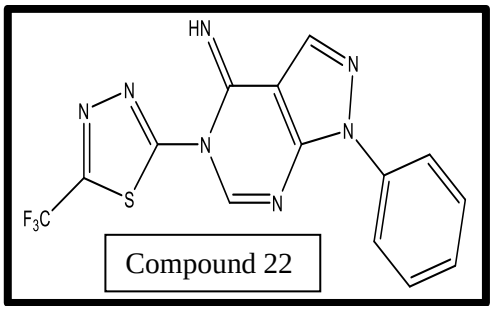


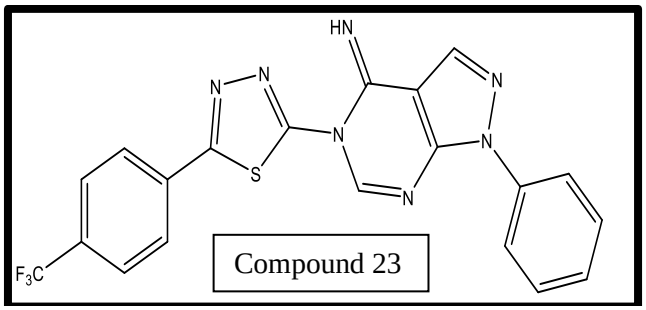




Compound 18: 3-(4-chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine
Compound 19: 2-(3-(p-tolyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)quinoline
Compound 20: 2-(3-(4-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)quinolone
Compound 21: 2-(3-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)quinolone

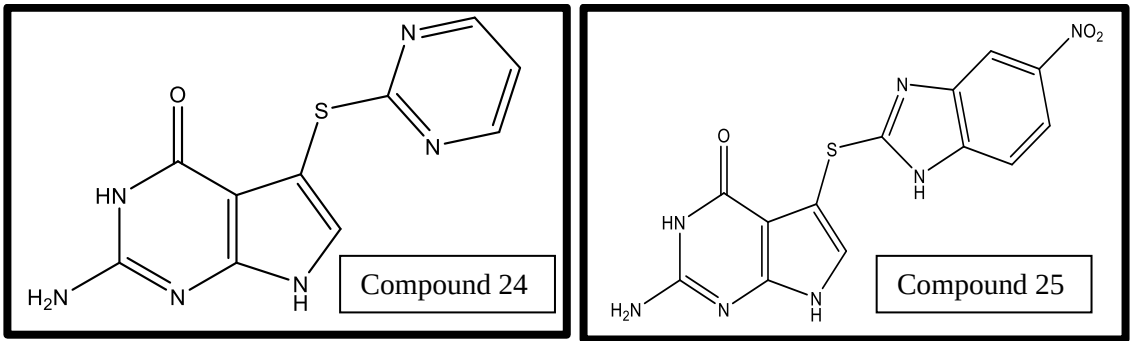
Song et al. synthesized a novel library of fluorinated pyrazolo[3,4-d]pyrimidine derivatives using a microwave (MW) irradiation method. These synthesized compounds were then evaluated for their in vitro antitumor potential against the human leukemia (HL-60) cancer cell line using the MTT assay. Preliminary results from the study revealed that some of the synthesized compounds exhibited potent antitumor inhibitory potential compared to doxorubicin, which served as the standard drug in this context. Specifically, compounds 22 and 23 were highlighted for their higher antitumor activity. The increased antitumor activity of compounds 22 and 23 was attributed to the presence of the CF (fluorine-substituted carbon) group in their molecular structures. This suggests that the introduction of fluorine atoms into the pyrazolo[3,4-d]pyrimidine derivatives enhanced their antitumor efficacy. [16]





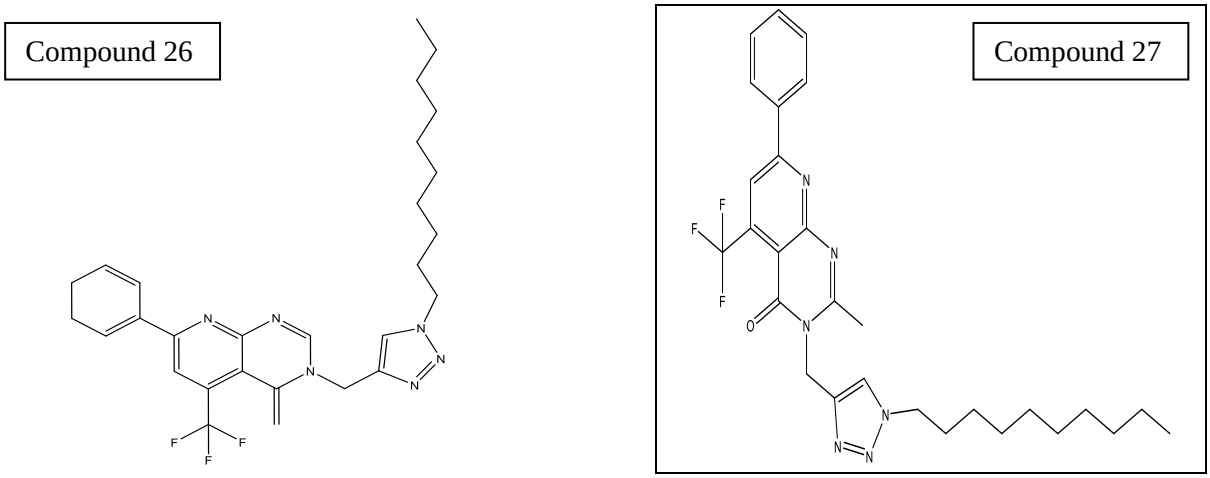
Compound 22: 1-phenyl-5-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-imine.
Compound 23: 1-phenyl-5-(5-(4-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-imine.

Tangeda and Garlapati developed novel molecules of pyrrolo[2,3-d]pyrimidine and conducted screening for their in vitro anti-cancer activity against the HCT116 colon cancer cell line. Among the tested compounds 24 and 25 emerged as the most potent ones against the HCT116 cell line, with IC50 values of 17.61 µM and 17.60 µM, respectively. Notably, the IC50 values of compounds 24 and 25 are comparable to that of 5-fluorouracil (5-FU), a commonly used chemotherapy drug, which exhibited an IC50 value of 3.03 µM. This suggests that compounds 24 and 25 possess significant anti-cancer activity against HCT116 cells, making them promising candidates for further investigation as potential anti-colon cancer agents. [17]



Compound 24: 1-amino-5-(pyrimidin-2-ylthio)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one.
Compound25: 1-amino-5-((5-nitro-1H-benzo[d]imidazol-2-yl)thio)-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one.

Kurumurthy et al. prepared a novel class of alkyltriazole tagged pyrido[2,3-d]pyrimidine derivatives and confirmed their molecular structures using various analytical techniques including infrared spectroscopy (IR), nuclear magnetic resonance (NMR), mass spectrometry (Mass)and elemental analyses. The synthesized derivatives were then evaluated for their in vitro anticancer activity against three different cancer cell lines: U937 (human leukemic monocytic lymphoma), THP-1 (human acute monocytic leukemia)and Colo205 (human colorectal cancer) using the MTT assay, a commonly used method to assess cell viability and proliferation. Among the synthesized molecules, compounds 26 and 27 demonstrated superior anticancer activity compared to the standard drug etoposide. This suggests that compounds 26 and 27 have potential as effective anticancer agents, particularly against the tested cancer cell lines. [18]



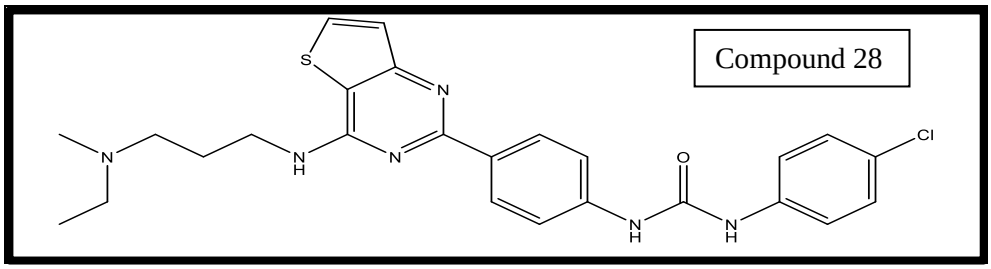
Compound 26: 7-(cyclohexa-1,5-dien-1-yl)-3-((1-decyl-1H-1,2,3-triazol-4-yl)methyl)-4-methylene-5-(trifluoromethyl)-3,4-dihydropyrido[2,3-d]pyrimidine.
Compound 27: 3-((1-decyl-1H-1,2,3-triazol-4-yl)methyl)-2-methyl-7-phenyl-5-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4(3H)-one.

Compound	Human Cancer Cell Lines		
	Type of Cancer	Cell Line	IC_{50} (µM)
26	Lung	U397	8.16 ± 0.68
		THP-1	16.91 ± 1.42
		Colo-205	19.25 ± 1.46

27	Lung	U397	6.20 ± 0.68
		THP-1	11.27 ± 1.67
		Colo-205	15.01 ± 1.54

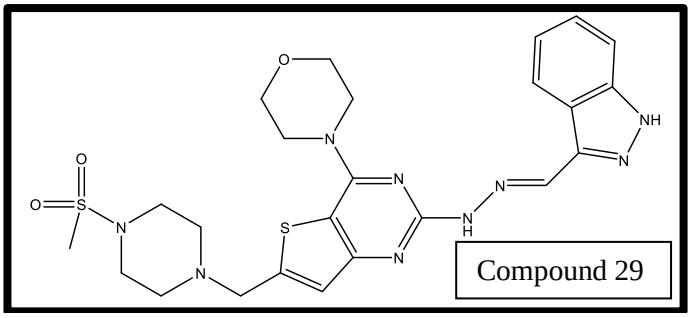
Table 4: Anti-cancer activity of compound 26,27 in human cancer cell lines

Liu et al. synthesized two series of thieno[3,2-d]pyrimidine molecules containing a diaryl urea moiety and evaluated their anticancer potential. In their preliminary investigation, most compounds demonstrated good to excellent potency against four tested cancer cell lines when compared with GDC-0941 and sorafenib, which served as standard drugs. Notably, the most promising compound 28, exhibited the most potent antitumor activities among the tested compounds. Its IC50 values were measured at 0.081 µM, 0.058 µM, 0.18 µMand 0.23 µM against the H460, HT-29, MKN-45and MDA-MB-231 cell lines respectively.[19]



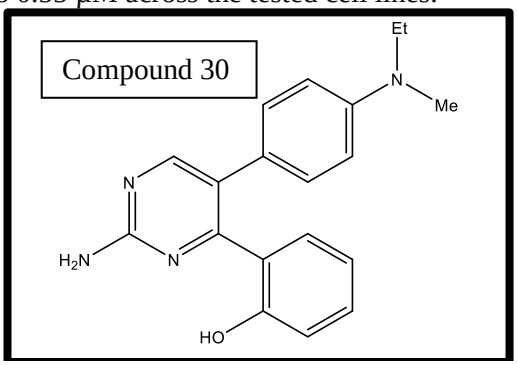
Compound 28: 1-(4-chlorophenyl)-3-(4-(4-((3-(ethyl(methyl)amino)propyl)amino)thieno[3,2-d]pyrimidin-2-yl)phenyl)urea.

Zhu et al. developed a series of 2,6-disubstituted-4-morpholinothieno[3,2-d]pyrimidine molecules and evaluated there in vitro cytotoxic activity against several cancer cell lines including H460, HT-29, MDA-MB-231, U87MG and H1975 with 0.84 µM, 0.23 µM, 2.52 µM, 1.80 µM and 28.82 µM respectively. In their study, most of the synthesized compounds demonstrated moderate to excellent activity against the tested cancer cell lines. The most promising compound, designated as 29, exhibited higher activity than the standard drug used in the study. This suggests that compound 29 has significant potential as an anticancer agent and may be more effective than the standard drug against the tested cancer cell lines. [20]

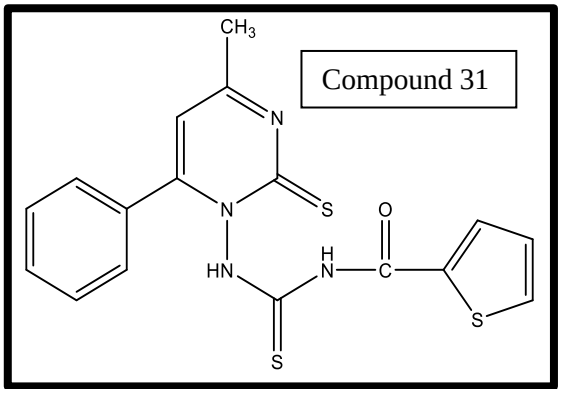


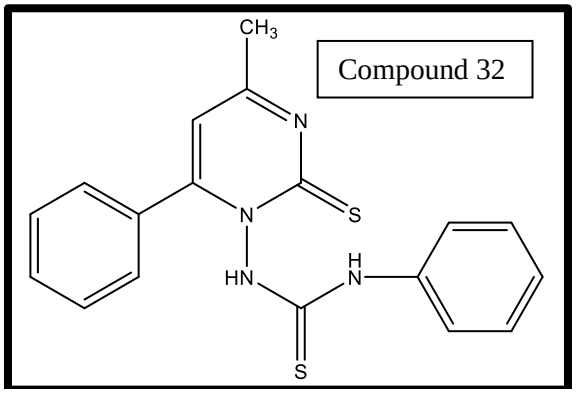
Compound 29: (E)-4-(2-(2-((1H-indazol-3-yl)methylene)hydrazineyl)-6-((4-(methylsulfonyl)piperazin-1-yl)methyl)thieno[3,2-d]pyrimidin-4-yl)morpholine.

Xie et al. prepared 2,4,5-substituted pyrimidine molecules and assessed their anticancer activity against various human cancer cell lines, including A549, Calu-3, H460, SK-BR3, SGC-7901 and HT29. Among the synthesized molecules, compound 30 exhibited significant inhibition of multiple human cancer cell lines. Its IC50 values ranged from 0.024 to 0.55 µM across the tested cell lines. [21]



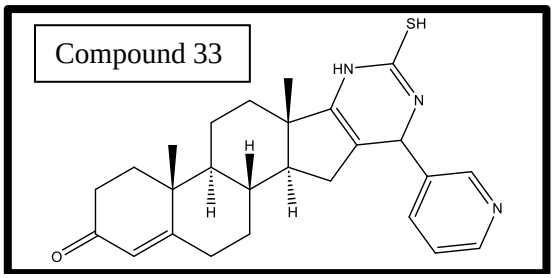
Compound 30: 2-(2-amino-5-(4-(ethyl(methyl)amino)phenyl)pyrimidin-4-yl)phenol.
Al-Issa et al. developed a new series of fused pyrimidines and related heterocycles and assessed their in vitro anti-tumor activity against the human liver cancer cell line HEPG2. The structures of all synthesized compounds were confirmed through spectral and elemental analyses. Among the synthesized compounds, compounds 31 and 32 demonstrated significant in vitro antitumor activity. Their IC50 values were reported as 17.4 µg/ml and 23.6 µg/ml, respectively.[22]

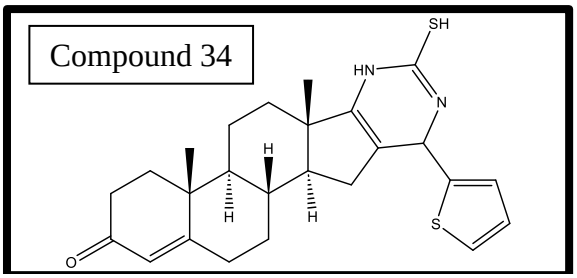




Compound 31: N- ((4-methyl-6-phenyl-2-thioxopyrimidin-1(2H)-yl)carbamothioyl)thiophene-2-carboxamide.
Compound 32: 1-(4-methyl-6-phenyl-2-thioxopyrimidin-1(2H)-yl)-3-phenylthiourea.

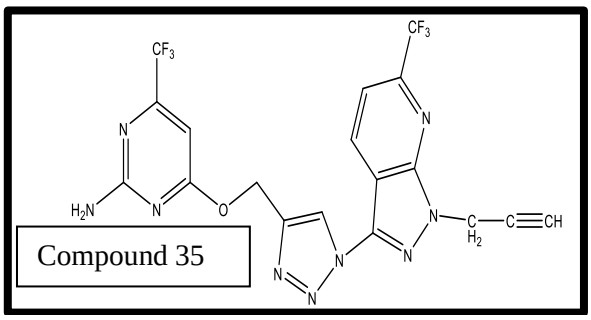
Mohareb et al. developed a novel class of fused pyran, pyrimidineand thiazole molecules and investigated there in vitro anticancer potential against various cancer cell lines, including NUGC (gastric), DLD1 (colon), HA22T (liver), HEPG2 (liver), HONE1 (nasopharyngeal carcinoma), HR (gastric), MCF (breast) with IC_{50} 180nM, 740180nM,180nM, 234180nM, 837180nM, 644nM and 269nM for compound 33; IC_{50} 40 nM, 64 nM, 82 nM, 328 nM, 260 nM and 173nM for compound 34 respectively.. From their study, compounds 33 and 34 demonstrated greater anticancer potential compared to other compounds tested. These two compounds exhibited notable activity against the range of cancer cell lines studied, indicating their broad-spectrum anticancer effects.[23]

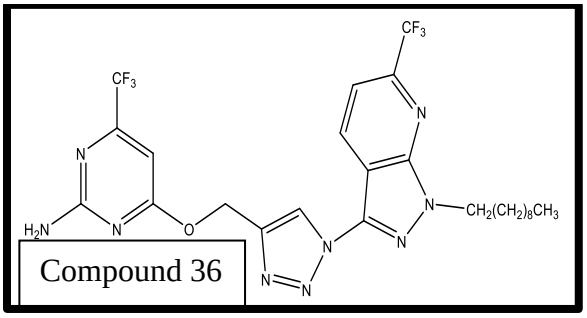


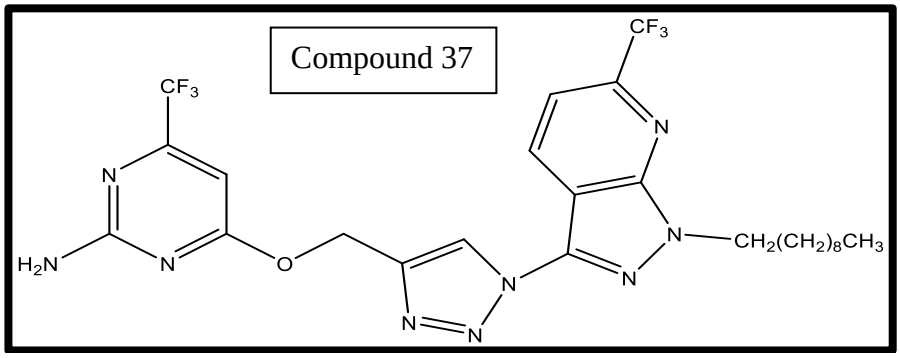


Compound 33: (6aR,6bS,8aS,13aS,13bR)-10-mercapto-6a,8a-dimethyl-12-(pyridin-3-yl)-1,2,5,6,6a,6b,7,8,8a,9,12,13,13a,13b-tetradecahydro-4H-naphtho[2',1':4,5]indeno[1,2-d]pyrimidin-4-one.
Compound 34: (6aR,6bS,8aS,13aS,13bR)-10-mercapto-6a,8a-dimethyl-12-(thiophen-2-yl)-1,2,5,6,6a,6b,7,8,8a,9,12,13,13a,13b-tetradecahydro-4H-naphtho[2',1':4,5]indeno[1,2-d]pyrimidin-4-one.

Nagender et al. synthesized a new series of novel pyrazolo[3,4-b]pyridine and pyrimidine functionalized 1,2,3-triazole derivatives from 6-trifluoromethylpyridine-2(1H)-one. These derivatives were then screened for their cytotoxicity against four human cancer cell lines: A549 (lung), MCF7 (breast), DU145 (prostate) and HeLa (cervical). Among the tested compounds, 35,36 and 37 demonstrated promising cytotoxicity against the cancer cell lines.[24]





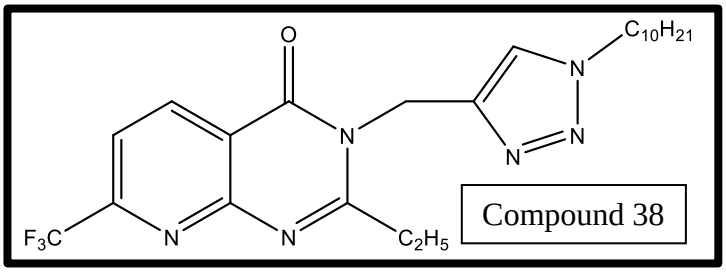


Compound 35: 1-((1-(1-(prop-2-yn-1-yl)-6-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-1H-1,2,3-triazol-4-yl)methoxy)-6-(trifluoromethyl)pyrimidin-2-amine.
Compound 36:1-((1-(1-decyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-1H-1,2,3-triazol-4-yl)methoxy)-6-(trifluoromethyl)pyrimidin-2-amine.
Compound 37: 4-((1-(1-decyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-1H-1,2,3-triazol-4-yl)methoxy)-6-(trifluoromethyl)pyrimidin-2-amine.

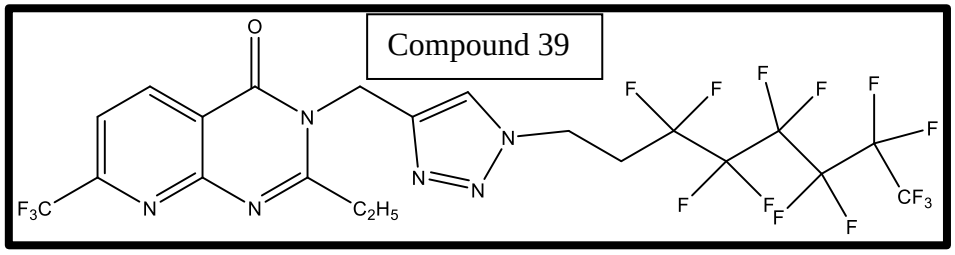
Compound	Human Cancer Cell Lines		
	Type of Cancer	Cell Line	IC_{50} (µM)
35	Lung	A549	4.1 ± 0.12
	Prostate	DU145	4.7 ± 0.18
36	Lung	A549	5.7 ± 0.22
	Breast	MCF7	24.7 ± 0.16
	Prostate	DU145	6.3 ± 0.21
	Cervical	HeLa	22.7 ± 0.11
37	Lung	A549	4.2 ± 0.31
	Breast	MCF7	37.2 ± 0.31
	Prostate	DU145	5.8 ± 0.14
	Cervical	HeLa	34.3 ± 0.32

Table 5: Anti-cancer activity of compound 35-37 in human cancer cell lines

Kumar et al. focused on the synthesis of a novel library of triazole/isoxazole functionalized 7-(trifluoromethyl)pyrido[2,3-d]pyrimidine derivatives. These compounds were then evaluated for their anticancer properties against four different human cancer cell lines. The reference compound used for comparison was nocodazole. Among the compounds synthesized, 38 exhibited the most significant activity against the PANC-1 cell line (GI_{50}= 0.02 ± 0.01µM), which is a pancreatic cancer cell line. Similarly, compound, 39 demonstrated the highest activity against the A549 cell line (GI_{50}= 0.73 ± 0.01 µM), which represents lung cancer.[25]

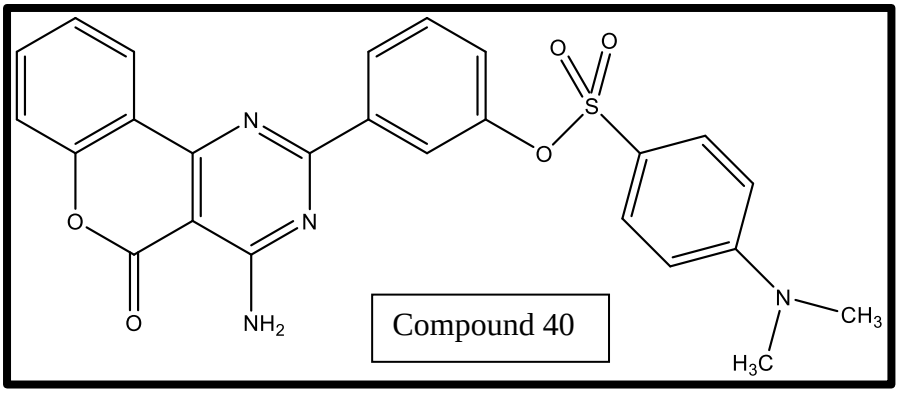


Compound 38: 1-((1-decyl-1H-1,2,3-triazol-4-yl)methyl)-2-ethyl-7-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4(3H)-one.



Compound 39: 1-ethyl-3-((1-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-1H-1,2,3-triazol-4-yl)methyl)-7-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4(3H)-one.

Lv et al. conducted a study wherein they synthesized a novel series of 2-phenylpyrimidine coumarin derivatives. These derivatives were then subjected to evaluation for their in vitro antiproliferative activity against three cancer cell lines: CNE2, KB and Cal27 with 1.92 ± 0.13 μM, 3.72 ± 0.54 μM and 1.97 ± 0.51 μM respectively. The results of their study indicated that the majority of the synthesized derivatives displayed promising effects in inhibiting tumor cell proliferation. Notably, compound 40 demonstrated the most potent antiproliferative activity among the derivatives tested. Its efficacy was comparable to that of the standard drug used in the study. [26]



Compound 40: 3-(4-amino-5-oxo-5H-chromeno[4,3-d]pyrimidin-2-yl)phenyl 4-(dimethylamino)benzenesulfonate.

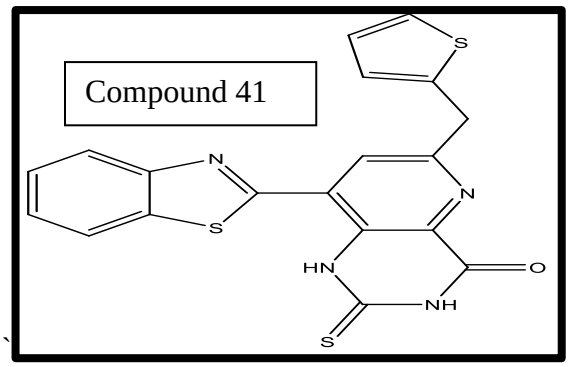
Al-Mutairi et al. described the synthesis and evaluation of novel compounds with potential antimicrobial, anticancerand antioxidant properties. Here's a breakdown of the key points:

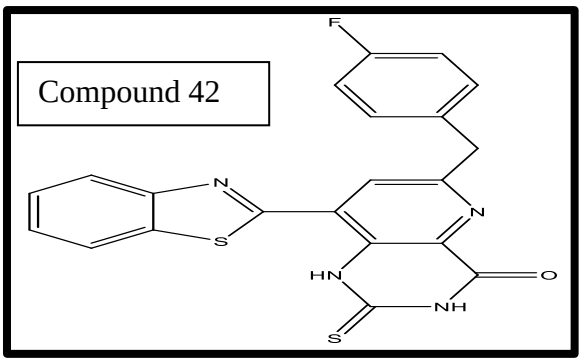
1. **Synthesis of Compounds:** A series of compounds including 2,3-dihydropyrido[2,3-d]pyrimidin-4-one and pyrrolo[2,1-b][1,3]benzothiazoles were synthesized. The synthesis involved the creation of a key intermediate, 2-(1,3-benzothiazol-2-yl)-3-(aryl)prop-2-enenitrile using a microwave efficient method.
2. **Methodology:** The synthesis utilized a new variety-oriented synthetic microwave pathway, allowing for the creation of highly functionalized building blocks. These building blocks facilitated access to various fused heteroaromatic compounds.
3. **Biological Activity Evaluation:**

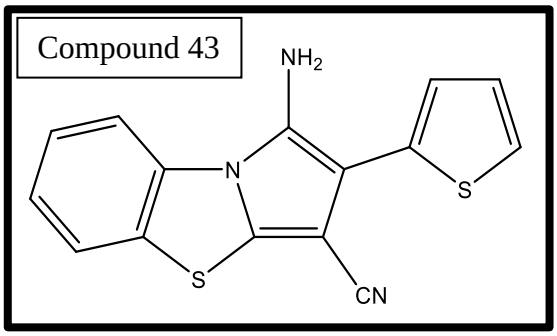
(i) **Antimicrobial Activity:** The synthesized compounds were evaluated for their antimicrobial activity. Compounds 41, 42, 43 and 44 exhibited higher antimicrobial activity compared to the antibiotics cefotaxime and fluconazole. Other compounds showed good to moderate activity against bacteria and fungi.

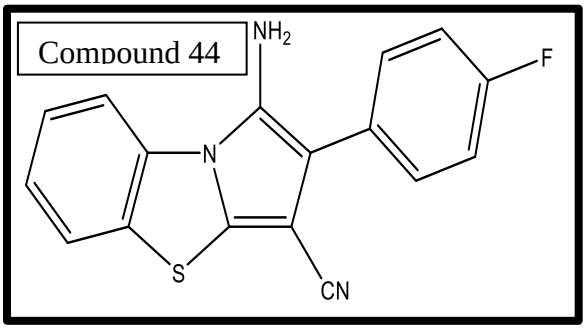
(ii) **Anticancer Activity:** The compounds were also evaluated for their anticancer activity against three tumor cell lines: lung cell NCI-H460, liver cancer HepG2and colon cancer HCT-116. Compounds 41, 42, 43 and 44 demonstrated higher cytotoxicity against these human cell lines compared to the reference drug doxorubicin.

(iii) **Antioxidant Activity:** The synthesized compounds exhibited higher antioxidant activity and showed a significant ability to protect DNA from damage induced.[27]









Compound 41: 7-(benzo[d]thiazol-2-yl)-6-(thiophen-2-ylmethyl)-2-thioxo-2,3-dihydropyrido[3,2-d]pyrimidin-4(1H)-one.
Compound 42: 8-(benzo[d]thiazol-2-yl)-6-(4-fluorobenzyl)-2-thioxo-2,3-dihydropyrido[3,2-d]pyrimidin-4(1H)-one.
Compound 43: 1-amino-2-(thiophen-2-yl)benzo[d]pyrrolo[2,1-b]thiazole-3-carbonitrile.
Compound 44: 1-amino-2-(4-fluorophenyl)benzo[d]pyrrolo[2,1-b]thiazole-3-carbonitrile.

CONCLUSION

Pyrimidine is a member of a heterocycle with a lot of electrons and nitrogen. The 4-heteroarylpyrimidine ring system holds great promise as an anticancer agent, owing to its unique chemical structure and multitargeted mechanism of action. Continued research efforts aimed at elucidating its therapeutic potential and overcoming existing challenges are essential for the development of novel anticancer drugs based on this scaffold. The review emphasizes the importance of pyridine and pyrimidine analogues in anticancer drug discovery and highlights the significant progress made in this area over the past few years. These compounds represent a valuable class of molecules with the potential to contribute to the development of novel and effective anticancer agents.

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